CHAPTER 21

Colloidal Dispersions

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The British chemist Thomas Graham applied the term "colloid" (derived from the Greek word for glue) *ca* 1850 to polypeptides such as albumin and gelatin; polysaccharides such as acacia, starch, and dextrin; and inorganic compounds such as gelatinous metal hydroxides and Prussian blue (ferric ferrocyanide). Contemporary colloid and surface chemistry deals with an unusually wide variety of industrial and biological systems. A few examples include catalysts, lubricants, adhesives, latexes for paints, rubbers and plastics, soaps and detergents, clays, ink, packaging films, cigarette smoke, liquid crystals, drug delivery systems, cell membranes, blood, mucous secretions, and aqueous humors.[1–3]

DEFINITIONS AND CLASSIFICATIONS

Colloidal Systems and Interfaces

Except for high molecular weight polymers, most soluble substances can be prepared as either low molecular weight solutions, colloidal dispersions, or coarse suspensions depending upon the choice of dispersion medium and dispersion technique.[4] Colloidal dispersions consist of at least two phases—one or more dispersed or internal phases, and a continuous or external phase called the *dispersion medium* or *vehicle.* Colloidal dispersions are distinguished from solutions and coarse dispersions by the particle size of the dispersed phase, not its composition. Colloidal dispersions contain one or more substances that have at least one dimension in the range of 1–10 nm at the lower end, and a few μm at the upper end (covering about three orders of magnitude). Thus blood, cell membranes, thinner nerve fibers, milk, rubber latex, fog, and beer foam are colloidal systems. Some materials, such as emulsions and suspensions of most organic drugs, are coarser than true colloidal systems but exhibit similar behavior. Even though serum albumin, acacia, and povidone form true or molecular solutions in water, the size of the individual solute molecules places such solutions in the colloidal range (particle size > 1 nm).[1–3,5–10]

Several features distinguish colloidal dispersions from coarse suspensions and emulsions. Colloidal particles are usually too small for visibility in a light microscope because at least one of their dimensions measures 1 μm or less. They are, however, often visible in an ultramicroscope and almost always in an electron microscope. Conversely, coarse suspended particles are usually visible to the naked eye and always in a light microscope. In addition, colloidal particles, as opposed to coarse particles, pass through ordinary filter paper but are retained by dialysis or ultrafiltration membranes. Also, unlike coarse particles, colloidal particles diffuse very slowly and undergo little or no sedimentation or creaming. Brownian motion maintains the dispersion of the colloidal internal phases.

An appreciable fraction of atoms, ions, or molecules of colloidal particles are located in the boundary layer between the particle and the dispersion medium. The boundary layer between a particle and air is commonly referred to as a *surface*; whereas, the boundary layer between a particle and a liquid or solid is commonly referred to as an *interface*. The ions/molecules within the particle and within the medium are surrounded on all side by similar ions/molecules and have balanced force fields; however, the ions/molecules at surfaces or interfaces are subjected to unbalanced forces of attraction. Consequently, a surface free energy component is added to the total free energy of colloidal particles and becomes important as the particles become smaller and a greater fraction of their atoms, ions, or molecules are located in the surface or interfacial region. As a result, the solubility of very fine solid particles and the vapor pressure of very small liquid droplets are greater than the corresponding values for coarse particles and drops of the same materials.

SPECIFIC SURFACE AREA—Decreasing particle size increases the surface-to-volume ratio, expressed as the *specific surface area* (A_{sp}). Specific surface area may expressed as the area (A, cm^2) per unit volume (V, cm^3) or per unit mass (M, gram). For a sphere, $A = 4\pi r^2$ and $V = 4/3\pi r^3$, then A_{sp} is:

$$A_{sp} = \frac{A}{V} = \frac{4\pi r^2}{4/3\pi r^3} = \frac{3}{r}\frac{cm^2}{cm^3} = \frac{3}{r}\,cm^{-1}$$

For density (d) of the material expressed as g/cm^3, the specific surface area is:

$$A_{sp} = \frac{A}{M} = \frac{A}{Vd} = \frac{4\pi r^2}{4/3\pi r^3 d} = \frac{3}{rd}\frac{cm^2}{g}$$

Table 21-1 illustrates the effect of comminution on the specific surface area of a material initially consisting of one sphere having a 1-cm radius. The specific surface area increases as the material is broken into a larger number of smaller and smaller spheres. Activated charcoal and kaolin are solid adsorbents having specific surface areas of about 6×10^6 cm^2/g and 10^4 cm^2/g, respectively. One gram of activated charcoal has a surface area equal to 1/6 acre because of its extensive porosity and internal voids.

Physical States of Dispersed and Continuous Phases

A useful classification of colloidal systems is based upon the state of matter of the dispersed phase and the dispersion medium (ie, whether they are solid, liquid, or gaseous).[2,7,8] Common examples and various combinations are shown in Table 21-2. The terms *sols* and *gels* are often applied to colloidal dispersions of a solid in a liquid or gaseous medium. *Sols* tend

Table 21-1. Effect of Comminution on the Specific Surface Area of a Volume of $4\pi/3$ cm^3, Divided into Uniform Spheres of Radius R[a]

NUMBER OF SPHERES	R	A_{sp} (cm^2/cm^3)
1	1 cm	3
10^3	0.1 cm = 1 mm	3×10
10^6	0.1 mm	3×10^2
10^9	0.01 mm	3×10^3
10^{12}	1 μm	3×10^4
10^{15}	0.1 μm	3×10^5
10^{18}	0.01 μm	3×10^6
10^{21}	1 nm	3×10^7
10^{23}	0.1 nm	3×10^8

[a] Shaded region corresponds to colloidal particle-size range.

to have a lower viscosity and are fluid. If the solid particles form bridged structures possessing some mechanical strength, the system is then called a *gel*. Prefixes typically designate the dispersion medium. For example, hydrosol (or hydrogel), alcosol (or alcogel), and aerosol (or aerogel), designate water, alcohol, and air, respectively.

Interaction Between Dispersed Phases and Dispersion Mediums

Ostwald originated another useful classification of colloidal dispersions based on the affinity or interaction between the dispersed phase and the dispersion medium.[2,3,8] This classification refers mostly to solid-in-liquid dispersions. Colloidal dispersions are divided into the two broad categories, *lyophilic* and *lyophobic*. Some soluble, low molecular weight substances have molecules with both tendencies and associate in solution, forming a third category called *association colloids*.

LYOPHILIC DISPERSIONS

The system is said to be *lyophilic* (solvent-loving) if there is considerable attraction between the dispersed phase and the liquid vehicle (ie, extensive solvation). The system is said to be *hydrophilic* if the dispersion medium is water. Due to the presence of high concentrations of hydrophilic groups, solids such as bentonite, starch, gelatin, acacia, and povidone swell, disperse, or dissolve spontaneously in water to the greatest degree possible without breaking covalent bonds. Hydrophilic colloids often contain ionized groups that dissociate into highly hydrated ions (eg, carboxylate, sulfonate, and alkylammonium ions) and/or organic functional groups that bind water through hydrogen bonding (eg, hydroxyl, carbonyl, amino, and imino groups).

Hydrophilic colloidal dispersions can be further subdivided as:

True solutions: water-soluble polymers (eg, acacia and povidone).

Gelled solutions, gels, or jellies: polymers present at sufficiently high concentrations and/or at temperatures where their water solubility is low. Examples include relatively concentrated solutions of gelatin and starch (which set to gels upon cooling) and methylcellulose (which gels upon heating).

Particulate dispersions: solids that do not form molecular solutions but remain as discrete though minute particles. Bentonite and microcrystalline cellulose are examples of these hydrosols.

Lipophilic or *oleophilic* substances have a strong affinity for oils. Oils are nonpolar liquids consisting mainly of hydrocarbons having few polar groups and low dielectric constants. Examples include mineral oil, benzene, carbon tetrachloride, vegetable oils (eg, cottonseed or peanut oil), and essential oils (eg, lemon or peppermint oil). Oleophilic colloidal dispersions include polymers such as polystyrene and unvulcanized or gum rubber dissolved in benzene, magnesium, or aluminum stearate dissolved or dispersed in cottonseed oil, and activated charcoal which forms sols or particulate dispersions in all oils.

LYOPHOBIC DISPERSIONS

The dispersion is said to be *lyophobic* (solvent-hating) when there is little attraction between the dispersed phase and the dispersion medium. *Hydrophobic* dispersions consist of particles that are only hydrated slightly or not at all because water molecules prefer to interact with one another instead of solvating the particles. Therefore, such particles do not disperse or dissolve spontaneously in water. Examples of materials that form hydrophobic dispersions include organic compounds consisting largely of hydrocarbon portions with few, if any, hydrophilic functional groups (eg, cholesterol and other steroids); some nonionized inorganic substances (eg, sulfur); and oleophilic materials such as polystyrene or gum rubber, organic lipophilic drugs, paraffin wax, magnesium stearate, and cottonseed or soybean oils. Materials such as sulfur, silver chloride, and gold form hydrophobic dispersions without being lipophilic. There is no sharp dividing line between hydrophilic and hydrophobic dispersions. For example, gelatinous hydroxides of polyvalent metals (eg, aluminum and magnesium hydroxide) and clays (eg, bentonite and kaolin) possess some characteristics of both.[2,3,6,8] Common *lipophobic* dispersions include water-in-oil emulsions, which are essentially lyophobic dispersions in lipophilic vehicles.

Table 21-2. Classification of Colloidal Dispersions According to State of Matter

DISPERSE PHASE	DISPERSION MEDIUM (VEHICLE)		
	SOLID	LIQUID	GAS
SOLID	Zinc Oxide Paste USP, toothpaste (dicalcium phosphate or calcium carbonate with aqueous sodium carboxymethylcellulose binder), and pigmented plastics (titanium dioxide in polyethylene).	Sols: Bentonite Magma NF, Trisulfapyrimidines Oral Suspension USP, Alumina and Magnesia Oral Suspension USP, Tetracycline Oral Suspension USP, Betamethasone Valerate Lotion USP, and Prednisolone Acetate Ophthalmic Suspension USP.	Solid aerosols: Epinephrine Bitartrate Inhalation Aerosol USP, Isoproterenol Sulfate Inhalation Aerosol USP, smoke, and dust.
LIQUID	Absorption bases (aqueous medium in Hydrophilic Petrolatum USP), emulsion bases (oil in Hydrophilic Ointment USP, Lanolin USP), and butter	Emulsions: Mineral Oil Emulsion USP, Benzyl Benzoate Lotion USP, and soybean oil in water for parenteral nutrition, milk, and mayonnaise.	Liquid aerosols: Metaproterenol Sulfate Inhalation Aerosol USP, Povidone-Iodine Topical Aerosol USP, mist, and fog.
GAS	Solid foams (foamed plastics and rubbers) and pumice	Foams, carbonated beverages, and effervescent salts in water.	No colloidal dispersions.

ASSOCIATION COLLOIDS

Organic compounds that contain large hydrophobic moieties on the same molecule with strongly hydrophilic groups are said to be *amphiphilic*. The individual molecules are generally too small to be in the colloidal size range, but they tend to associate into larger aggregates when dissolved in water or oil. These compounds are designated *association colloids* because their aggregates are large enough to qualify as colloidal particles. Examples include surfactant molecules that associate into micelles above their critical micelle concentration (CMC) and phospholipids that associate into cellular membranes and liposomes, which have been used for drug delivery.

PROPERTIES OF COLLOIDAL DISPERSIONS

Particle Shape

Particle shape depends upon the chemical and physical nature of the dispersed phase and the method employed to prepare the dispersion *(preparation methods are described in later sections)*. Primary particles exist in a wide variety of shapes, and their aggregation produces an even wider variety of shapes and structures. Preparation methods such as mechanical comminution and precipitation generally produce randomly shaped particles unless the precipitating solids possess pronounced crystallization habits or the solids being ground possess strongly developed cleavage planes. For example, micronized particles of sulfonamides and other organic powders and precipitated aluminum hydroxide gels typically have irregular random shapes. An exception is bismuth subnitrate; hydrolyzing bismuth nitrate solutions with sodium carbonate precipitates lath-shaped particles. In addition, precipitated silver chloride particles show their cubic nature under the electron microscope. Lamellar or plate-like solids often preserve their lamellar shape during mechanical comminution because milling and micronization break up the stacks of thin plates, in addition to fragmenting plates in the lateral dimensions. In these materials, the molecular cohesion between layers is much weaker than the cohesion within layers. Examples of such materials include graphite, mica, and kaolin (Fig 21-1). In a like manner, macroscopic asbestos and cellulose fibers consist of bundles of microscopic and submicroscopic fibrils that have very small diameters. Mechanical comminution splits these bundles into their component fibrils as well as cutting them shorter. Figure 21-2 shows the individual, needle- or rod-shaped cellulose crystallites formed after breaking up the aggregated bundles of *microcrystalline cellulose*. These crystallites average 0.3 μm in length and 0.02 μm in width, which places them in the colloidal size range. Microcrystalline cellulose is a fibrous thickening agent and tablet additive made by the controlled hydrolysis of cellulose. Its manufacture is described in the 16–18th editions of this text, which also contain an electron micrograph of the porous, spongy, and compressible fibril bundle aggregates used in tableting.

Except in the special cases of clay and cellulose just mentioned, regular shaped particles are typically produced by condensation rather than disintegration methods. For example, *colloidal silicon dioxide* is a white powder consisting of submicroscopic spherical particles of rather uniform size (ie, narrow particle size distribution). It is manufactured by high-temperature, vapor-phase hydrolysis of silicon tetrachloride in an oxy-hydrogen flame (ie, a flame produced by burning hydrogen in a stream of oxygen). It is commonly referred to as fumed or pyrogenic silica because of this manufacturing process. Different grades are produced by different reaction conditions. Figure 21-3 shows the relatively large, single spherical particles of colloidal silicon dioxide. Their average diameter of 50 nm corresponds to the comparatively small specific surface area of 50 m^2/g. Smaller spherical particles have a larger specific surface area. For example, the grade with the smallest average diameter, 5 nm, has a specific surface area of 380 m^2/g. The finer-grade particles tend to sinter or grow together into chain-like aggregates resembling pearl necklaces during the manufacturing process (Fig 21-4). *Latexes* of polymers, such as latex-based paints, are aqueous dispersions prepared by emulsion polymerization. Their particles

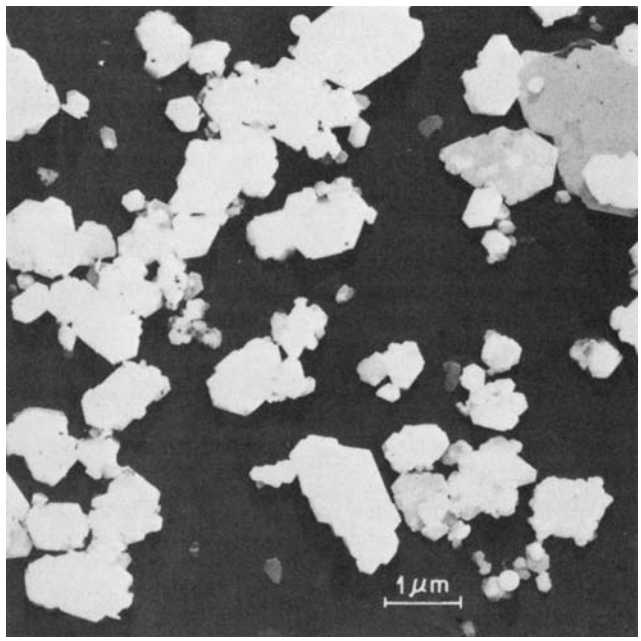


Figure 21-1. Transmission electron micrograph of a well-crystallized, fine-particle kaolin. Note hexagonal shape of the clay platelets (courtesy, John L. Brown, Engineering Experiment Station, Georgia Institute of Technology).

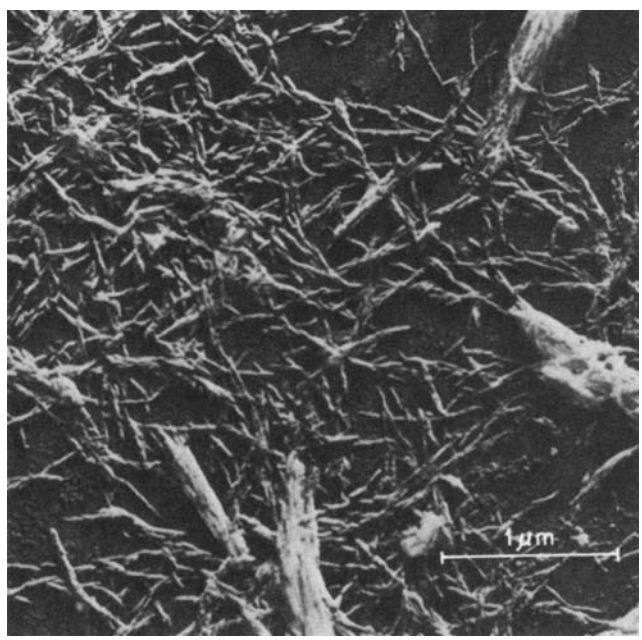


Figure 21-2. Transmission electron micrograph of Avicel RC-591 thickening grade microcystalline cellulose. The needles are individual cellulose crystallites; some are aggregated into bundles (courtesy, FMC Corporation; Avicel is a registered trademark of FMC Corporation).

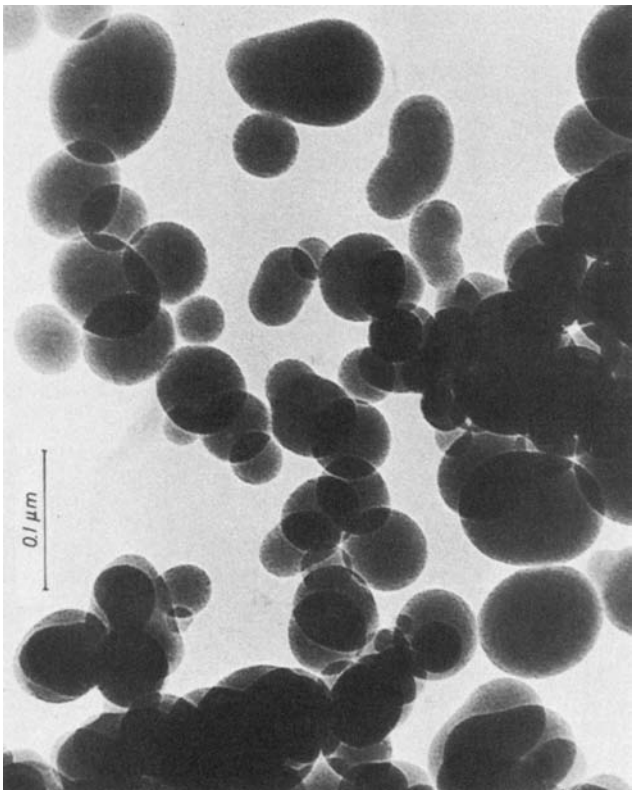


Figure 21-3. Transmission electron micrograph of Aerosil OX 50, ground and dusted on. The spheres are translucent to the electron beam, causing overlapping portions to be darker owing to an increased thickness (courtesy, Degussa AG of Hanau, Germany; Aerosil is a registered trademark of Degussa). The suffix 50 indicates the specific surface area in m^2/g.

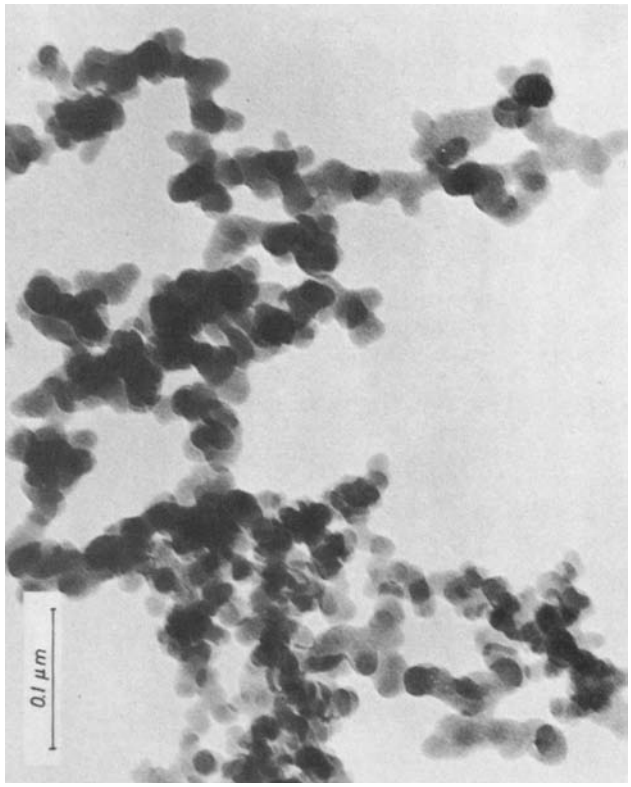


Figure 21-4. Transmission electron micrograph of Aerosil 130, ground and dusted on. The spheres are fused together into chain-like aggregates (courtesy, Degussa AG of Hanau, Germany; Aerosil is a registered trademark of Degussa). The suffix 130 indicates the specific surface area in m^2/g.

are spherical because polymerization of the solubilized liquid monomers takes place inside spherical surfactant micelles. Some *clays* grow as plate-like particles possessing straight edges and hexagonal angles (eg, bentonite and kaolin) (Fig 21-1). Other clays have lath-shaped (nontronite) or rod-shaped particles (attapulgite).[11]

Emulsification produces spherical droplets to minimize the oil-water interfacial area. Cooling an emulsion below the melting point of the dispersed phase freezes the dispersed particles in a spherical shape. For instance, paraffin may be emulsified in 80°C water and then cooled to room temperature to produce a hydrosol containing spherical particles. Sols of viruses and globular proteins, which are hydrophilic, contain compact particles possessing definite geometric shapes. For example, the poliomyelitis virus is spherical, the tobacco mosaic virus is rod-shaped, and the serum albumins and globulins are prolate ellipsoids of revolution (football-shaped).

Diffusion and Sedimentation

The molecules of a gas or liquid are engaged in a perpetual and random thermal motion causing collisions with one another and with the container wall billions of times per second. Each collision changes the direction and the velocity of these molecules. The continuous motion of molecules of a dispersion medium randomly buffets any dissolved molecules and suspended colloidal particles. The random bombardment imparts an erratic movement called *Brownian motion* to solutes and particles. This phenomenon is named after the botanist Robert Brown who first observed it under the microscope in an aqueous pollen suspension. The Brownian motion of colloidal particles magnifies the random movements of molecules in the liquid or gaseous suspending medium and represents a three-dimensional random walk.

Suspended colloidal particles and solute molecules undergo both rotational and translational Brownian movements. For translational motion, Einstein derived the equation:

$$\bar{x} = \sqrt{2Dt}$$

where $\bar{x}$ is the mean displacement in the x-direction in time, t, and D is the *diffusion coefficient*. Einstein also showed that for spherical particles of radius, r, under conditions valid for Stokes' law and Einstein's law of viscosity:

$$D = \frac{RT}{6\pi\eta rN}$$

where R is the gas constant, T is the absolute temperature, N is Avogadro's number, and η is the viscosity of the suspending medium.

A common measure of the mobility of a dissolved molecule or suspended particle in a liquid medium is the diffusion coefficient. At room temperature, using units of cm^2/sec, the value of sucrose in water is 4.7×10^{-6} and the value of serum albumin in water is 6.1×10^{-7}. Diffusion is a slow process on a macroscopic scale. Using the value of 1×10^{-7} cm^2/sec, Brownian motion causes a particle to move in one direction an average distance of 1 cm in 58 days, 1 mm in 14 hours, or 1 μm in 0.05 seconds. As seen in the above equation, smaller molecules diffuse faster in a given medium. The radius of a sucrose molecule is smaller than that of a serum albumin molecule; the calculated values are 0.44 nm and 3.5 nm, respectively (assuming a spherical shape). Steroids have only slightly higher molecular weights than sucrose; however, their diffusion coefficients in petrolatum-based absorption bases are in the 10^{-10} to 10^{-8}

cm^2/sec range. These much smaller diffusion coefficients are caused by the much higher vehicle viscosity. Passive diffusion (driven by a concentration gradient and carried out through Brownian motion) is important in the release of drugs from topical preparations and in the gastrointestinal absorption of drugs.

Brownian motion and convection currents maintain dissolved molecules and small colloidal particles in suspension indefinitely. This is true for all intrinsically stable systems when dissolution or dispersion occurs spontaneously and the corresponding free energy change is negative (see below). In metastable or diuturna dispersions, Brownian motion prevents sedimentation and may extend their life for years.

As particle size or r increases, Brownian motion decreases as seen by the $\bar{x}$ proportionality to $r^{-1/2}$. Larger particles have a greater tendency than smaller particles of the same material to settle to the bottom of the dispersion, provided the densities of the dispersed phase, d_P, and the liquid vehicle, d_L, are sufficiently different (sedimentation, when $d_P > d_L$). On the other hand, larger particles will rise to the top of the dispersion when $d_P < d_L$. This is known as creaming. The Stokes equation reflects the rate of *sedimentation/creaming*; it is expressed as:

$$h = \frac{2(d_P - d_L)r^2gt}{9\eta}$$

where h is the height (or distance) that a spherical particle moves in time, t, and g is the acceleration of gravity. The equation illustrates that this rate is proportional to r^2. Consequently, as Brownian motion diminishes with increasing particle size, the tendency of particles to sediment or cream is increased. At a critical radius, the distance, h, that a particle settles/creams equals the mean displacement, $\bar{x}$, due to Brownian motion over the same time interval, t, and therefore, the two are equal.[12] Intravenous vegetable oil emulsions have little tendency to cream because their mean droplet size, ~0.2 μm, is smaller than the critical radius. In most pharmaceutical suspensions, sedimentation prevails.

Light Scattering

The optical properties of a medium are determined by its refractive index. Light will pass through the medium undeflected when the refractive index is uniform throughout. However, when there are discrete variations in the refractive index from the presence of particles or caused by small-scale density fluctuations, part of the passing light will be scattered in all directions. When a narrow beam of sunlight is admitted through a small hole into a darkened room, bright flashing points reveal the presence of the minute dust particles suspended in the air. A beam of light striking a particle polarizes the atoms and molecules of that particle and induces dipoles, which act as secondary sources and reemit weak light of the same wavelength as the incident light. This phenomenon is called *light scattering*. The scattered radiation propagates in all directions away from the particle. In a bright room, the light scattered by the dust particles is too weak to be noticeable.

Colloidal particles suspended in a liquid also scatter light. When an intense, narrowly defined beam of light is passed through a suspension, its path becomes visible because of the light scattered by the particles in the beam. This *Tyndall Beam* is characteristic of colloidal systems and becomes most visible when viewed against a dark background in a direction perpendicular to the incident beam. The magnitude of the turbidity or opalescence depends upon the nature, size, and concentration of the dispersed particles. For example, when clear mineral oil is dispersed in an equal volume of a clear, aqueous surfactant solution, the resultant emulsion is milky white and opaque due to light scattering. However, microemulsions containing emulsified droplets that are only about 40 nm in diameter (ie, much smaller than the wavelength of visible light) are transparent and clear to the naked eye.

The concentration of inorganic and organic colloidal dispersions and of bacterial suspensions can be measured by their Tyndall effect or turbidity. Turbidity, τ, is defined by an equation analogous to Beer's law for the absorption of light,[2,5–8] namely:

$$\tau = \frac{1}{l} \ln \frac{I_0}{I_t}$$

where I_0 and I_t are the intensities of the incident and transmitted light beams, and l is the length of the dispersion through which the light passes. The concentration of dispersed particles may be measured in two ways using turbidity. In *turbidimetry*, a spectrophotometer or photoelectric colorimeter is used to measure the intensity of the light transmitted in the incident direction. The theoretical and practical aspects of determining the particle size of suspensions by *turbidimetry* and the feasibility of estimating their particle-size distribution are discussed in two chapters by Kourti et al.[13] If the dispersion is less turbid, the intensity of light scattered at 90° to the incident beam is measured with a *nephelometer*. Both methods require careful standardization, using suspensions that contain known amounts of particles similar to those being studied. The turbidity of hydrophilic colloidal systems such as aqueous solutions of gums, proteins, and other polymers is far weaker than that of lyophobic dispersions. These solutions appear clear to the naked eye; however, their turbidity can be measured with a photoelectric cell/photomultiplier tube and used to determine the molecular weight of the solute.

The theory of light scattering was developed in detail by Lord Rayleigh. For white, nonabsorbing nonconductors or dielectrics like sulfur and insoluble organic compounds, the equation obtained for spherical particles whose radius is small compared to the wavelength of light (λ) is:[2,5–8]

$$I_s = I_0 \frac{4\pi^2 n_0^2 (n_1 - n_0)^2}{\lambda^4 d^2 c} (1 + \cos^2 \theta)$$

I_0 is the intensity of the unpolarized incident light; I_s is the intensity of light scattered in a direction making an angle, θ, with the incident beam and measured at a distance, d. The scattered light is largely polarized. The concentration, c, is expressed as the number of particles per unit volume. The refractive indices, n_1 and n_0, refer to the dispersion and the dispersion medium, respectively. Since the intensity of scattered light is inversely proportional to the fourth power of the wavelength, blue light ($\lambda \cong 450$ nm) is scattered much more strongly than red light ($\lambda \cong 650$ nm). Colloidal dispersions of colorless particles appear blue when the incident white light is viewed in scattered light (ie, in lateral directions such as 90° to the incident beam). Loss of the blue rays due to preferential scattering leaves the transmitted light yellow or red. Preferential scattering of blue radiation sideways accounts for the blue color of the sky, sea, cigarette smoke, and diluted milk and for the yellow-red color of the rising and setting sun viewed head-on.

The particles in pharmaceutical suspensions, emulsions, and lotions are generally larger than the wavelength of light, λ. When the particle size exceeds λ/20, destructive interference between the light scattered by different portions of the same particle lowers the intensity of the scattered light and changes its angular dependence. Rayleigh's theory was extended to large and strongly absorbing and conducting particles by Mie and to nonspherical particles by Gans.[1,2,5–8] It is possible to determine the average particle size and even the particle size distribution of colloidal dispersions and coarser suspensions by means of turbidity measurements using appropriate precautions in experimental techniques and interpretations.

DYNAMIC LIGHT SCATTERING—Light scattered by a moving particle undergoes a Doppler shift; its frequency increases slightly when the particle moves towards the photodetector and decreases slightly when it moves away. This shift is so small that it can only be detected by very intense, strictly monochromatic laser light. Because they are engaged in random Brownian motion, a set of colloidal particles scatters light

with a broadened frequency. Smaller particles diffuse faster than larger ones and therefore produce greater Doppler broadening. If the particles are spherical, monodisperse, and their concentration is so dilute that they neither attract nor repel one another, the frequency broadening can be used to estimate the particle diffusion coefficient, D. As noted above, the diffusion coefficient is inversely proportional to the particle radius. The measured radius is actually the hydrodynamic radius (r_H), which comprises the particle plus its attached water of hydration. The technique is called *dynamic* or *quasi-elastic light scattering*. The technique is also called *photon correlation spectroscopy* (PCS) because it counts and correlates the number of scattered photons over very short time intervals. For polydisperse spherical colloidal particles, it estimates the particle size distribution.[2,5,8,9] Particles that are asymmetric rather than spherical and/or extensively hydrated have a larger r_H and hence smaller D value than unsolvated spherical particles with the same dry volume. It is not possible to separate the effect of hydration upon r_H, and D from the effect of asymmetry by PCS alone; either hydration or particle shape must be determined by other means.[2,5,7–9]

In a related technique that uses a *fiber-optic Doppler anemometer* (FODA), a laser beam is carried into the interior of a colloidal dispersion via a fiber-optic cable. Particles in the small volume of dispersion around the immersed tip scatter light with the Doppler frequency shift back into the same fiber to the detector. This method is suitable for concentrated dispersions that are opaque to the laser beam and would have to be diluted extensively for conventional dynamic light scattering measurements[14] (see also the chapter by JC Thomas in reference 13).

Viscosity

Most lyophobic dispersions have viscosities only slightly greater than that of the liquid vehicle. This holds true even at comparatively high volume fractions of the disperse phase unless the particles form continuous network aggregates throughout the vehicle, in which case yield stresses are observed. By contrast, the apparent viscosities of lyophilic dispersions, especially of polymer solutions, are several orders of magnitude greater than the viscosity of the solvent or vehicle even at concentrations of only a few percent solids. Lyophilic dispersions are also generally much more pseudoplastic or shear-thinning than lyophobic dispersions.

Gel Formation

The flexible chains of dissolved polymers interpenetrate and entangle because of the constant Brownian motion of their segments. The chains constantly writhe and change their conformations. Each chain is encased in a sheath of solvent molecules that solvate its functional groups. For example, water molecules are hydrogen-bonded to the hydroxyl groups of polyvinyl alcohol, hydroxyl groups, and ether linkages of polysaccharides, ether linkages of polyethylene oxide or polyethylene glycol, amide groups of polypeptides and povidone, and carboxylate groups of anionic polyelectrolytes. This envelope of water of hydration prevents chain segments that are in close proximity from touching and attracting one another through interchain hydrogen bonds and van der Waals forces as they do in the solid state. The free solvent between the chains' solvation sheaths acts as a lubricant allowing the solvated chains to slip past one another when the solution flows. However, any factor that lowers the hydration of dissolved macromolecules will reduce or thin out the sheath of hydration separating adjacent chains. When hydration is low, contiguous chains tend to attract one another through secondary valence forces such as hydrogen bonds and van der Waals forces, which establish weak and reversible cross-links between the chains at their points of contact or entanglement, thus bringing about phase separation or precipitation. Hydrophobic bonding is an important contribution to the interchain attraction between polypeptide chains even in solution.

Most water-soluble polymers have a higher solubility in hot water than in cold water and tend to precipitate upon cooling because the sheaths of hydration surrounding adjacent chains become too sparse to prevent interchain attraction. Cooling dilute solutions tends to separate them into a solvent phase and a viscous liquid phase that contains practically the entire amount of polymer but still a large excess of solvent. This process is called *simple coacervation* and the polymer-rich liquid phase is referred to as a *coacervate.*[1,15] If the polymer solution is concentrated enough and/or the temperature is low enough, cooling causes the formation of a continuous network of precipitating chains attached to one another through weak crosslinks that consist of interchain hydrogen bonds and van der Waals forces at the points of mutual contact. Segments of regularly sequenced polymer chains will associate laterally into crystalline bundles or crystallites. However, irregular chain structures, such as those found in random copolymers, randomly substituted cellulose ethers and esters, and highly branched polymers like acacia, will prevent crystallization during precipitation from solution. In these cases, chain entanglements provide the sole temporary crosslinks. A network of associated polymer chains immobilizes the solvent, which may result in the separation of gelatinous precipitates or highly swollen flocs, and in the case of more concentrated polymer solutions, may even cause the solution to set to a gel.

The most important factors causing phase separation, precipitation, and gelation of polymer solutions are the chemical nature of the polymer and the solvent, temperature, polymer concentration, and polymer molecular weight. Lower temperatures, higher concentrations, and higher molecular weights promote *gelation* and produce stronger gels. For a typical *gelatin,* 10% solutions acquire yield values and begin to gel at about 25° C, 20% solutions gel at about 30° C, and 30% solutions gel at about 32° C. The gelation is reversible, and the gels liquefy when heated above these temperatures. Regardless of concentration, gelation is rarely observed above 34° C, and therefore, gelatin solutions do not gel at body temperature (ie, 37° C). Agar and pectic acid solutions set to gels at only a few percent of solids. Unlike most water-soluble polymers, methylcellulose, hydroxypropyl cellulose, and polyethylene oxide are more soluble in cold water than in hot water. Therefore, their solutions tend to gel upon heating (ie, *thermal gelation*) instead of cooling.

When dissolving powdered polymers in water, temporary gel formation often slows dissolution considerably. As water diffuses into loose clumps of the powder, their exterior frequently turns to a cohesive gel of solvated particles encasing the remaining dry powder. Such globs of gel dissolve very slowly because of their high viscosity and the low diffusion coefficients of the polymers. For large-scale dissolution, it is helpful to disperse the polymer powder in water at temperatures where the solubility of the polymer is lowest before it can agglomerate into lumps of gel. Most polymer powders, such as sodium carboxymethylcellulose, are dispersed with high shear in *cold* water before the particles can hydrate and swell into sticky gel grains that agglomerate into lumps. Once the powder is well dispersed, the mixture is heated with moderate shear to about 60°C for the quickest dissolution. Because methylcellulose hydrates more slowly in hot water, the powder is dispersed with high shear in 1/5 to 1/3 of the required amount of water heated to 80–90° C. Once the powder is finely dispersed, the remaining amount of water is added cold, or even as ice, and moderate stirring causes prompt dissolution. For maximum clarity, fullest hydration, and highest viscosity, the solution should be cooled to 0–10° C for about an hour. Alternatively, the polymer powder may be prewetted with a water-miscible organic solvent (eg, ethyl alcohol or

propylene glycol) that does not swell the polymer. The solvent should be added in a proportion of 3–5 parts of solvent to one part of polymer. If other nonpolymeric, powdered adjuvants are to be incorporated into the solution, they are dry-blended with the polymer powder and should comprise only 1/4 or less of the blend for the best results.

Large increases in the concentration of polymer solutions may lead to precipitation and gelation. One way of effectively increasing the concentration of aqueous polymer solutions is to add inorganic salts. The salts will bind part of the water in the solution in order to become hydrated. Competition for water of hydration dehydrates the polymer molecules and precipitates them. This phenomenon is called *salting out* and may cause the polymer to separate as a concentrated, viscous liquid solution, a simple coacervate, or a solid gel. Because of its high solubility in water, ammonium sulfate is often used to precipitate and separate proteins from dilute solutions. However, salting out is reversible and subsequent addition of water redissolves the precipitated polymers and liquefies their gels.

HOFMEISTER OR LYOTROPIC SERIES—The effectiveness of electrolytes to cause salting out depends upon their extent of hydration. The *Hofmeister or lyotropic series* arranges ions in order of increasing hydration and increasing effectiveness in salting out hydrophilic colloids. The series for monovalent and divalent cations are

$$Cs^+ < Rb^+ < NH_4^+ < K^+ < Na^+ < Li^+$$

and

$$Ba^{2+} < Sr^{2+} < Ca^{2+} < Mg^{2+}$$

The Hofmeister series governs many colloidal phenomena, including the effect of salts upon the temperature of gelation, the swelling of aqueous gels, and the viscosity of hydrosols, and the permeability of membranes towards salts. The series is observed in many phenomena involving small atoms or ions and true solutions, including the ionization potential and electronegativity of metals; the heats of hydration of cations; the size of hydrated cations; the viscosity, surface tension, and infrared spectra of salt solutions; and the solubility of gases in salt solutions. This series also arranges cations in order of increasing ease in displacement from cation-exchange resins based on the smaller hydrated specie size (eg, K^+ displaces Na^+ and Li^+). Adsorption in the Stern layer of particles (see below) also illustrates the series. The lithium ion is more extensively hydrated, and therefore, Li^+ (aq), including the hydration shell, is larger than Cs^+ (aq). Due to its smaller size, the hydrated cesium ion can approach a negative particle's surface more closely than the hydrated lithium ion. Moreover, because of its greater electron cloud, the Cs^+ ion is more polarizable than the Li^+ ion. Therefore, the Cs^+ ion is more strongly adsorbed in the Stern layer.

For anions, in order of decreasing effectiveness in salting out, the lyotropic series is

$$F^- > \text{citrate}^{3-} > HPO_4^{2-} > \text{tartrate}^{2-} > SO_4^{2-} > \text{acetate}^- >$$
$$Cl^- > NO_3^- > ClO_3^- > Br^- > ClO_4^- > I^- > CNS^-$$

Iodides and thiocyanates, and to a lesser extent bromides and nitrates, actually tend to increase the solubility of polymers in water (ie, salt them in).[1,2,5–8] These large polarizable anions reduce the extent of hydrogen bonding among water molecules, and thereby, make more of the hydrogen-bonding capacity of water available to the solute. Most salts, except for nitrates, bromides, perchlorates, iodides, and thiocyanates, raise the temperature of precipitation or gelation of most hydrophilic colloidal solutions. Exceptions among hydrophilic colloids are methylcellulose, hydroxypropyl cellulose, and polyethylene oxide, whose gelation temperatures or gel melting points are lowered by salting out.

Most hydrophilic sols require electrolyte concentrations of 1 *M* or higher to induce precipitation or gelation. In addition, hydrophilic colloids disperse or dissolve spontaneously in water and their sols are intrinsically stable. Therefore, the polymer may be redissolved by removing the coagulating salt through dialysis or by adding more water. Whenever hydrophilic colloidal dispersions undergo irreversible precipitation or gelation, chemical reactions are involved. Neither dilution with water, heating, nor attempts to remove the gelling or precipitating agent by washing or dialysis will liquefy these gels.

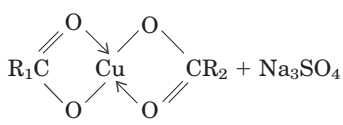
Most of the hydrophilic and water-soluble polymers mentioned previously are only slightly soluble or insoluble in alcohol. Addition of alcohol to their aqueous solutions may cause precipitation or gelation because it lowers the dielectric constant of the medium and tends to dehydrate the hydrophilic solute. Alcohol also lowers the concentrations at which electrolytes salt out hydrophilic colloids. Therefore, alcohol is often referred to as a nonsolvent or precipitant. However, the addition of alcohol to an aqueous polymer solution may cause coacervation (ie, the separation of a concentrated viscous liquid phase) rather than precipitation or gel formation. Sucrose also competes for water of hydration with hydrophilic colloids and may cause phase separation. However, most hydrophilic sols tolerate substantially higher concentrations of sucrose than of electrolytes or alcohol. Lower viscosity grades of a given polymer are usually more resistant to the effects of electrolytes, alcohol, and sucrose than grades having higher viscosities and molecular weights.

The gelation temperature or gel point of gelatin is highest at its isoelectric point, where the attachment of adjacent chains through ionic bonds between carboxylate ions and alkylammonium, guanidinium, or imidazolium groups is most extensive. Since carboxyl groups are not ionized in strongly acidic media such as gastric juices, interchain ionic bonds are practically nonexistent in this environment and interchain attraction is limited to hydrogen bonds and van der Waals forces. Therefore, the combination of an acidic pH that is considerably below the isoelectric point and a temperature of 37° C completely prevents the gelation of gelatin solutions. Conversely, if a polymer owes its solubility to the ionization of these weakly acid groups, reducing the pH of its solution below 3 may lead to precipitation or gelation. This is observed with carboxylated polymers such as many gums, sodium carboxymethylcellulose, and carbomer. Adjusting the media to higher pH values returns the carboxyl groups to their ionized state and reverses the gelation or precipitation. However, gelation temperatures typically depend more upon temperature and concentration than pH.[16,17]

Hydrogen carboxymethylcellulose swells and disperses but does not dissolve in water. Only the sodium, potassium, ammonium, and triethanolammonium salts of carboxylated polymers are well soluble in water. In the case of carboxymethylcellulose, salts with heavy metal cations (eg, silver, copper, mercury, lead) and trivalent cations (eg, aluminum, chromic, ferric) are practically insoluble. Salts with divalent cations, especially of the alkaline earth metals, have borderline solubilities. Generally, higher degrees of substitution tend to increase the tolerance of carboxymethylcellulose toward salts.

When inorganic salts of heavy or trivalent cations are mixed with alkali metal salts of carboxylated polymers in solution, precipitation or gelation occurs due to metathesis. For instance, if a soluble copper salt is added to a solution of sodium carboxymethylcellulose, the double decomposition can be schematically written as:

$$R_1COO^-Na^+ + R_2COO^-Na^+ + CuSO_4 \rightarrow$$



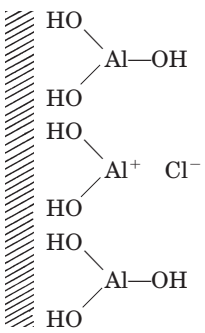
R_1 and R_2 represent two carboxymethylcellulose chains, which are cross-linked by a chelated copper ion. Dissociation of the cupric carboxylate complex is negligible.

Electric Properties

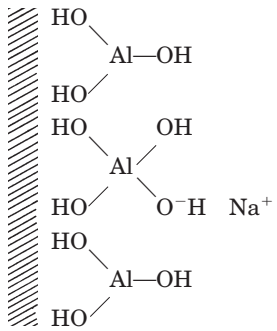
ORIGIN OF ELECTRIC CHARGES—Particles can acquire charges from several sources. In *proteins,* one end group of the polypeptide chain and any aspartic and glutamic acid units contribute carboxylic acid groups, which are ionized into negatively charged carboxylate ions in neutral to alkaline media. The other chain end group and any lysine units contribute amino groups, while arginine units contribute guanidine groups, and histidine units contribute imidazole groups. The nitrogen atoms of these groups become protonated in neutral to acid media. These covalently attached anions and cations confer a negative and positive charge to the molecule, respectively. Therefore, proteins may be referred to as *polyelectrolytes* (polymeric electrolytes or salts). However, they are not the only organic polymers that contain ionic groups, and thus, many substances may be considered to be polyelectolytes. For example, natural polysaccharides of vegetable origin such as acacia, tragacanth, alginic acid, and pectin contain carboxylic acid groups, which are ionized in neutral to alkaline media. Agar and carrageenan, as well as the animal polysaccharides heparin and chondroitin sulfate, contain sulfate groups, which are strongly acidic and ionize even in acid media. Cellulosic polyelectrolytes include *sodium carboxymethylcellulose,* while synthetic carboxylated polymers include *carbomer,* a copolymer of acrylic acid.

Counterions are required for electroneutrality of the ionizing groups on polyelectrolytes. Counter-ions dissociate from ionogenic functional groups and can be replaced by other ions of like charge. For example, in neutral and alkaline media, Na^+, K^+, Ca^{2+}, and Mg^{2+} are among the counterions neutralizing the negative charges of the carboxylate groups, and if hydrochloric acid was used to make the medium acidic and to supply the protons, Cl^- is present to neutralize any of the cationic groups mentioned previously. These counterions are not an integral part of the protein particle but are located in its immediate vicinity. Alternatively, at a specific intermediate pH value (4.5–7 for most proteins), the carboxylate anions and the alkylammonium, guanidinium, and imidazolium cations on the same molecule neutralize each other exactly. There is no need for counterions because the ionized functional groups are in exact balance. At this pH value, called the *isoelectric point,* the protein particle or molecule is neutral; its electrical charge is neither negative nor positive, but zero.[2,6,8]

Most inorganic particulate compounds are also charged. *Aluminum hydroxide*, $Al(OH)_3$, may be dissolved by acids and alkalis to form aluminum ions, Al^{3+}, and aluminate ions, $Al(OH)_4^-$, respectively. In neutral or weakly acid media (ie, acid concentrations too low to cause dissolution), an aluminum hydroxide particle has some positive charges attributed to Al^{3+} valences that have not been completely neutralized. The schematic below represents a portion of the surface of an aluminum hydroxide particle that has one such positive charge neutralized by a Cl^- counterion:



In weakly alkaline media (ie, base concentrations too low to transform the aluminum hydroxide particles completely into aluminate and dissolve them), the aluminum hydroxide particles bear some negative charges due to the presence of a few aluminate groups. The schematic below represents a portion of the surface of an aluminum hydroxide particle that has one such negative group neutralized by a Na^+ counterion:



At a pH of 8.5 to 9.1, there are neither $Al(OH)_2^+$ nor $Al(OH)_4^-$ ions on the particle surface but only neutral $Al(OH)_3$ molecules.[18,19] Therefore, the particles have no charge and do not need counterions for charge neutralization. This pH is considered to be the isoelectric point. In the case of inorganic particulate compounds such as aluminum hydroxide, it also is called the *zero point of charge.*

Bentonite clay is a lamellar aluminum silicate. Each lattice layer consists of a sheet of hydrated alumina sandwiched between two silica sheets. Isomorphous replacement of Al^{3+} by Mg^{2+} or of Si^{4+} by Al^{3+} confers net negative charges to the thin clay lamellas in the form of cation-exchange sites resembling silicate ions built into the lattice. The counterions producing electroneutrality are usually Na^+ (sodium bentonite) or Ca^{2+} (calcium bentonite).

Silver iodide sols can be prepared by the reaction:

$$AgNO_3 + NaI \rightarrow AgI(s) + NaNO_3$$

In the bulk of the silver iodide particles, there is a 1:1 stoichiometric ratio of Ag^+:I^- ions. If the above reaction is carried out with an excess of silver nitrate, there will be more Ag^+ ions than I^- ions in the surface layer of the particles. The particles will then be positively charged and the counterions surrounding them will be NO_3^-. If the reaction is carried out using an exact stoichiometric 1:1 ratio of silver nitrate to sodium iodide or with an excess sodium iodide, the surface of the particles will contain more I^- ions than Ag^+ ions.[6–8] The particles will then be negatively charged and the counterions surrounding them will be Na^+.

An additional mechanism through which particles acquire electric charges is by the adsorption of ions,[5,7,8,10] including ionic surfactants. This is discussed in more detail in a later section.

ELECTRIC DOUBLE LAYERS—As described previously, the surface layer of a silver iodide particle prepared using an excess of sodium iodide contains more I^- ions than Ag^+ ions; whereas, the bulk of the particle contains the two ions in an equimolar proportion. The aqueous solution in which such particles are suspended contains relatively high concentrations of Na^+ and NO_3^-, a lower concentration of I^-, and traces of H^+, OH^-, and Ag^+. The negatively charged particle surface attracts positive ions from the solution and repels negative ions. Therefore, the solution immediately surrounding the particle surface contains a much higher concentration of Na^+ (counterions) and a much lower concentration of NO_3^- ions than in the bulk solution. A number of Na^+ ions equal to the number of excess I^- ions in the surface (ie, the number of I^- ions in the surface layer minus the number of Ag^+ ions in the surface layer) and equivalent to the net negative surface charge of a particle are pulled towards its surface. These counterions tend to approach the particle surface as closely as their hydration spheres permit (Helmholtz double layer); however, thermal agitation of the water molecules tends to disperse them throughout the solution. Consequently, the layer of counterions surrounding the particle is spread out. The Na^+ ion concentration is highest in the immediate vicinity of the negative surface, where the ions form a

compact layer called the Stern layer. The Na^+ ion concentration decreases with distance from the surface, throughout a diffuse layer called the Gouy-Chapman layer. Therefore, the sharply defined, negatively charged particle surface is surrounded by a cloud of Na^+ counterions required for electroneutrality. The combination of the two layers of oppositely charged ions constitutes an electric double layer, which is illustrated in the top part of Figure 21-5.

The electric potential of a plane is equal to the work required to bring a unit electric charge from infinity (in this case, from the bulk of the solution) to that plane against electrostatic forces. If the plane is the surface of a particle, the potential is called surface or ψ_0 potential, which measures the total potential of the double layer (Fig 21-5). This is the thermodynamic potential that operates in galvanic cells. Upon moving away from the particle surface towards the bulk solution in the direction of the horizontal axis, the potential drops rapidly across the Stern layer because the Na^+ ions in the immediate vicinity of the particle surface screen Na^+ ions that are farther removed in the diffuse part of the double layer from the effect of the negative surface charge. The decrease in potential across the Gouy-Chapman layer is more gradual. As the composition of the diffuse double layer gradually approaches that of the bulk liquid, where the anion concentration equals the cation concentration, the potential asymptotically approaches zero. In view of this indefinite end point, the thickness of the diffuse double layer (δ) is arbitrarily defined as the distance over which it takes the potential at the boundary between the Stern and Gouy-Chapman layers to drop to 0.37 *(equal to 1/e)* of its value (Fig 21-5).[1,2,4,6–10] The thickness of double layers usually ranges from 1 to 100 nm and decreases as the concentration of electrolytes in solution increases. This occurs more rapidly for higher valence counterions. The value of δ is approximately equal to the reciprocal of the Debye-Hückel theory parameter (κ).

The electrokinetic or ζ (zeta) potential has practical importance because it can be measured experimentally. In aqueous dispersions, organic particles containing polar functional groups, and even relatively hydrophobic inorganic particles, are surrounded by a layer of water of hydration, which is associated with the particles through ion-dipole and dipole-dipole interactions. When a particle moves, this shell of water, and all of the ions located inside it, moves along with the particle. Conversely, if water or an aqueous solution flows through a fixed bed of these solid particles, the hydration layer surrounding each particle remains attached to it. The electric potential at the plane of shear or slip separating the bound water from the free water is the ζ potential. It does not include the Stern layer and includes only the part of the Gouy-Chapman layer that lies outside the hydration shell (Fig 21-5).

STABILIZATION BY ELECTROSTATIC REPULSION— When two uncharged hydrophobic particles are in close proximity, they attract each other by van der Waals secondary valences, mainly London dispersion forces. For individual atoms and molecules, these forces decrease with the seventh power of the distance between them. In the case of two particles, every atom of one particle attracts every atom of the other particle. Because the attractive forces are nearly additive, they decay much less rapidly with interparticle distance, approximately with the second or third power of the distance between them. Therefore, whenever two particles approach each other closely, the attractive forces take over and cause them to adhere. Coagulation occurs as the primary particles aggregate into increasingly larger secondary particles or flocs. If the dispersion consists of two kinds of particles, one having positive and the other negative charges, the electrostatic attraction between such oppositely charged particles is superimposed on the attraction by van der Waals forces and coagulation is accelerated. If the dispersion contains only one kind of particle with the same surface charge and charge density (the most common case) then electrostatic repulsion tends to prevent the particles from approaching closely enough to come within the effective range of each other's van der Waals attractive forces. This stabilizes the dispersion against interparticle attachments or coagulation. The electrostatic repulsive energy has a range in the order of δ.

A quantitative theory of the interaction between lyophobic disperse particles was worked out independently by Derjaguin

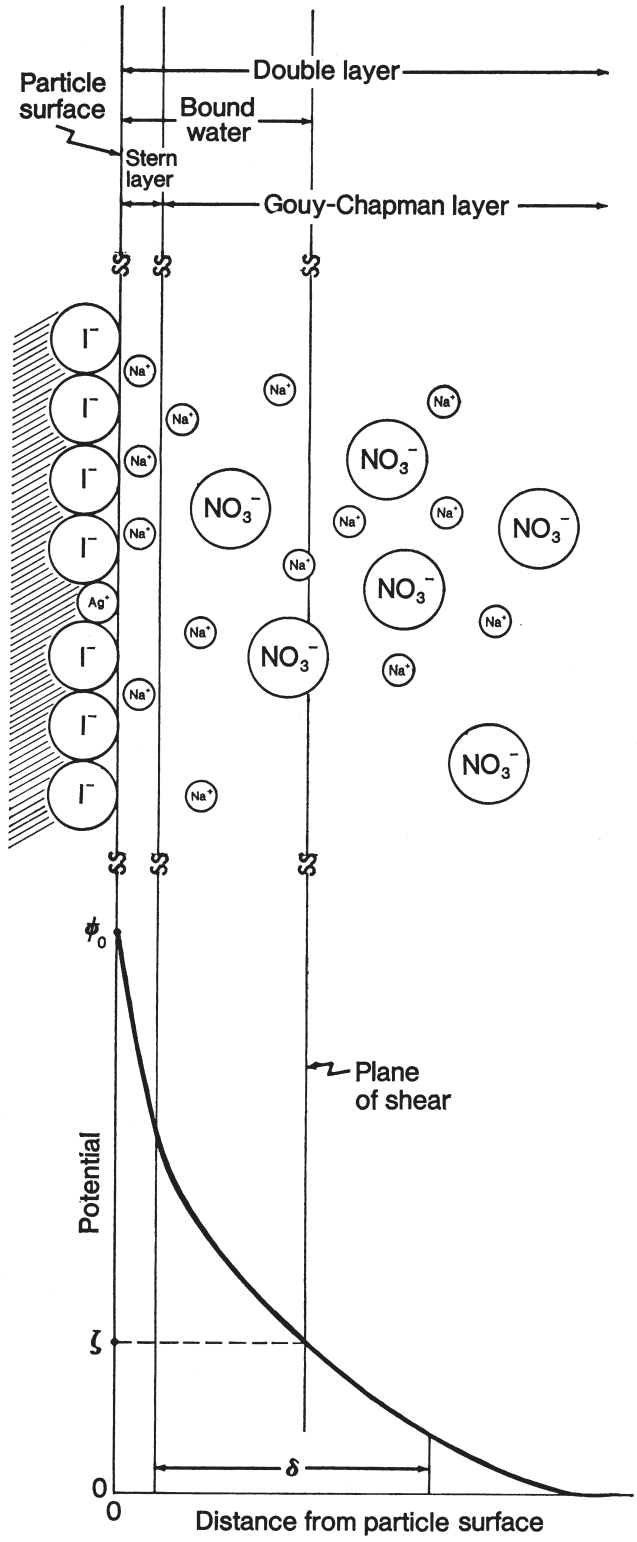


Figure 21-5. Electric double layer at the surface of a silver iodide particle (upper part) and the corresponding potentials (lower part). The distance from the particle surface, plotted on the horizontal axis, refers to both the upper and lower portions of the figure.

and Landau in the USSR and by Verwey and Overbeek in the Netherlands in the early 1940s.[1–3,5,7–9] Detailed calculations may be found in Chapter 21 of RPS-17. The so-called DLVO theory predicts and explains many, but not all, experimental data; its refinement to account for discrepancies is ongoing. The DLVO theory is summarized in Figure 21-6, where curve *WA* represents the van der Waals attractive energy, which decreases approximately by the second power of the interparticle distance, and curve *ER* represents the electrostatic repulsive energy, which decreases exponentially with interparticle distance. Because of the combination of these two opposing effects, attraction predominates at small and large distances; whereas repulsion may predominate at intermediate distances. Negative energy values indicate attraction and positive values indicate repulsion. The resultant curve *DPBAS,* obtained by algebraic addition of curves *WA* and *ER,* gives the total, net energy of interaction between two particles.

Interparticle attraction depends mainly upon the chemical nature and particle size of the dispersed material. Once these have been selected, the attractive energy between particles is fixed and cannot be readily altered. Electrostatic repulsion depends upon the ψ_0 potential, or the density of the surface charge, and upon the thickness of the double layer, both of which govern the magnitude of the ζ potential. Thus, dispersion stability correlates to some extent with this potential.[6] The ζ potential can be widely adjusted using additives, especially ionic surfactants, water-miscible solvents, and electrolytes. If the absolute value of the ζ potential is small, the resultant potential energy is negative and van der Waals forces of attraction predominate over electrostatic repulsion at all interparticle distances. Such sols coagulate rapidly.

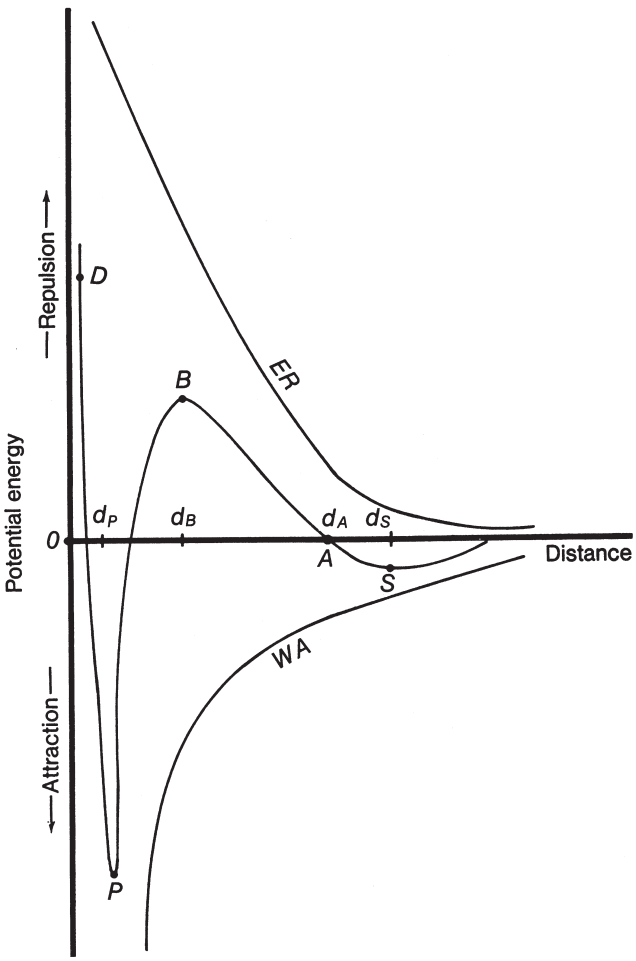


Figure 21-6. Curves representing the van der Waals energy of attraction (*WA*), the energy of electrostatic repulsion (*ER*), and the net energy of interaction (*DPBAS*) between two identical charged particles, as a function of the interparticle distance.

The two identical particles, whose interaction is depicted in Figure 21-6, have a large (positive or negative) ζ potential, resulting in an appreciable positive or repulsive potential energy at intermediate distances. However, Brownian motion, convection currents, sedimentation, or stirring of the dispersion will eventually put them on a collision course. As the two particles approach each other, the two counterion atmospheres begin to interpenetrate or overlap at point *A*, corresponding to the distance, d_A. This produces a net repulsive (positive) energy because of the work involved in distorting the diffuse double layers and pushing water molecules and counterions aside. If the particles continue to approach each other, the repulsion between their surface charges increases the net potential energy of interaction to its maximum positive value at *B*, where most of the intervening water and counterions have been displaced. If the height of the potential energy barrier *B* exceeds the kinetic energy of the approaching particles, they will not come any closer to each other than the distance d_B and will then move away from each other. A net positive potential energy of about 25 kT units usually suffices to keep them apart and renders the dispersion stable (k is the Boltzmann constant and T is absolute temperature). At $T = 298°K$, the required potential energy for stabilization corresponds to 1×10^{-12} erg or 1×10^{-5} J. The kinetic energy of a particle is of the order of kT.

On the other hand, if the kinetic energy of the approaching particles exceeds the potential energy barrier *B,* the particles will continue to approach each other past d_B, where the van der Waals forces of attraction become increasingly more important compared to the electrostatic repulsion. Therefore, the net potential energy of particle interaction decreases to zero and then becomes negative. This now pulls the particles closer together. When the particles touch, at a distance, d_P, the net energy has acquired a large negative value of *P.* This deep minimum in potential energy corresponds to a very stable situation in which the particles adhere. Since it is unlikely that enough kinetic energy can be supplied to the particles or that their ζ potential can be increased sufficiently to cause them to climb out of the potential energy well *P,* they are permanently attached to each other. When most or all of the primary particles agglomerate into secondary particles by this process, the sol coagulates. Any closer approach of the two particles than the touching distance d_P will cause a very rapid rise in potential energy along *PD* because the solid particles would interpenetrate each other and cause atomic orbitals to overlap (Born repulsion).

COAGULATION OF HYDROPHOBIC DISPERSIONS— The height of the potential energy barrier and the range over which the electrostatic repulsion is effective (or the thickness of the double layer) determine the stability of hydrophobic dispersions. Both factors are reduced by the addition of electrolytes. The transition between a coagulating and a stable sol is gradual and depends upon the time of observation. Therefore, standardized conditions must be used to classify a sol as either coagulated or coagulating, or stable (ie, fully dispersed).

To determine the coagulating concentration of a given electrolyte for a given sol, a series of test tubes is filled with equal portions of the sol. Identical volumes of electrolyte solutions having increasing concentrations are added to the test tubes with vigorous stirring. After a certain rest period (eg, 2 hours), the mixtures are agitated again. After an additional, shorter rest period (eg, 1/2 hour), they are inspected for signs of coagulation. The tubes are then classified into two group; one showing no signs of coagulation and the other showing at least some signs such as visible flocs. Alternatively, they can be classified into one group showing complete coagulation and another showing none or incomplete coagulation, such as some deflocculated colloid left in the supernatant. In either case, the separation between the two classes is quite sharp. The intermediate agitation breaks the weakest interparticle bonds and brings

smaller particles into contact with larger ones, thus sharpening the distinction between coagulation and stability. After repeating the experiment with a narrower range of electrolyte concentrations, the coagulation value (c_{cv}) of the electrolyte (ie, the lowest concentration at which the electrolyte coagulates the sol) is established with good reproducibility.[2,6–8]

Typical c_{cv} values for a silver iodide sol prepared with an excess of iodide are listed in Table 21-3. The following conclusions can be drawn from the left half of Table 21-3:

1. The c_{cv} does not depend upon the valence of the anion. For example, nitrate and sulfate salts of the same metal have nearly identical c_{cv} values.
2. The differences between the c_{cv}'s of cations having the same valence are relatively minor. However, there is a slight but significant trend of decreasing c_{cv} with increasing atomic number in both the alkali and the alkaline earth metal groups. Arranging these cations in order of decreasing c_{cv} produces the Hofmeister or lyotropic series in decreasing size of hydrated specie. For monovalent cations, the lyotropic series is described above. The atomic weight of cesium is 19x greater than that of lithium, but the Cs+ ion in aqueous solution is less hydrated and therefore smaller than the hydrated Li+ ion. It is also more polarizable. Therefore, the Cs+ ion can approach the surface of a negatively charged particle suspended in water more closely and is more extensively adsorbed. This reduces its c_{cv} making cesium salts more effective coagulants than lithium salts for negatively charged hydrosols.
3. The coagulation values depend primarily upon the valence of the counterions, decreasing by one to two orders of magnitude for each unit increase in the valence of the counterions (Schulze-Hardy rule). According to the DLVO theory, the coagulation values vary inversely with the sixth power of the valence of the counterions. For mono-, di-, and trivalent counterions, they should be in the ratio:

$$\frac{1}{1^6} : \frac{1}{2^6} : \frac{1}{3^6} \; or \; 100 : 1.6 : 0.14$$

The mean c_{cv} values for the mono-, di-, and trivalent counterions in Table 21-3 are 141, 2.45, and 0.068 $mmol/L$, respectively. This results in a ratio of 100:1.7:0.05, which is in satisfactory agreement with the DLVO theory.

The following conclusions can be drawn from the right half of Table 21-3:

4. The cations on the right side of Table 21-3 constitute obvious exceptions to the preceding conclusions. Ag^+ is a potential-determining counterion, those whose concentration determines the surface potential. When silver nitrate is added to the negatively charged silver iodide dispersion, some of its silver ions are incorporated into the negatively charged surface of the particles. This lowers the magnitude of the particle's surface charge by reducing the excess of I^- ions in the surface. Therefore, silver salts are exceptionally effective coagulating agents because they reduce the magnitude of both the ψ_0 potential and the ζ potential. Indifferent salts, which only reduce the ζ potential, require much higher salt concentrations for comparable reductions in this potential. The other potential-determining ion of silver iodide is the I^- ion. Alkali iodides have c_{cv} values higher than 141 mmol/L because they supply iodide ions that enter the surface layer of the silver iodide particles and increase its excess of I^- ions over Ag^+ ions, thereby making the ψ_0 potential more negative. Bromide and chloride ions act similarly but less effectively. The principal potential-determining ion for proteins is H^+ (and hence OH^-); those for aluminum hydroxide are OH^- (and hence H^+) and, Al^{3+} as well as Fe^{3+} and Cr^{3+}, which form mixed hydroxides with Al^{3+}.
5. The cationic surfactant and the alkaloidal salts (which also behave as cationic surfactants) on the right side of Table 21-3 constitute the second exception to the Schulze-Hardy rule. Surface-active compounds contain both hydrophilic and hydrophobic moieties within the same molecule. The dual nature of these compounds causes them to accumulate at interfaces. Dodecylammonium and alkaloidal cations are able to displace inorganic monovalent cations from the Stern layer of a negatively charged silver iodide particle. This occurs because they are not only attracted to the particle by electrostatic forces but also by van der Waals forces between their hydrocarbon moieties (ie, dodecyl chains in the case of the dodecylammonium ions) and the solid particle. Since they are strongly adsorbed from solution onto the particle surface and do not tend to dissociate from it, surface-active cations are very effective in reducing the negative ζ potential of silver iodide particles. Therefore, they have lower c_{cv} values than purely inorganic cations with the same valence.
6. Anionic surfactants, like those containing lauryl sulfate ions, also have a tendency to adsorb at solid-liquid interfaces. However, electrostatic repulsion between the negatively charged surface of the silver iodide particles, whose surface layer contains an excess of iodide ions, and the surface-active anions usually prevents adsorption from occurring below the critical micelle concentration. If adsorption does occur, it increases the density of the negative charges in the particle surface, and therefore, raises the ccv value of the anionic surfactant above the value corresponding to its valence.

Table 21-3. Coagulation Values for Negative Silver Iodide Sol[a]

ELECTROLYTE	c_{cv} (*mmol/L*)	ELECTROLYTE	c_{cv} (*mmol/L*)
$LiNO_3$	165	$AgNO_3$	0.01
$NaNO_3$	140	$1/2(C_{12}H_{25}NH_3)_2SO_4$	0.07
$1/2(Na_2SO_4)$	141	Strychnine nitrate	1.7
KNO_3	136	1/2(Morphine sulfate)	2.5
$1/2(K_2SO_4)$	138		
$RbNO_3$	126		
Mean	141		
$Mg(NO_3)_2$	2.60	Quinine sulfate	0.7
$MgSO_4$	2.57		
$Ca(NO_3)_2$	2.40		
$Sr(NO_3)_2$	2.38		
$Ba(NO_3)_2$	2.26		
$Zn(NO_3)_2$	2.50		
$Pb(NO_3)_2$	2.43		
Mean	2.45		
$Al(NO_3)_3$	0.067		
$La(NO_3)_3$	0.069		
$Ce(NO_3)_3$	0.069		
Mean	0.068		

[a] Data from Kruyt HR. Colloid Science, vols I and II. Houston: Elsevier, 1949 and 1952 and unpublished data.

The addition of water-miscible solvents such as alcohol, glycerin, propylene glycol, or polyethylene glycols to aqueous dispersions lowers the dielectric constant of the medium. This reduces the thickness of the double layer and, therefore, reduces the range over which electrostatic repulsion is effective, and lowers the size of the potential energy barrier. As a result, the addition of sufficient amounts of such solvents tends to coagulate aqueous dispersions. At lower concentrations, these solvents do not induce coagulation themselves, but make the dispersions more sensitive to coagulation by added electrolytes (ie, they lower the c_{cv} value).

Progressive addition of salts having counterions of high valence gradually reduces the ζ potential of colloidal particles to zero. Eventually, the sign of the ζ potential may be inverted, and its magnitude may then increase in the opposite direction. The ψ_0 and ζ potentials of aqueous sulfamerazine suspensions are negative above their isoelectric points, and those of bismuth subnitrate are positive. However, the addition of Al^{3+} to the former and of PO_4^{3-} to the latter in large enough amounts inverts the sign of their ζ potentials, while their ψ_0 potentials remain unchanged. Surface-active ions of opposite charge may also produce such charge inversions.

The superposition of the van der Waals attractive energy, with its long-range effectiveness, and the electrostatic repulsive energy, with its intermediate-range effectiveness, frequently produces a shallow minimum (designated S in Fig 21-6) in the resultant energy-distance curve at interparticle distances d_S that are several times greater than δ. If this minimum in potential energy is small compared to kT, Brownian motion prevents aggregation. For large particles, such as those of many pharmaceutical suspensions, and for particles that are large in one or two dimensions (eg, rods and plates), this *secondary minimum*

may be deep enough to trap them at distances d_S from each other. This requires a depth of several kT units. Such fairly long-range and weak energies of attraction produce loose aggregates or flocs that can be redispersed by agitation or by reducing the concentration of flocculating electrolytes.[1,2,5,7,8,10,20] This reversible aggregation process involving the secondary minimum is called *flocculation.* By contrast, aggregation in the deep primary minimum P is called *coagulation* and is irreversible.

ELECTROKINETIC PHENOMENA—When a dc electric field is applied to a dispersion, the particles move towards the electrode having a charge opposite to that on their surface. The counterions located inside their hydration shell are dragged along while the counterions in the diffuse double layer outside the plane of slip, in the free or mobile solvent, move toward the other electrode. This phenomenon is called *electrophoresis.* If the charged surface is immobile, as is the case with a packed bed of particles or a tube filled with water, application of an electric field causes the counterions in the free water to move towards the opposite electrode, dragging solvent with them. This flow of liquid is called *electroosmosis*, and the pressure produced by it is called *electroosmotic pressure.* Conversely, if the liquid is made to flow past charged surfaces by applying hydrostatic pressure, displacement of the counterions in the free water produces a potential difference between the two ends of the tube or bed called *streaming potential.* These three phenomena depend upon the relative motion of the charged surface and the diffuse double layer outside the plane of slip surrounding the surface. Actually, most of the diffuse double layer lies within the free solvent and, therefore, can move along the surface.[5–8, 21] All three electrokinetic phenomena measure the same ζ potential, which is the potential at the plane of slip.

Microelectrophoresis—The particles of pharmaceutical suspensions and emulsions, bacteria, erythrocytes and other isolated cells, latex particles, and many contaminant particles in pharmaceutical solutions are visible in a microscope. Therefore, their ζ potentials are conveniently measured by *microelectrophoresis.* A potential difference, E, applied between two electrodes that are dipped into a dispersion and separated by a distance, d, produces the potential gradient or field strength, E/d, expressed as V/cm. The average velocity, v, of the particles in response to the applied potential difference is determined using the eyepiece micrometer of a microscope and a stopwatch, and used to calculate the ζ potential by the Smoluchowski equation:

$$\xi = \left(\frac{4\pi\eta}{D}\right)\left(\frac{v}{E/d}\right) = \left(\frac{4\pi\eta}{D}\right)\mu$$

The electrophoretic mobility, μ, is equal to $v/(E/d)$ and is the velocity caused by a potential gradient of 1 V/cm. According to the Smoluchowski equation, particle size and shape do not affect the ζ potential. However, if the particle radius is smaller than or comparable to δ (in which case the particles cannot be detected in a microscope), a factor of 6 replaces the 4. The viscosity, η, and the dielectric constant, D, refer to the aqueous medium within the double layer and cannot be measured directly.[22] By using the values for water at 25°C, expressing the velocity in μm/sec and the electrophoretic mobility in (μm/sec)/(volts/cm), and converting into the appropriate units, the Smoluchowski equation is reduced to $\zeta = 12.9\ \mu$ with ζ given as millivolts (mV). Zeta potentials as high as ±180 mV have been reported.[1,6,21] If the particle surface has appreciable conductance, the absolute value of the ζ potential calculated by this equation may be too small.[2,7,21,22] Dispersions of hydrophobic particles having ζ potentials below ±20–30 mV are frequently unstable and tend to coagulate.

The chief experimental precautions in microelectrophoresis measurements are:

1. Electroosmosis causes liquid to flow along the walls of the cell containing the dispersion. This in turn produces a return flow into the center of the cell. Therefore, the microscope must be focused on the stationary boundary between the two liquid layers that are flowing in opposite directions in order to measure the true velocity of the particles.
2. Following the motion of single particles in a microscopic field and measuring their velocity is only possible using very dilute dispersions. Therefore, many dispersions must be diluted before making such determinations. Since the ζ potential depends largely upon the nature, ionic strength, and pH of the suspending medium, dispersions should not be diluted with water but with solutions having compositions identical to their continuous phase (eg, with their own serum that has been separated by ultrafiltration or centrifugation).

When the particles cannot be individually observed using a microscope, other electrophoresis methods are employed.[6,8,21,23,24] In m*oving boundary electrophoresis*, the movement of the boundary formed between a sol or solution and the pure dispersion medium in an electric field is studied. If the dispersed phase is colorless, the boundary is located by the refractive index gradient (Tiselius apparatus, frequently used with protein solutions). If several species of particles or solutes with different mobilities are present, each will form a boundary moving with a characteristic velocity. Unlike microelectrophoresis, this method permits the identification of different colloidal components in a mixture, the measurement of the electrophoretic mobility of each, and an estimation of the relative amounts present.

Capillary Electrophoresis—Capillary electrophoresis (CE)[25,26] is a widely used separation technique best suited for charged, water-soluble molecules having molecular weights ranging from those of amino acids and peptides to nucleic acids. CE has the following advantages: it provides fast and efficient separations, requires only minute amounts of sample, is applicable to a wide range of analytes, and (in contrast to HPLC) employs aqueous media rather than organic solvents.

Electrophoresis is carried out in horizontal capillaries of fused silica (which is transparent to ultraviolet) of 20 to 100 μm bore and 20 to 100 cm length. Both capillary ends are bent downward. Each end is immersed in a vial filled with a buffer solution that contains an electrode assembly. The electrodes are connected to an adjustable high-voltage dc power supply. As the dissolved analytes migrate past a detection window in the capillary, their concentrations are measured by ultraviolet absorption or by (often laser-induced) fluorescence. The silica capillaries are often coated externally with a very thin layer of polyimide to reduce their fragility. This plastic coating is burned off in the window area.

The capillary is filled with buffer solution, the sample is injected at one end, and a constant high potential difference E is applied, which produces a potential gradient or field strength in the range of 300 to 400 V/cm. If E = 20,000 V and the total capillary length d_r = 57 cm, then E/d_r = 350 V/cm. The velocity of migration, v, is the capillary length to the detector, d_L, divided by the migration time, t, of the analyte from the capillary injection end to the detection window. If d_L = 50 cm and t = 10 min = 600 sec, then v = 50/600 = 0.083 cm/sec. The electrophoretic mobility ($v/(E/d)$) is (0.083 cm/sec)/(350 V/cm) = 2.4×10^{-4} cm^2/Vsec.

In addition to electrophoresis, electro-osmosis may play an important role in CE. The isoelectric point of hydrated silica is approximately 1.8. The weakly acidic silanol groups become increasingly ionized with increasing pH. Conditioning the capillary with a NaOH solution and then with the buffer ensures that its wall is charged uniformly with partially ionized silanol groups. These negatively charged sites attract cationic counterions from the buffer to form an electric double layer. When an electric potential is applied, the cations in the diffuse part of the double layer beyond the plane of shear (Fig 21-5) migrate toward the negative electrode, entraining water of hydration. Because of the small bore of the capillaries compared to the diffuse double layer thickness, the electro-osmotic flow (EOF) can be substantial. The EOF moves in a plug profile rather in the customary parabolic profile of laminar flow. At high pH, the EOF is strong because the silanol groups are extensively ionized. Amphoteric peptides are negatively charged and try to migrate toward the positive electrode or anode. This motion is often overwhelmed by a strong and opposite EOF, which drags them toward the negative electrode or cathode. These analytes move from the injection point in the anode compartment toward the cathode. The order of arrival at the detection window is: cationic analytes (whose electrophoretic migration toward the cathode is superimposed and accelerated by the EOF), nonionic analytes (which migrate exclusively by EOF), and anionic analytes (whose net migration velocity is that of the EOF minus their electrophoretic migration velocity toward the anode).

At low pH, the EOF is small and the peptides are positively charged. Their migration toward the cathode is then superimposed and accelerated by the EOF in the same direction. The direction of the EOF can be reversed by adding a cationic surfactant, such as cetyltrimethylammonium bromide, to the buffer. It will react and neutralize the silanol groups, and excess surfactant adsorbed on the silica will confer a positive charge to it. The Br^- counterions cause an EOF toward the anode. The EOF can be suppressed by coating the silica capillaries with a polymer or by using Teflon capillaries.

Unless the heat generated by the electric resistance of the buffer solution (Joule heating) is dissipated, it causes the temperature to increase with time and promotes temperature gradients across the capillary. This interferes with reproducibility and sharpness of the CE separations. The amount of heat generated is directly proportional to the square of the field strength (which is large) and to the conductivity of the buffer solution. While decreasing the voltage, using longer or smaller-bore capillaries and/or more dilute buffer solution would reduce the rate of heat generation; it would also increase the separation times.

Short separation times reduce the band broadening due to analyte diffusion, improving the resolution. Therefore, the capillary is cooled with a thermostatted liquid.

A variation of CE is micellar electrokinetic (capillary) chromatography (MEKC).[25, 26] The analytes are solubilized in micelles of an ionic surfactant, such as sodium dodecyl sulfate, which is added to the buffer solution at a concentration well above its critical micelle concentration of $8 \times 10^{-3}M$. MEKC is suited particularly to separate neutral analytes of limited water solubility, which are extensively partitioned into the micelles, but is also applicable to ionic analytes. Anionic analytes, being well soluble in water, either do not partition into the micelles or form mixed micelles with the anionic surfactant. Cationic analytes often form precipitates with anionic surfactants. Therefore, their separation by MEKC is best carried out with cationic surfactants.

The combination of a nonionic and an ionic surfactant produces mixed micelles. These have lower surface charge densities and larger sizes than the micelles of ionic surfactants, and hence they have lower electrophoretic mobilities. Thus, addition of a nonionic to an ionic surfactant narrows the migration time window, which is the difference between the migration times of the bulk solution in EOF and of the micelles, and often shortens the analysis time.

Analytes with molecular weights of 5000 or higher are not solubilized by micelles. Therefore, while they can be analyzed by CE, they cannot be analyzed by MEKC. Although anionic micelles tend to migrate toward the anode, a strong EOF in neutral or alkaline media will drag them toward the cathode, but with a velocity retarded by their own migration velocity. If a neutral analyte is partly solubilized in micelles and partly dissolved molecularly in the buffer solution, the latter portion has a shorter migration time because its velocity is that of the EOF.

Capillary gel electrophoresis[25,26] employs capillaries filled with a gel of cross-linked polyacrylamide, which suppresses EOF. Isotachophoresis and isoelectric focusing,[26] described in previous editions of this text, are other modalities of CE.

LYOPHILIC DISPERSIONS

Lyophilic dispersions consist either of polymers dissolved in a good solvent or of insoluble but extensively solvated particles dispersed in a liquid medium that has a high affinity or attraction for them. The free energy of dissolution or dispersion is $\Delta G_s = \Delta H_s - T\Delta S_s$, where ΔH_s and ΔS_s are the heat or enthalpy change, and the entropy change of dissolution or dispersion, respectively. For dissolution of polymers and dispersion of particulate solids to occur spontaneously, ΔG_s must be negative. Since both of these processes are exothermic (ie, occur with the evolution of heat), their ΔH_s is negative. Since the number of available conformations of the polymer chains increases considerably upon dissolution, and the number of positions and orientations of the solid particles increases considerably upon their dispersion in the liquid, their ΔS_s is positive (ie, there is an increase in randomness). The negative enthalpy change and the positive entropy change of dissolution/dispersion both contribute to making ΔG_s negative. Therefore, both types of colloidal systems are formed spontaneously when powders of solid polymers and particulate solids are brought into contact with the liquid dispersion medium. They are thermodynamically stable and reversible (ie, they are easily reconstituted after the dispersion medium has been removed). The van der Waals energies of attraction between dissolved macromolecules or between dispersed lyophilic solid particles are smaller than ΔG_s and are therefore insufficient to cause flocculation or coagulation of the dispersed phase. Furthermore, the solvation layers surrounding dissolved macromolecules and dispersed lyophilic particles form a physical barrier preventing their close approach.

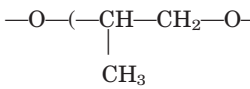
Most liquid dispersed systems of pharmaceutical interest are aqueous. Therefore, most of the lyophilic colloidal systems discussed below consist of hydrophilic solids dissolved or dispersed in water. Most of the products mentioned below are official in the USP or NF, where more detailed descriptions may be found; they are also discussed in detail elsewhere in this text. Hydrophilic colloids can be divided into two classes (ie, soluble and particulate materials). Solutions of water-soluble polymers molecularly dissolved in water may be classified as colloidal dispersions because the individual molecules are in the colloidal particle size range: the diameter of a randomly coiled polymer chain commonly exceeds 10 nm. Particulate or corpuscular hydrophilic colloidal dispersions are formed by solids that swell and are peptized in water but whose primary particles do not dissolve or break down into individual molecules or ions.

Water-Soluble Polymers

Most of the hydrophilic colloidal systems used to prepare pharmaceutical dosage forms are molecular solutions of water-soluble, high molecular weight polymers. These polymers are either linear or slightly branched but not cross-linked. Water-soluble polymers may be divided into three classes according to their origin:

- *Natural polymers* include polysaccharides (acacia, agar, heparin sodium, pectin, sodium alginate, tragacanth, xanthan gum) and polypeptides (casein, gelatin, protamine sulfate). Of these, agar and gelatin are only soluble in hot water.
- *Cellulose derivatives* are produced by chemically modifying cellulose obtained from wood pulp or cotton to produce soluble polymers. *Cellulose* is an insoluble, linear polymer of glucose units in the ring or pyranose form joined by β-1,4 glucosidic linkages. Each glucose unit (except for the two at the terminal chain ends) contains a primary hydroxyl group on the No. 6 carbon and two secondary hydroxyls on the No. 2- and 3-carbons. Chemical modification of cellulose involves substitutions at these hydroxyl groups with the primary hydroxyl group being the most reactive. The extent of such reactions is expressed as *degree of substitution* (DS), the number of substituted hydroxyl groups per glucose residue. The highest value for DS is 3. Fractional values are most common because the DS is averaged over a multitude of glucose residues. A DS value of 0.6 indicates that some glucose repeat units are not substituted while others substituted once or even twice.

  Some soluble cellulose derivatives are listed below. Their DS values correspond to their respective pharmaceutical grades; the groups shown replace the hydrogen atoms of the cellulosic hydroxyls. Official derivatives include *methylcellulose* (DS = 1.65–1.93); (—O—CH_3) and *sodium carboxymethylcellulose* (DS = 0.60–1.00); (—O—$CH_2COO^-Na^+$). *Hydroxyethylcellulose* (DS ≅ 1.0); (—O—$(CH_2CH_2O)_nH$) and *hydroxypropylcellulose* (DS ≅ 2.5);



  are manufactured by adding ethylene oxide and propylene oxide, respectively, to alkali-treated cellulose. The value of n is about 2.0 for hydroxyethylcellulose and not much greater than 1.0 for hydroxypropylcellulose. *Hydroxypropylmethylcellulose* is prepared by reacting alkali-treated cellulose first with methyl chloride to introduce methoxy groups (DS = 1.1–1.8) and then with propylene oxide to introduce propylene glycol ether groups (DS = 0.1–0.3). In general, the introduction of hydroxypropyl groups into cellulose slightly reduces its water solubility while promoting its solubility in polar organic solvents such as short-chain alcohols, glycols, and some ethers.

  The molecular weight of native cellulose is so high that soluble derivatives of approximately the same degree of polymerization would dissolve too slowly and their solutions would be excessively viscous even at concentrations of ≤1%. To overcome these difficulties, controlled degradation is used to break the cellulose chains into shorter segments. Commercial grades cellulose derivatives, such as sodium carboxymethylcellulose, come in various molecular weights or viscosity grades as well as with various degrees of substitution.

  Official cellulose derivatives that are insoluble in water but soluble in some organic solvents include *ethylcellulose* (DS = 2.2–2.7); (—OC_2H_5); *cellulose acetate phthalate* (DS = 1.70 for acetyl and 0.77 for phthalyl); *hydroxypropylmethylcellulose phthalate*; and *polyvinyl acetate phthalate. Collodion,* a 4.0% (w/v) solution of pyroxylin (cellulose dinitrate) in a mixture of 75% (v/v) ether and 25% (v/v) ethyl alcohol, is also a cellulose based, lyophilic colloidal system.

- W*ater-soluble synthetic polymers* consist mostly of high molecular weight polyethylene glycols, or *polyethylene oxides*, and vinyl derivatives such as *polyvinyl alcohol, povidone* or polyvinylpyrrolidone, and *carbomer* (*Carbopol*), a copolymer of acrylic acid.

A second classification of hydrophilic polymers is based upon their charge. *Nonionic* or uncharged polymers include methylcellulose, hydroxyethyl and hydroxypropyl cellulose, ethylcellulose, pyroxylin, polyethylene oxide, polyvinyl alcohol, and povidone. *Anionic* or negatively charged *polyelectrolytes* include carboxylated polymers (eg, acacia, alginic acid, pectin, tragacanth, xanthan gum, and carbomer) at pH values that result in the ionization of their carboxyl groups. Sodium alginate, sodium carboxymethylcellulose, and polypeptides (eg, sodium caseinate) at pH values above their isoelectric points are also anionic. Sulfuric acid is a stronger acidic group that exists as a monoester in agar and heparin and as a monoamide in heparin. *Cationic* or positively charged *polyelectrolytes* are rare. Examples include chitin, a polysaccharide found in the shells of beetles and crustaceans, and polypeptides at pH values below their isoelectric points. Protamines such as protamine sulfate are strongly basic due to their high arginine content and have isoelectric points around pH 12.

Particulate Hydrophilic Dispersions

The dispersed phase of these sols consists of solids that swell in water and spontaneously break up into particles having colloidal dimensions. The dispersed particles have high specific surface areas and are extensively hydrated. *Bentonite NF* is a hydrated aluminum silicate that crystallizes in a layer structure with individual lamellas 0.94 nm thick. Their top and bottom surfaces consist of sheets of oxygen ions from silica and an occasional sodium ion neutralizing a silicate ion-exchange site. The clay particles contain stacks of these lamellas. Water penetrates between these lamellas to hydrate the oxygen ions and causes extensive swelling. The bentonite particles in bentonite magma consist of single lamellas or packets of a few lamellas with intercalated water. Their specific surface area amounts to several hundred square meters per gram. *Kaolin USP* is also a hydrated aluminum silicate having a layer structure. In kaolin, hydrated alumina lattice layers alternate with silica layers. Therefore, one of the two external surfaces of a kaolin plate consists of a sheet of oxygen ions from silica whereas the other is a sheet of hydroxide ions from hydrated alumina. Both surfaces are well hydrated but water cannot penetrate into the individual lattice layers. Therefore, the particles do not swell in water or exfoliate into thin plates. As a result, kaolin plates dispersed in water are much thicker than those of bentonite, about 0.04 to 0.2 μm. *Magnesium Aluminum Silicate NF*, also known as Veegum®, is a clay similar to bentonite but contains magnesium; it is white whereas bentonite is gray. *Colloidal Activated Attapulgite USP* also consists of magnesium aluminum silicate. However, rather than having a lamellar habit like the other three clays, it crystallizes in the form of long needles approximately 20 nm in width.[27]

The following additional hydrophilic particles can also produce colloidal dispersions in water. *Titanium dioxide* is a white pigment with excellent covering power. *Colloidal silicon dioxide* consists of roughly spherical particles that are covered with siloxane and silanol groups. *Microcrystalline cellulose* is hydrophilic because of the hydroxyl and ether groups on the surface of the cellulose crystals. Gelatinous precipitates of hydrophilic compounds such as *aluminum hydroxide gel, aluminum phosphate gel,* and *magnesium hydroxide* consist of coarse flocs produced by agglomeration of the colloidal particles formed in the initial stages of precipitation.

LYOPHOBIC DISPERSIONS

Lyophobic dispersions are intrinsically unstable and irreversible because of the lack of attraction between the dispersed and continuous phases. Unlike lyophilic dispersions, their large surface free energy is not lowered by solvation, their dispersion process does not take place spontaneously, and they are not easily reconstituted. For lyophobic dispersions, ΔG_s is positive because of a positive (endothermic) ΔH_s term, which makes the reverse process (agglomeration) the spontaneous one. Aqueous dispersions of hydrophobic solids or liquids can be prepared by physical means that supply an appropriate amount of energy to the system. However, they are unstable. The van der Waals attractive forces between the particles are stronger than the solvation forces that promote particle dispersal, and therefore, the particles tend to aggregate. Most of the discussion of lyophobic dispersions deals with hydrosols consisting of hydrophobic solids or liquids dispersed in an aqueous media because water is the most widely used vehicle. Such hydrosols consist of aqueous dispersions of insoluble organic and inorganic compounds, which usually have low degrees of hydration. Organic compounds that are preponderantly hydrocarbon in nature and possess few hydrophilic or polar groups are hydrophobic, and therefore, insoluble in water.

Like all lyophobic dispersions, hydrophobic dispersions are intrinsically unstable. In their most thermodynamically stable state, the dispersed phase has coalesced into large crystals or drops, so that the specific surface area and surface free energy are minimized. Therefore, mechanical, chemical, or electrical energy must be supplied to break up the dispersed phase into smaller particles and overcome the resulting increase in surface free energy that occurs from the parallel increase in specific surface area.

Hydrophobic dispersions can be prepared by either dispersion methods (the reduction of coarse particles to colloidal dimensions through comminution or peptization) or condensation methods (the aggregation of small molecules or ions into particles having colloidal dimensions). Dispersion methods tend to produce sols that have wide particle size distributions. Conversely, condensation methods *may* produce essentially monodisperse sols provided specialized techniques are employed. Methods of purification to remove low molecular-weight, water-soluble impurities from hydrosols have been reviewed in the corresponding chapter of the previous *Remington* edition.

Preparation by Dispersion Methods

The first method, *mechanical disintegration* of solids and liquids into smaller particles before or during dispersion within a fluid vehicle, is frequently carried out by the input of mechanical energy via shear or attrition. Equipment such as colloid and ball mills, micronizers and, for emulsions, homogenizers is described elsewhere in this text and in Reference 27. Dry grinding with inert, water-soluble diluting agents also produces colloidal dispersions. For example, sulfur hydrosols may be prepared by triturating the powder with urea or lactose followed by shaking with water. Ultrasonic generators provide exceptionally high concentrations of energy. However, the successful dispersion of solids by means of ultrasonic waves can only be achieved with comparatively soft materials such as many organic compounds, sulfur, talcum, and graphite. In cases where fine emulsions are mandatory, such as soybean oil-in-water emulsions for intravenous feeding, emulsification by ultrasound waves is the method of choice.[27] The formation of aerosols is described elsewhere in this text.

Peptization is a second dispersion method used to prepare colloidal dispersions. The term is defined as the breaking up of aggregates (or secondary particles) into smaller aggregates (or primary particles) that are within the colloidal size range. Primary particles are those particles that are not formed from smaller ones. Peptization is synonymous with *deflocculation*. It can be brought about by the removal of flocculating agents, usually electrolytes, or by the addition of deflocculating or peptizing agents, usually surfactants, water-soluble polymers, or ions that adsorb onto the particle surface.[6,8] When powdered activated charcoal is added to water with stirring, the aggregated grains cannot be completely broken up and the resulting suspension is gray and translucent. The addition of

≤0.1% sodium lauryl sulfate or octoxynol 9 deflocculates the grains into finely dispersed particles and results in a deep black and opaque dispersion. Ferric or aluminum hydroxide that has been freshly precipitated with ammonia can be peptized with small amounts of acids which reduce the pH below the isoelectric points of the hydroxides. Even washing the gelatinous precipitate of $Al(OH)_3$ with water tends to peptize it. Therefore, in quantitative analyses, the precipitate is instead washed with dilute solutions of ammonium salts that act as flocculating agents.

Preparation by Condensation Methods

Sulfur is insoluble in water but somewhat soluble in alcohol. When an alcoholic solution of sulfur is mixed with water, a bluish-white colloidal dispersion results. In the absence of added stabilizing agents, the particles tend to agglomerate and precipitate upon standing. This technique of first dissolving a material in a water-miscible solvent such as alcohol or acetone and then producing a hydrosol by precipitation with water is applicable to many organic compounds. It has been used to prepare hydrosols of stearic acid, natural resins like mastic, and the so-called pseudo-latexes. Another less common physical condensation method is to introduce a current of sulfur vapor into water, which produces colloidal particles. Alternatively, the very fine powder produced by condensing sulfur vapor onto cold solid surfaces (sublimed sulfur or flowers of sulfur) can be dispersed in water by the addition of a suitable surfactant to produce a hydrosol.

Organic compounds that are weak bases, such as the alkaloids, are usually much more soluble at lower pH values, where they are ionized, than at higher pH values, where they exist as the free base. Therefore, increasing the pH of their aqueous solutions above their pKa may cause precipitation of the free base. Conversely, organic compounds that are weak acids, such as the barbiturates, are usually much more soluble at higher pH values, where they are ionized, than at lower pH values, where they exist as the free acid form. Therefore, lowering the pH of their aqueous solutions well below their pKa usually causes precipitation of the free acid. Depending upon the supersaturation (defined below) of the unionized bases or acids and the presence of stabilizing agents, the resultant dispersions may be within the colloidal range.

Chemical condensation methods include the reaction between hydrogen sulfide and sulfur dioxide (eg, by bubbling H_2S into an aqueous SO_2 solution):

$$2\ H_2S + SO_2 \rightarrow 3\ S + 2\ H_2O$$

The same reaction occurs when aqueous solutions containing sodium sulfide and sulfite are acidified with an excess of sulfuric or hydrochloric acid. Another reaction is the decomposition of sodium thiosulfate by sulfuric acid, using either very dilute or very concentrated solutions to obtain colloidally dispersed sulfur:

$$H_2SO_4 + 3\ Na_2S_2O_3 \rightarrow 4\ S + 3\ Na_2SO_4 + H_2O$$

Both reactions also produce pentathionic acid ($H_2S_5O_6$) as a by product. The preferential adsorption of the pentathionate anion onto the surface of the sulfur particles confers a negative electric charge to the particles, thereby stabilizing the sol.[2,8,9] When powdered sulfur is boiled with a slurry of lime, it dissolves with the formation of calcium pentasulfide and thiosulfate. Subsequent acidification produces the colloidal "milk of sulfur," which upon washing and drying yields Precipitated Sulfur USP.

Sols of ferric, aluminum, chromic, stannic, and titanium hydroxides or hydrous oxides are produced by the hydrolysis of the corresponding chlorides or nitrates:

$$AlCl_3 + 3\ H_2O \rightleftharpoons Al(OH)_3 + 3\ HCl$$

Hydrolysis is promoted by boiling the solution and/or adding a base to neutralize the formed acid.[2]

Double decompositions that produce insoluble salts can also lead to colloidal dispersions. An example is silver chloride:

$$NaCl + AgNO_3 \rightarrow AgCl + NaNO_3$$

In addition, the reduction of gold, silver, copper, mercury, platinum, rhodium, and palladium salts with formaldehyde, hydrazine, hydroxylamine, hydroquinone, or stannous chloride forms hydrosols of the metals, which are strongly colored (eg, red or blue).[1,2,6,8]

KINETICS OF PARTICLE FORMATION—When the solubility of a compound in water is exceeded, its solution becomes supersaturated and the compound may precipitate or crystallize. The rate of precipitation, the resulting particle size (whether colloidal or coarse), and the particle size distribution (which can be narrow for mono- or homodispersed particles or broad for poly- or heterodispersed particles) depend upon two successive and largely independent processes. These are *nucleation* and *crystallization* (ie, growth of nuclei). When a solution of a salt or sucrose is supercooled or when a chemical reaction produces a salt in a concentration exceeding its solubility product, the separation of excess solid from the supersaturated solution is far from instantaneous. Clusters of ions or molecules called nuclei must exceed a critical size before they become stable and capable of growing into colloidal size crystals. These embryonic particles have much more surface for a given weight of material than larger and more stable crystals. Therefore, they have a higher surface free energy and greater solubility.

The occurrence of *nucleation* depends upon the *relative supersaturation*. If C is the actual concentration of the solute before crystallization and C_s is its solubility limit, then $C - C_s$ is the supersaturation and $(C - C_s)/C_s$ is the relative supersaturation. Von Weimarn recognized that the rate or velocity of nucleation (number of nuclei formed per liter per second) is proportional to the relative supersaturation. Nucleation seldom occurs at relative supersaturations below 3. However, this statement refers to homogeneous nucleation, where the nuclei have the same chemical composition as the crystallizing phase. If the solution contains solid impurities, such as dust particles in suspension, these may act as nuclei or centers of crystallization (heterogeneous nucleation).

Once nuclei have formed, *crystallization* begins. Nuclei grow by the aggregation of ions or molecules from solution. Crystallization continues until the supersaturation is relieved (i.e. until $C = C_s$) and may result in the formation of either colloidal or coarse particles. The rate of crystallization or growth of nuclei is proportional to the supersaturation:

$$\frac{dm}{dt} = \frac{A_{sp}D}{\delta}(C - C_s)$$

This equation is similar to the Noyes-Whitney equation that governs particle dissolution except that $C < C_s$ for the latter process, making dm/dt negative. In both equations, m is the mass of material crystallizing out in time t, D is the diffusion coefficient of the solute molecules or ions, δ is the length of the diffusion path or the thickness of the liquid layer adhering to the growing particles, and A_{sp} is their specific surface area. The presence of dissolved impurities may affect the rate of crystallization and even change the crystal habit, provided that these impurities are surface-active and become adsorbed onto the nuclei or growing crystals.[6] For instance, 0.005% polysorbate 80 or octoxynol 9 significantly retards the growth of methylprednisolone crystals in aqueous media.

Von Weimarn found that the particle size of the crystals depends strongly upon the concentration of the precipitating substance. At very low concentrations and slight relative supersaturation, diffusion is quite slow because the concentration gradient that drives the process is very small. Sufficient nuclei will usually form to relieve the slight supersaturation. However, crystal growth is limited by the small amount of excess dissolved material available to each particle and, therefore, the particles cannot grow beyond colloidal dimensions. This condition is represented by points A, D, and G of the schematic plot

of von Weimarn (Fig 21-7). At intermediate concentrations, the extent of nucleation is somewhat greater and much more material is available for crystal growth. Therefore, coarse crystals form rather than colloidal particles. This condition is represented by points B, E, and H in Figure 21-7. At high concentrations, nuclei appear so quickly and in such large numbers that supersaturation is relieved before any appreciable diffusion can occur. The high viscosity of the medium also slows down the diffusion of excess dissolved ions or molecules, retarding crystal growth without substantially affecting the rate of nucleation. Therefore, a large number of very small particles results which, because of their proximity, tend to link and produce a translucent gel. This condition is represented by points C and F in Figure 21-7. Upon subsequent dilution with water, such gels usually yield colloidal dispersions. Thus, colloidal systems are usually produced at very low and high supersaturations.

Low solubility is a necessary condition for producing colloidal dispersions. If the solubility of the precipitate is increased, for instance by heating the dispersion, a new family of curves will result similar in shape to those shown in Figure 21-7 but are displaced to the right (towards higher concentrations) and upwards (towards larger particle sizes).[7,9,28,29] An additional phenomennon illustrated in Figure 21-7 is that aging increases particle size. Curves ABC, DEF, and GHI correspond to increasing time periods after mixing the reagents, namely, 10–30 minutes, several hours, and weeks to years, respectively. This gradual increase in the particle size of crystals in their mother liquor is a recrystallization process called *Ostwald ripening*. Very small particles have a higher solubility than large particles of the same substance due to their greater specific surface area and higher surface free energy. In a saturated solution containing precipitated particles with a wide range of particle sizes, the very smallest particles dissolve spontaneously and deposit onto the larger particles. The growth of the larger crystals at the expense of the very small ones occurs because this process lowers the free energy of the dispersion. Adding small amounts of surface-active compounds that adsorb at the particle surface slows down the process.

Increasing the solubility of the precipitate accelerates the spontaneous coarsening of colloidal dispersions upon aging. For instance, barium sulfate precipitated by mixing concentrated solutions of sodium sulfate and barium chloride is largely in the colloidal size range and passes through filter paper. The colloidal particles gradually grow in size by Ostwald ripening, forming large crystals that can be removed quantitatively by filtration. Heating the aqueous dispersion speeds recrystallization by increasing the solubility of barium sulfate in water.

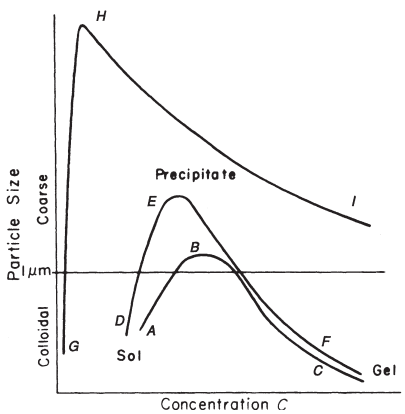


Figure 21-7. Effect of aging and concentration of the precipitating material upon particle size. Curves *ABC, DEF,* and *GHI* correspond to increasing aging. Both axes are on a logarithmic scale. Data from von Weimarn PP. In Alexander J, ed. *Colloid Chemistry*, vol I. New York: Chemical Catalog Co (Reinhold), 1926. See also *Chem Rev* 1926; 2:217 and Overbeek JThG. *Adv Colloid Interface Sci* 1982; 15:251.

Conversely, the addition of ethyl alcohol lowers the solubility of barium sulfate and slows Ostwald ripening, which allows the dispersion to remain in the colloidal state for years.

The relationship between particle size and solubility is given by the Ostwald-Freundlich or Kelvin equation which, for nonionic solutes, is[2,8,9]:

$$\ln \frac{S}{S_\infty} = \frac{2\gamma M}{rdRT}$$

where S and S_∞ are the solubility of colloidal particles having a radius r and the solubility of large, flat particles ($r = \infty$), respectively. For electrolytes, the mean ionic activity is included. The solid/solvent interfacial free energy, γ, can only be determined indirectly (for instance, by means of this equation). The ratio of the molecular weight of the solute to its density (M/d) equals its molar volume. Assuming $M = 500\ g/mol$, $d = 1.00\ g/mL$, and $\gamma = 30\ erg/cm^2$, and using the values of $8.314 \times 10^7\ erg/mol\text{-}K$ for the gas constant R and $298\ K$ for the absolute temperature T, dispersed particles having radii of 1×10^{-6} cm (10 nm), 1×10^{-5} cm (0.1 μm), 1×10^{-4} cm (1 μm), and 1×10^{-3} cm (10 μm) correspond to S/S_∞ ratios of 3.36, 1.13, 1.012, and 1.0012 respectively. Therefore, while particles having sizes at the lower end of the colloidal range are appreciably more soluble than coarser particles of the same compound, the solubility of finely ground drug or excipient powders (particle radii typically in the 1–10 μm range) is only increased by ≤1%.

Condensation methods generally produce polydisperse sols because nucleation continues while established nuclei grow. However, monodispersed colloidal sols may be prepared by precipitation using a technique that involves the formation of all nuclei in a single, brief burst. A sufficiently brief period of homogeneous nucleation relieves the supersaturation to such an extent that no new nuclei can subsequently form. Therefore, the nuclei created during the initial burst grow uniformly as the remaining excess of precipitating material diffuses and deposits onto them. The supersaturation never again reaches sufficiently high values for forming new nuclei because it is relieved by the continuous growth of the existing nuclei.[7,9,28,29] The controlled hydrolysis of salts of di- and trivalent cations in aqueous solutions at elevated temperatures has been used to produce colloidal dispersions of metal (hydrous) oxides having uniform sizes in a variety of well-defined shapes (eg, spheres or laths or cubes or discs). Complexation of the cations, concentration, and temperature control the rate of hydrolysis, and therefore, the chemical composition, crystallinity, shape, and size of the dispersed phase.[28,30]

Stabilization

It should be reiterated that hydrosols of hydrophobic substances are intrinsically unstable. While mechanical disintegration may break up the dispersed phase into colloidal particles, flocculation or coagulation causes the dispersed particles to become progressively coarser and fewer, ultimately resulting in the complete separation of a macroscopic phase. The reduction in surface area and in surface free energy accompanying flocculation or coagulation is small because irregular solid particles are rigid and only touch at a few points upon aggregation. However, these loose initial contacts may grow with time by sintering or recrystallization. Sintering is the "fusion" of primary particles into larger primary particles, which propagates from the initial small areas of contact. This recrystallization process is spontaneous because it decreases the specific surface area of the dispersed solid and the surface free energy of the dispersion. Sintering is analogous to Ostwald ripening, the recrystallization process that transfers solids from colloidal to coarse particles. Low solubility and the presence of adsorbed surface-active substances retard both processes.

If aqueous dispersions of hydrophobic solids are to resist reaggregation (ie, flocculation and coagulation), they must be

stabilized during or shortly after the dispersion process. Stabilizing factors include the presence of electrical charges at the particle surface and the presence of adsorbed macromolecules or nonionic surfactants. The presence of positive or negative charges may result from the dissociation of the solid's ionogenic groups or the adsorption of ions such as ionic surfactants. These stabilizing factors do not alter the intrinsic thermodynamic instability of lyophobic dispersions, and therefore, ΔG_s remains positive and phase separation or aggregation is still energetically favored over dispersal. However, they establish kinetic barriers that delay the aggregation processes almost indefinitely; the dispersed particles cannot come together close enough for van der Waals attractive forces to produce coagulation.[5,6,8]

Stabilization may be provided by adsorbed surfactants. In a flocculated dispersion, groups of several particles are agglomerated into flocs. Frequently, the particles of a floc are in physical contact. When a surfactant is added to a flocculated sol, the dissolved surfactant molecules adsorb onto the surface of the particles. Surfactant molecules also tend to pry apart the flocs by wedging themselves in between the particle contact points. This action frees up additional surface area for surfactant adsorption. The breaking up of flocs or secondary particles is defined as deflocculation or peptization. Ophthalmic suspensions should be deflocculated because the large particle size of flocs causes irritation to the eye. Parenteral suspensions should also be deflocculated to prevent the larger particles from clogging hypodermic syringes, causing tissue irritation, or blocking capillary blood vessels. However, deflocculated suspensions tend to cake (ie, the sediment formed by gravitational settling is compact and may be hard to redisperse upon shaking). Caking in oral suspensions is prevented by controlled flocculation.

Surfactants tend to accumulate at interfaces because of their amphiphilic nature. This process is an *oriented physical adsorption*. Surfactant molecules arrange themselves at the interface between water and an organic solid or liquid of low polarity in such a way that the hydrocarbon chain is in contact with the surface of the solid particle or sticks inside the oil droplet while the polar head group is oriented towards the water phase. This orientation leaves the polar head group in contact with the water so that it can be hydrated and removes the surfactant's hydrophobic hydrocarbon chain from the bulk of the water, where it is unwelcome because it inferences with the hydrogen bonding between water molecules. Figure 21-8 shows that at a low surfactant concentration and at low surface coverage, the hydrocarbon chains of the adsorbed surfactant molecules lie flat against the solid surface. At higher surfactant concentrations, the surfactant molecules are adsorbed in an upright position to allow for the greatest number of molecules per unit surface area. In this position, the terminal methyl groups of the hydrocarbon tails are in contact with the hydrophobic particle surface and the hydrocarbon tails are in lateral contact with each other. London dispersion forces promote the attraction between both types of adjoining groups.

The adsorption of ionic surfactants increases the charge density and the ζ potential of the dispersed particles. These two parameters are low for water-insolubel organic substances. The increase in electrostatic repulsion between nonpolar particles due to the adsorption of surface-active ions stabilizes the dispersion against coagulation. This "charge stabilization" is described by the DLVO theory.

Most water-soluble nonionic surfactants are polyoxyethylated. Each molecule consists of a hydrophobic hydrocarbon chain combined with a hydrophilic polyethylene glycol chain (eg, $CH_3(CH_2)_{15}(OCH_2CH_2)_{10}OH$). Hydration of the ether groups and the terminal hydroxyl group renders the surfactant molecule water-soluble. It adsorbs at the interface between a hydrophobic solid and water, with the hydrocarbon moiety adhering to the solid surface and the polyethylene glycol moiety protruding into the water, where it is hydrated. Therefore, the particle surface is surrounded by a thin layer of hydrated polyethylene glycol chains. This hydrophilic shell forms a steric barrier that prevents close contact between particles and inhibits coagulation

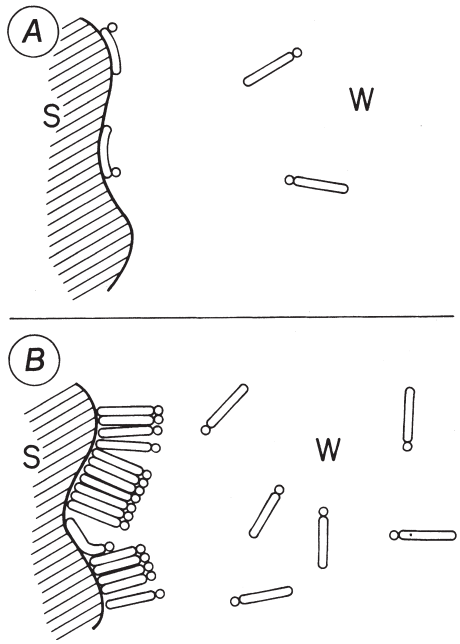


Figure 21-8. Schematic representation of the physical adsorption of surfactant molecules at a hydrophobic solid (S)/water (W) interface. Cylindrical portions and spheres represent the hydrocarbon chains and polar headgroups of the surfactant molecules, respectively. *A.* Low surfactant concentration/low surface coverage. *B.* Near critical micelle concentration/surface coverage near saturation.

("steric stabilization"). Nonionic surfactants also reduce the sensitivity of hydrophobic dispersions towards coagulation by salts (ie, they increase the coagulation values).[31]

The adsorption of water-soluble polymers provides a second mechanism for the stabilization of hydrophobic dispersions. Water-soluble polymers that have some hydrophobic groups may be surface active and adsorb at the interface between water and a hydrophobic organic solid because their hydrophobic groups limit their water solubility and render them amphiphilic. Such polymers also tend to accumulate at the air-water interface and, therefore, lower the surface tension of the aqueous phase. Conversely, polyelectrolytes that have a high concentration of ionic groups are excessively water-soluble, which reduces or eliminates their surface activity and tendency to adsorb at interfaces (eg, *sodium* carboxymethylcellulose). *Polyvinyl alcohol* is another polymer that does not adsorb extensively at interfaces due to a high concentration of hydroxyl groups, which makes it very water-soluble. Polyvinyl alcohol is manufactured by the hydrolysis of polyvinyl acetate, which is water-insoluble. Hydrolysis of ;85% of the acetyl groups produces a copolymer that is both water-soluble and surface-active. Other surface-active polymers include methylcellulose, hydroxypropyl cellulose, high-molecular-weight polyethylene glycols (polyethylene oxides), and proteins. The surface activity of proteins is due to the presence of hydrophobic groups at concentrations too low to cause insolubility in water. Proteins are denatured upon adsorption at air-water and solid-water interfaces.

As shown in Figure 21-9*A*, polymer molecules adsorb onto solid surfaces in the form of loops projecting into the aqueous phase rather than lying flat against the solid substrate. Only a small portion of an adsorbed polymer is in direct contact with the solid surface. However, because of its great chain length, there are enough of these contact points to anchor the adsorbed macromolecule firmly onto the surface. At sufficiently high concentrations, adsorbed polymers may form a layer surrounding the entire dispersed particles. This layer consists of the polymer chains as well as the water of hydration associated with

them and any water mechanically trapped inside the chain loops. This sheath becomes an integral part of the particle surface and may prevent coagulation. The mechanisms by which adsorbed nonionic macromolecules prevent the coagulation of hydrophobic sols are the same ones operative in the stabilization of sols by nonionic surfactants. The hydrophilic polyethylene glycol moieties of the adsorbed surfactant molecules that protrude into the aqueous phase resemble the chain ends of the adsorbed macromolecules rather than their looped segments.

The following protective mechanisms are operative:

1. The layer of adsorbed polymer and enmeshed water surrounding the particles forms a *mechanical* or *steric barrier* ("*steric stabilization*") that prevents the particles from approaching each other closely enough for the interparticle attraction of London dispersion forces to produce coagulation. These forces are only effective over interparticle distances smaller than twice the thickness of the adsorbed polymer layer. These layers are somewhat elastic; they may be dented by a collision between two particles but tend to return to their original shape.
2. When two particles approach so closely that their adsorbed polymer layers overlap, the chain loops of the opposing layers compress and mix with or interpenetrate each other. The freedom of motion of the chain segments in the overlapped region becomes restricted, which produces a negative entropy change. Therefore, any reduction in interparticle distance, which is required for coagulation, results in a positive change in free energy. As a result, the reverse process of particle separation occurs spontaneously because disentangling the two opposing adsorbed polymer layers is more energetically favorable. The particles are thus prevented from coagulating by *entropic repulsion* through the mechanism of *entropic stabilization* of the sol. This mechanism predominates when the concentration of polymer in the adsorbed layer is low.
3. As the adsorbed polymer layers on two approaching particles overlap, the polymer concentration in the overlap region causes a local increase in osmotic pressure, which is relieved by an influx of water. This influx of water to dilute the polymer loops pushes the two particles apart, preventing coagulation.
4. If the adsorbed polymer has some ionic groups, stabilization by electrostatic repulsion or charge stabilization, as previously described, is an additional factor that prevents a close interparticle approach and coagulation.
5. The adsorption of water-soluble polymers changes the nature of the surface of hydrophobic particles to hydrophilic, resulting in an increased resistance to coagulation by salts.[32]

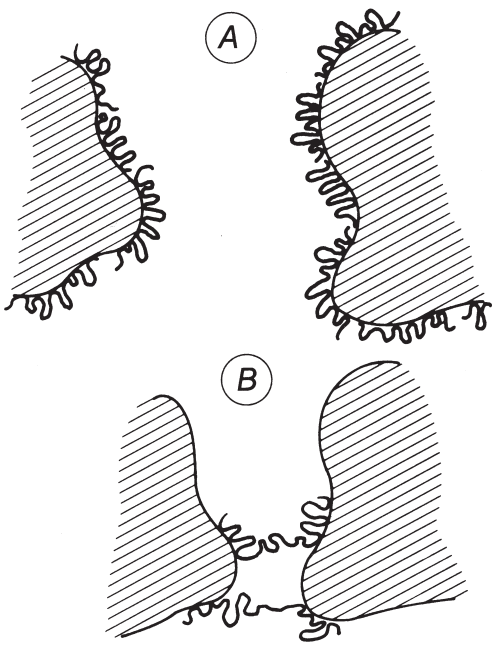


Figure 21-9. Protective action (*A*) and sensitization (*B*) of adsorbed polymer chains upon sols containing hydrophobic particles.

The water-soluble polymers whose adsorption stabilizes hydrophobic sols and protects them against coagulation are called *protective colloids*. *Gelatin* and *serum albumin* are the preferred protective colloids for stabilizing parenteral suspensions because of their biocompatibility. These two polymers, as well as casein (milk protein), dextrin (partially hydrolyzed starch), and vegetable gums like acacia and tragacanth are metabolized in the human body. Cellulose derivatives and most synthetic protective colloids such as *povidone* are not biotransformed. Because of this and their large molecular size, these polymers are not absorbed but excreted intact when administered in an oral dosage form.

Sensitization

Sensitization is the opposite of protective action (ie, a decrease in the stability of the hydrophobic sols). At concentrations well below those at which it exerts a protective action, a protective colloid may flocculate a sol in the absence of added salts and/or lower the coagulation values of the sol. In the case of nonionic polymers and of polyelectrolytes having charges of the same sign as the sol particles, flocculation results from the bridging mechanism illustrated in Figure 21-9*B*. At very low polymer concentrations, there are not nearly enough polymer molecules present to completely cover each sol particle. Since the particle surfaces are largely bare, a single macromolecule may be adsorbed onto two particles, thereby bridging the gap between them and pulling them close together. Flocs are formed when several particles become connected through polymer molecules that are adsorbed jointly onto two or possibly even three particles. Such flocculation usually occurs over a narrow range and at very low polymer concentrations. At higher concentrations, bridging is unlikely to occur because there is enough polymer to completely cover all of the particles and the adsorbed polymer stabilizes or peptizes the sol.[9,32]

If the polymer contains ionic groups of charge opposite to that of the sol particles, a limited amount of polymer adsorption neutralizes the charge of the particles and reduces their ζ potential to nearly zero. This eliminates stabilization by electrostatic repulsion. In addition, steric stabilization is ineffective because of the low surface coverage of the adsorbed polymer. Therefore, the sol either coagulates by itself or may be coagulated with a very small amount of sodium chloride. At higher polymer concentrations, where adsorption is more extensive, the charge on the particles is converted to the sign of the polyelectrolyte, which reactivates charge stabilization and adds steric stabilization. As a result, the coagulation value of the sol increases well above the original value. For example, partly hydrolyzed polyacrylamide containing about 20% of ammonium acrylate repeat units is an anionic polyelectrolyte. Addition of this polyacrylamide to aluminum hydroxide sols at a polymer concentration of 1:1,000,000 and a pH of 6–7, where the sols are positively charged and the polyelectrolyte is fully ionized, results in flocculation. At a polymer concentration of 1:10,000, the sols become negatively charged because extensive polymer adsorption introduces an excess of $—COO^-$ groups over the $=Al^+$ ions on the particle surface. This creation of negatively charged particles introduces electrostatic and steric stabilization, which makes the sols more stable against flocculation by salts than they were before the addition of the polyacrylamide.

Polymer B in Figure 21-10 illustrates this example. The curve in the lower plot indicates sensitization, with the coagulation value for sodium chloride lowered by as much as 60%. Zeta potential measurements may be used to distinguish between sensitization by bridging and sensitization by charge neutralization. The charge reversal caused by the adsorption of Polymer B is illustrated in the upper plot and indicates that charge neutralization is the cause of sensitization. If Polymer B had a ζ potential-polymer concentration plot similar to Polymer A, sensitization would be ascribed to bridging. The nonionic Polymer A in Figure 21-10 stabilizes the sol at all

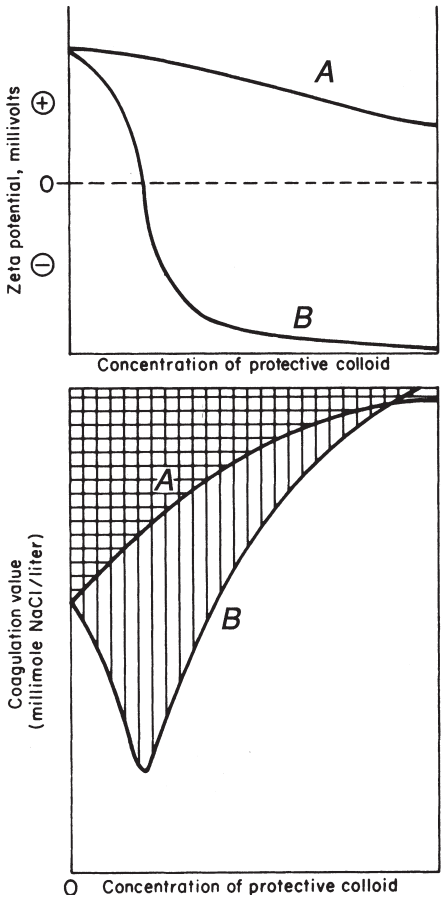


Figure 21-10. Protective action and sensitization: Polymer A exerts protective action at all concentrations, while Polymer B sensitizes at low concentrations and stabilizes at high concentrations. Horizontal and vertical hatching indicates region of flocculation for a sol treated with various concentrations of Polymers A and B, respectively. Clear region underneath indicates sol is deflocculated.

concentrations. Neither sensitization by bridging nor by charge neutralization is observed. The reason that Polymer A slightly lowers the positive ζ potential of the sol is that the increasing amounts of adsorbed polymer chains gradually shift the plane of shear outward and away from the positively charged surface. If Polymer A were a cationic polyelectrolyte, the ζ potential-polymer concentration plot would gradually rise with an increase in polymer adsorption rather than drop.

Even water-soluble polymers which are too thoroughly hydrophilic to be adsorbed by hydrophobic sol particles can stabilize such sols. Their thickening action increases the viscosity of the sols. This slows down Brownian motion and sedimentation, giving the particles less opportunity to come in contact with each other and, therefore, decreasing flocculation.

ASSOCIATION COLLOIDS

Association colloids are formed by self-assembling enough small molecules to produce aggregates in the colloidal size range. This group of colloids includes surfactant micelles, microemulsions, and liposomes.

Formation of Surfactant Micelles

The dual or amphiphilic nature of surfactants or surface-active agents was discussed previously. Water attracts their polar head groups but repels their hydrocarbon tails. Consequently, surfactants tend to concentrate and adsorb at air-water, oil-water, and solid-water interfaces. The surface tension of aqueous surfactant solutions decreases with increasing surfactant concentration up to a point, beyond which it remains nearly constant (Fig 21-11). Curves *A* and *B* in Figure 21-11 illustrate the surface tension (against air) and the interfacial tension (against oil) of an aqueous surfactant solution as a function of surfactant concentration. Surface-active impurities may cause a minimum in the surface tension (shown as a dotted curve) rather than a mere leveling off. Abrupt changes occur not only to the surface and interfacial properties but also to the surfactant solution's bulk properties such as equivalent conductivity (Curve *D*), co-ion and counterion activities in the case of ionic surfactants, colligative properties like osmotic pressure (Curve *C*), turbidity (but the increase is far too weak to be visible to the naked eye), refractive index, UV and NMR spectra, partial molar volume, relative viscosity, and the diffusion coefficients and solubility of water-insoluble, oil-soluble compounds (Curve *E*). All of these changes occur over a very narrow concentration range, which is shown as a crosshatched band and is referred to as the *critical micelle concentration* (CMC).

As the surfactant concentration in a liquid is increased, the amount of the surfactant adsorbed at the liquid-air and liquid-container interfaces increases and these interfaces become increasingly crowded. When the concentration is increased further, the surfactant molecules will continue to adsorb at these interfaces until tightly packed monolayers are formed and there is no longer any room for further surfactant adsorption. At this point, the surface and interfacial tensions reach their constant values,[33] and it would seem that the bulk solubility limit of the surfactant has been reached. However, if more surfactant is added to the solution, the excess surfactant molecules will begin to associate into small aggregates called *micelles* (at the CMC), while the concentration of nonassociated surfactant molecules remains nearly constant. Above the CMC, the concentration of micellar surfactant is equal to the total surfactant concentration minus the CMC. Diluting the surfactant solution to below the CMC causes the micelles to disperse or break up into single or nonassociated surfactant molecules.

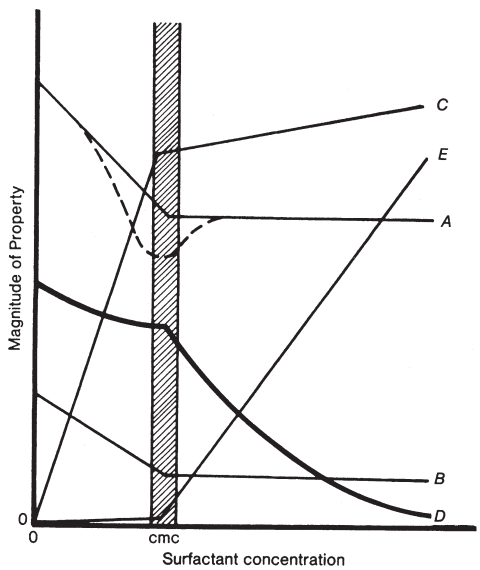


Figure 21-11. Effect of surfactant concentration and micelle formation on various properties of the aqueous solution of an ionic surfactant. *A:* Surface tension; *B:* interfacial tension; *C:* osmotic pressure; *D:* equivalent conductivity; *E:* solubility of a compound with very low solubility in pure water. (From Schott H, Martin AN. In Dittert LW, ed, *American Pharmacy*, 7th ed. Philadelphia: JB Lippincott, 1974.)

Micelles are not static aggregates; they dissociate, regroup and reassociate rapidly. The half-life of ionic surfactant micelles in the absence of additives is a small fraction of a second. Furthermore, there is a dynamic equilibrium (ie, an incessant exchange) between single surfactant molecules in solution, surfactant molecules adsorbed in monolayers at the interfaces, and surfactant molecules associated as micelles.

The shape of micelles in dilute aqueous surfactant solutions is approximately spherical (Fig 21-12*A*). The polar head groups of the surfactant molecules are arranged in an outer spherical shell while their hydrocarbon chains are oriented towards the center where they form a spherical core. These hydrocarbon chains are randomly coiled and entangled. The micellar interior has a nonpolar, liquid-like character resembling a liquid normal paraffin such as dodecane. In nonionic surfactant micelles, the polyoxyethylene moieties are oriented outwards and permeated by water while the hydrocarbon moieties form an "oil droplet" core similar to ionic micelles (Fig 21-12*B*): this arrangement is energetically favorable. The hydrophilic head groups, located externally, are in contact with water and remain extensively hydrated. The hydrocarbon moieties are removed from the aqueous medium and partly shielded from contact with water by the polar head groups. Therefore, they no longer interfere with hydrogen bonding among the water molecules. This interference is the reason why surfactant molecules are pushed out of aqueous media towards interfaces. The hydrocarbon tails of the surfactant molecules, located in the micellar interior, attract one another by weak dispersion forces.[31,34–36]

Representative CMC values and aggregation numbers (number of surfactant molecules/micelle) are listed in Table 21-4.[36,37] Ionic surfactants have higher CMC values than nonionic surfactants because electrostatic repulsion of the charged head groups makes micellization more difficult. The addition of simple salts

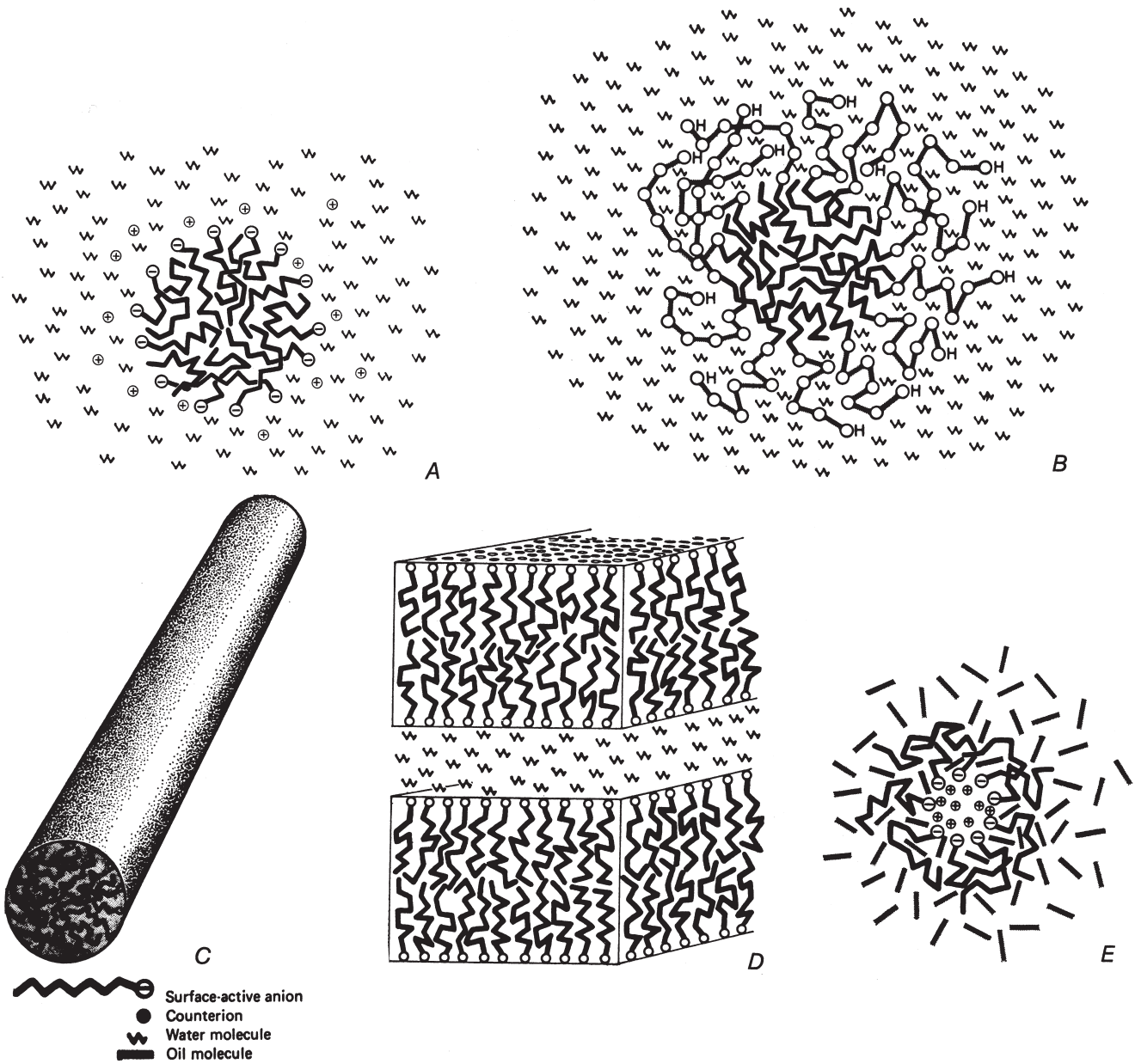


Figure 21-12. Different types of micelles. **A.** Spherical micelle of an anionic surfactant; **B.** spherical micelle of a nonionic surfactant; **C.** cylindrical micelle of an ionic surfactant; **D.** lamellar micelle of an ionic surfactant; **E.** reverse micelle of an anionic surfactant in oil. (From Schott H, Martin AN. In Dittert LW, ed, *American Pharmacy*, 7th ed. Philadelphia: JB Lippincott, 1974.)

Table 21-4. Critical Micelle Concentrations and Micellar Aggregation Numbers of Various Surfactants in Water at Room Temperature

STRUCTURE	NAME	CMC (*mmol/L*)	SURFACTANT MOLECULES/ MICELLE
n-$C_{11}H_{23}COOK$	Potassium laurate	24	50
n-$C_8H_{17}SO_3Na$	Sodium octane sulfonate	150	28
n-$C_{10}H_{21}SO_3Na$	Sodium decane sulfonate	40	40
n-$C_{12}H_{25}SO_3Na$	Sodium dodecane sulfonate	9	54
n-$C_{12}H_{25}OSO_3Na$	Sodium lauryl sulfate	8	62
n-$C_{12}H_{25}OSO_3Na$	Sodium lauryl sulfate[a]	1	96
	Docusate sodium	5	48
n-$C_{10}H_{21}N(CH_3)_3Br$	Decyltrimethylammonium bromide	63	36
n-$C_{12}H_{25}N(CH_3)_3Br$	Dodecyltrimethylammonium bromide	14	50
n-$C_{14}H_{29}N(CH_3)_3Br$	Tetradecyltrimethylammonium bromide	3	75
n-$C_{14}H_{29}N(CH_3)_3Cl$	Tetradecyltrimethylammonium chloride	3	64
n-$C_{12}H_{25}NH_3Cl$	Dodecylammonium chloride	13	55
n-$C_{12}H_{25}O(CH_2CH_2O)_8H$	Polyoxyl 8 dodecyl ether	0.13	132
n-$C_{12}H_{25}O(CH_2CH_2O)_8H$[b]	Polyoxyl 8 dodecyl ether	0.10	301
n-$C_{12}H_{25}O(CH_2CH_2O)_{12}H$	Polyoxyl 12 dodecyl ether	0.14	78
n-$C_{12}H_{25}O(CH_2CH_2O)_{12}H$[b]	Polyoxyl 12 dodecyl ether	0.091	116
p-$C_9H_{19}C_6H_4O(CH_2CH_2O)_{10}H$	Nonoxynol 10	0.07	276
p-$C_9H_{19}C_6H_4O(CH_2CH_2O)_{30}H$	Nonoxynol 30	0.24	44

[a] Interpolated for physiologic saline, 0.154 *M* NaCl.
[b] At 55° instead of 20°.

reduces these repulsive forces and, therefore, lowers the CMC values of ionic surfactants. Within any homologous surfactant series, the CMC decreases regularly with increasing hydrocarbon chain length and, therefore, with increasing surface activity of the surfactant. As is seen in Table 21-4, each additional methylene group decreases the CMC by approximately one-half. This is a consequence of Traube's rule, which states that, within a homologous series of surfactants, each additional methylene group decreases the molar concentration required to produce an equal lowering of the surface tension of water threefold. The addition of a methylene group reduces the CMC by a factor of antilog (1/3) = 2. The CMC of nonionic surfactants increases as the temperature decreases and as the percentage of polyoxyethylene increases.

The micelles of the surfactants listed in Table 21-4 are either spherical or ellipsoidal. They are rather small because their sizes were determined in relatively dilute solutions (containing only a few percent of surfactant) and mostly in pure water at room temperature. Their diameters are between 2 and 8 nm, which places them at the lower end of the colloidal size range. For this reason, surfactants are sometimes called *association colloids*. Adding salts increases the size of ionic micelles. Raising the temperature increases the size of nonionic micelles, especially if the temperatures are within 20° of their respective cloud points. These factors reduce the water solubility of ionic and nonionic surfactants, thereby rendering them more surface-active.

As micelles become larger, they also become more asymmetric. Their shape changes from spherical or ellipsoidal to cylindrical and eventually to lamellar. In cylindrical micelles, the polar head groups form the periphery and the hydrocarbon tails fill the interior of the cylinders (Fig 21-12*C*). In lamellar micelles, the surfactant molecules are arranged in parallel bimolecular sheets with a tail-to-tail orientation (ie, the hydrocarbon tails form the inner layer). Water is stratified between the sheets, thereby hydrating the external polar head groups (Fig 21-12*D*). In both types of micelles, the hydrocarbon tails are randomly coiled and in a liquid-like state.[12] In concentrated aqueous solutions containing 20% or more of surfactant, cylindrical micelles often line up parallel to each other and arrange themselves in hexagonal arrays. Likewise, lamellar micelles are often packed parallel and equidistant from each other with the intervening water layers having a uniform thickness. These ordered solutions are liquid crystals or mesophases; they are birefringent and very viscous. Even though they are liquids, they have some of the properties of crystalline solids.[8,31,35,36]

Oil-soluble surfactants (eg, heavy metal soaps, docusate sodium, and nonionic surfactants with HLB values < 7) form aggregates when dissolved in organic liquids having low polarity such as hydrocarbons and chlorinated hydrocarbons. These micelles are inverted or turned inside out; their hydrocarbon tails are oriented outwards into the oil phase while their polar head groups are in the center of the micelle, where water can be solubilized (Fig 21-12*E*). Because the bulky head groups are in the center, the aggregation numbers for *reverse micelles* are small, usually between 3 and 20.[35,38]

Microemulsions

Microemulsions are liquid dispersions of water and oil that are made homogeneous, transparent, and stable by the addition of relatively large amounts of a surfactant and a cosurfactant.[10,39–41] *Oil* is defined as any liquid having low polarity and low miscibility with water (eg, toluene, cyclohexane, and mineral or vegetable oils). Microemulsions have intermediate properties between micelles containing solubilized oils and emulsions. Emulsions are lyophobic and unstable. Their preparation requires the input of considerable amounts of mechanical energy, which may be supplied by colloid mills, homogenizers, or ultrasonic generators. Conversely, microemulsions are on the borderline between lyophobic and lyophilic colloids. True microemulsions are thermodynamically stable and, therefore, form spontaneously when oil, water, surfactants, and cosurfactants are mixed together.[42]

Both emulsions and microemulsions may contain high volume fractions of the internal phase. For instance, some O/W systems contain 75% (v/v) of oil dispersed in 25% water, although lower volume fractions of the internal phase are more common.

Microemulsions droplet have a mean diameter range of approximately 6 to 100 nm and a narrow droplet size distribution. Since the droplet diameters are less than 1/4 of the wavelength

of light (420 nm for violet and 660 nm for red light), microemulsions scatter little light. Therefore, they are transparent or at least translucent. By contrast, emulsions have broad droplet-size distributions and are generally opaque because the bulk of their droplets are greater than the wavelength of light and most oils have higher refractive indices than water.

Emulsions contan three components, namely, oil, water, and surfactant; whereas, microemulsions generally require a fourth component, a *cosurfactant*. Commonly used cosurfactants include linear alcohols of medium chain length that are sparingly miscible with water. The combination of surfactant and cosurfactant promote the generation of extensive interfaces through the spontaneous dispersion of oil in water, or vice-versa. The large interfacial area between the oil and water consists of a mixed interfacial film containing both surfactant and cosurfactant molecules. This film is called the "interphase" because it is thicker than the typical surfactant monolayers formed at the oil-water interfaces in emulsions. The interfacial tension at the oil-water interface in microemulsions approaches zero, which also contributes to their spontaneous formation. According to another viewpoint, microemulsions are regarded as micelles extensively swollen by large amounts of solubilized oil.

Micellar solutions, microemulsions, and emulsions can be of the O/W (oil-in-water) or W/O type. As mentioned previously, aqueous micellar solutions can solubilize oils in the hydrocarbon cores of the micelles. Conversely, oil-soluble surfactants like sorbitan monooleate and docusate sodium form reverse micelles in oils (Fig 21-12*E*) that are capable of solubilizing water in their polar centers. The solubilized oil in the former micelles and the solubilized water in the latter may in turn enhance the micellar solubilization of oil-soluble and water-soluble drugs, respectively.

Typical formulations for an O/W and a W/O microemulsion are shown in Table 21-5. The ratio of grams of surfactant to grams of solubilized or emulsified oil or water ranges from 2 to 20 for micellar solutions and 0.01 to 0.1 for emulsions. Microemulsions have intermediate values. For example, the ratios for the formulations in Table 21-5 are near unity. In industrial formulations, the ratios are closer to 0.1 to reduce costs. Microemulsions are used for a variety of applications including floor polishes, agricultural pesticides, tertiary petroleum recovery, and pharmaceutical delivery systems.

Liposomes

Liposomes are discussed by Crommelin and Schreier,[43] and by Rosoff.[44] They are spherical vesicles whose walls consist of hydrated bilayers of phospholipids. Phosphatidylcholines (lecithins), dispersed in excess water at temperatures where they are in a "fluid" or liquid-crystalline state, spontaneously form closed vesicles filled with trapped aqueous medium. Cooling the dispersion below the phase transition temperature of the lecithins orders the hydrocarbon chains of their fatty acids into a close—packed and more rigid structure (the gel state) and drastically lowers the permeability of solute molecules trapped inside the vesicles. The transition temperatures of dioleylphosphatidyl choline and dipalmityl phosphatidyl choline are −15° and 41° C, respectively. Intercalating cholesterol molecules between adjacent lecithin molecules has a condensing effect on the bilayers, reducing their permeability considerably. The addition of stearylamine confers a positive charge to liposomes and renders them impermeable towards cations. The incorporation of phosphatidic acids confers a negative charge and makes the liposomes permeable to cations. Anions generally diffuse rapidly through positive, negative, and neutral liposome membranes.

Liposomes are classified as unilamellar and multilamellar. The former are vesicles enclosed by a 6 to 7 nm thick single phospholipid bilayer. They range in size from 20 to 1000 nm (1 μm), depending on the method of preparation. Multilamellar liposomes consist of concentric phospholipid bilayers separated by aqueous layers of about 2.8 nm thickness. They have an onion-like structure with an aqueous core.

Methods of preparing liposomes include: subjecting aqueous lipid dispersions to high shear (including ultrasonication); forming their lipid films by solvent evaporation, followed by their hydration and dispersal in water; injecting solutions of lipids as water-immiscible (ether, petroleum ether) or water-miscible (alcohol) solvents into water. Vesicle formation is not restricted to lipids. Dioctadecyldimethylammonium chloride, dihexadecyl phosphate, and select nonionic surfactants also form vesicles, the latter called niosomes.

PHARMACEUTICAL APPLICATIONS

Colloidal materials are used for a variety of pharmaceutical applications including therapeutic and diagnostic agents, drug delivery systems, and pharmaceutical excipients. With the recent advances in biotechnology and protein engineering, many new drug substances are colloids including recombinant human insulin, interferons, interleukins, and monoclonal antibodies. Drug substances may also be prepared as colloidal sized particles to improve bioavailability or therapeutic activity (eg, colloidal sulfur).

Radioactive Colloids

Colloidal dispersions containing radioactive isotopes are being used as diagnostic and therapeutic agents in nuclear medicine.[45] *Colloid gold Au 198* is made by reducing a solution of gold (^{198}Au) chloride either by treatment with ascorbic acid or by heating with an alkaline glucose solution. Gelatin is added as a protective colloid. The particle size ranges from 5 to 50 nm with a mean of 30 nm, and the color of the sol is cherry-red in transmitted light. Violet or blue sols have excessively large particle sizes and should be discarded. Colloidal gold is used as a diagnostic and therapeutic aid and. The half-life of ^{198}Au is 2.7 days. *Technetium 99m sulfur colloid* is prepared by reducing sodium pertechnetate ^{99m}Tc with sodium thiosulfate. The product, a mixture of technetium sulfide and sulfur in the colloidal particle size range, is stabilized with gelatin. It is primarily used in liver, spleen, and bone scanning and has a half-life of 6.0 hours.

Crosslinked Polymers

When linear, water-soluble polymers are crosslinked, they swell in water but no longer dissolve. The crosslinks tie the macromolecular chains together by primary covalent bonds, transforming each particle into a single, giant molecule. The

Table 21-5. Microemulsion Formulations

		CONTENT IN MICROEMULSIONS, %	
COMPOUND	FUNCTION	O/W	W/O
Sodium lauryl sulfate	Surfactant	13	10
1-Pentanol	Cosurfactant	8	25
Xylene	Oil	8	50
Water		71	15

water-swollen grains of crosslinked polymers are permeable to low molecular weight solutes. Examples of crosslinked polyelectrolytes include the cation-exchange resin sodium polystyrenesulfonate copolymerized with divinylbenzene (used to reduce hyperkalemia by exchanging some of its Na^+ with $K^{+)}$ and the anion-exchange resins cholestyramine and colestipol hydrochloride (which reduce hypercholesterolemia by binding bile salt anions). Polycarbophil, a lightly crosslinked polymer of acrylic acid, only ionizes and swells in the nearly neutral small intestine, where it absorbs water and reduces the fluidity of diarrheal stool.

Colloidal Delivery Systems

Colloidal delivery systems include micelles, microemulsions, liposomes, parenteral emulsions, microspheres, nanoparticles, and drug-polymer conjugates.

MICELLES AND SOLUBILIZATION—Micelles have been used to solubilize poorly water-soluble compounds. For example, *Aquamephyton Injection* contains phytonadione (vitamin K_1) dissolved in the core of micelles of a polyoxyethylated fatty acid derivative. *Cernevit-12 for Infusion* consists of a mixture of fat-soluble vitamins (A, D, & E) solubilized by micelles, and water-soluble vitamins dissolved in water. As illustrated in Figure 21-12, the interior of surfactant micelles formed in an aqueous media consists of hydrocarbon tails in a liquid-like, disordered state. Therefore, the micelles resemble miniscule pools of liquid hydrocarbon surrounded by shells of polar head groups. Compounds that are poorly soluble in water but soluble in hydrocarbon solvents can be dissolved inside these micelles, and thereby brought homogeneously into the overall aqueous medium.

Being oleophilic, the solubilized molecules are primarily located in the hydrocarbon core of the micelles (Figure 21-13*A*). However, many water-insoluble drugs also contain polar functional groups such as hydroxyl, carbonyl, ether, amino, amide, and cyano groups. Upon solubilization, these hydrophilic groups are located among the polar headgroups of the surfactant in the periphery of the micelle in order to become hydrated (Figure 21-13*B*). For instance, when cholesterol or dodecanol is solubilized by sodium lauryl sulfate micelles, their hydroxyl groups penetrate between the sulfate ions and are even bound to them through hydrogen bonds, while their hydrocarbon portions are immersed among the dodecyl tails of the surfactant in the micelle core. Micelles of polyoxyethylated nonionic surfactants consist of an outer shell of hydrated polyethylene glycol moieties and a core of hydrocarbon moieties. Compounds like phenol, cresol, benzoic acid, salicylic acid, and esters of *p*-hydrobenzoic and *p*-aminobenzoic acids have some solubility in water and oils but considerable solubility in liquids of intermediate polarity such as ethanol, propylene glycol, or aqueous solutions of polyethylene glycols. When solubilized by nonionic micelles, these compounds are located in the outer hydrated polyethylene glycol shell as shown in Figure 21-13*C*. Since these compounds have hydroxyl or amino groups, they frequently form complexes with the ether oxygens of the surfactant through hydrogen bonding.[31,34–36,38]

Micellar solubilization is generally nonspecific; any drug that is appreciably soluble in oils can be solubilized. Each compound has a solubilization limit, which depends upon temperature and the nature and concentration of the surfactant. There are two general categories of solubilizates. The first consists of comparatively large, asymmetrical and rigid molecules such as steroids and dyes that form crystalline solids. Because of a dissimilarity in structure, these compounds do not blend in with the normal paraffin tails that make up the micellar cores but remain as distinct solute molecules. They are sparingly solubilized by micelles with only a few molecules/micelle at saturation (Table 21-6). The number of carbon atoms in the micellar hydrocarbon core required to solubilize one molecule of a steroid or dye at saturation is of the same order of magnitude as the number of carbon atoms in bulk liquid dodecane or hexadecane required to dissolve one molecule of steroid or dye at saturation.

Since solubilization depends on the presence of micelles, it does not take place below the CMC. Therefore, such solubilization may be used to determine the CMC, particularly when the solubilizate is a dye or another compound easy to assay. Plotting the maximum amount of a water-insoluble dye solubilized by an aqueous surfactant, or the absorbance of its saturated solutions, versus the surfactant concentration produces a straight line that intersects the surfactant concentration axis at the CMC. Above the CMC, the amount of solubilized dye is directly proportional to the number of micelles, and therefore, proportional to the overall surfactant concentration. Below the CMC, no solubilization takes place. This is represented by Curve E in Figure 21-11.

The second category of compounds that may be solubilized is often liquid at room temperature and consist of relatively small, symmetrical and/or flexible molecules such as many constituents of essential oils. These molecules mix and freely blend in with the hydrocarbon portions of the surfactants in the core of the micelles and, therefore, become indistinguishable from them. Such compounds are extensively solubilized and in the process usually swell the micelles. They augment the volume of the hydrocarbon core and increase the number of surfactant molecules per micelle. Their solubilization frequently lowers the CMC.

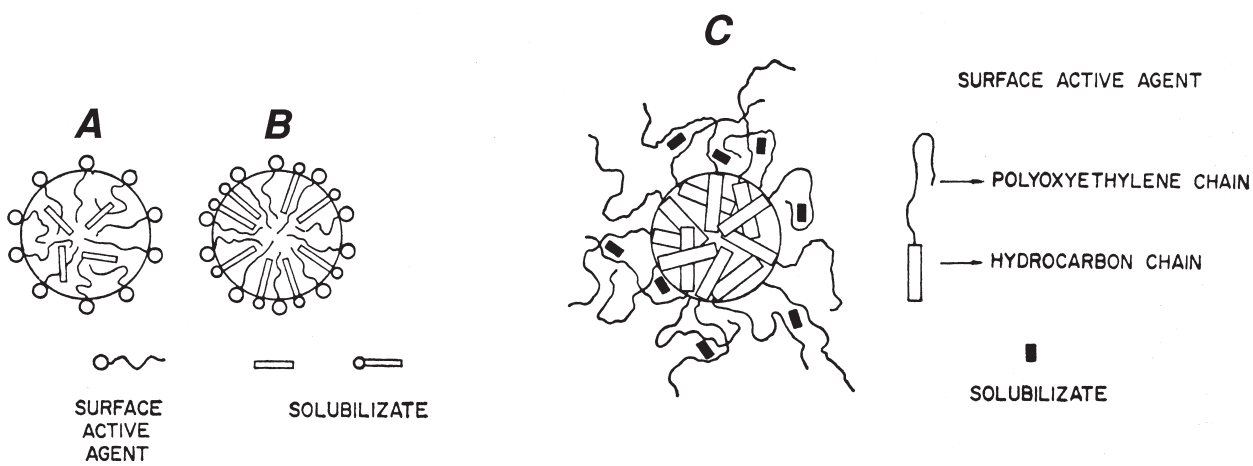


Figure 21-13. The locations of solubilizates in spherical micelles. **A.** Ionic surfactant (solubilized molecule has no hydrophilic groups); **B.** ionic surfactant (solubilized molecule has a hydrophilic group); **C.** nonionic surfactant (polar solubilizate). (From Shinoda K, Nakagawa T, Tamamushi B-I, Isemura T. *Colloidal Surfactants.* New York: Academic Press, 1963.)

Table 21-6. Micellar Solubilization Capacities of Different Surfactants for Estrone

SURFACTANT	CONCENTRATION RANGE (*M*)	TEMPERATURE (°C)	MOLES SURFACTANT/ MOLE SOLUBILIZED ESTRONE
Sodium laurate	0.025–0.23	40	91
Sodium oleate	0.002–0.35	40	53
Sodium lauryl sulfate	0.004–0.15	40	71
Sodium cholate	0.09–0.23	20	238
Sodium deoxycholate	0.007–0.36	20	476
Diamyl sodium sulfosuccinate	0.08–0.4	40	833
Dioctyl sodium sulfosuccinate	0.002–0.05	40	196
Tetradecyltrimethylammonium bromide	0.005–0.08	20	45
Hexadecylpyridinium chloride	0.001–0.1	20	32
Polysorbate 20	0.002–0.15	20	161
Polysorbate 60	0.0008–0.11	20	83

Data from Shinoda K, ed. *Solvent Properties of Surfactant Solutions.* New York: Dekker, 1967.

MICROEMULSIONS—O/W microemulsions are also formulated as aqueous vehicles for oil-soluble drugs to be administered by the percutaneous, oral, or parenteral routes. Oil-soluble drugs are incorporated into O/W emulsions by dissolving them in the oil phase before emulsification. Similarly, oil-soluble drugs are incorporated into microemulsions by prior dissolution within the oil phase. The advantage of microemulsions as dosage forms as compared to conventional emulsions is their smaller droplet size, which increases drug release, and their superior physical stability.

LIPOSOMES—Liposomes can be used as vehicles to deliver synthetic drugs, polypeptides, proteins, including enzymes and antibodies, and nucleic acids as well as recombinant DNA. Oil-soluble drugs are added to solutions of the lipid in organic solvents. Once the liposomes are formed, the drugs are solublilized by the hydrocarbon chains of the lipid bilayers. Water-soluble drugs are incorporated into the aqueous phase in which the liposomes are formed. The unencapsulated drug remaining in the external aqueous phase is then removed by dialysis, centrifugation, or ion exchange. *AmBisome Liposome for Injection* contains amphotericin B entrapped within a liposomal bilayer. Drugs have also been trapped within the inner, aqueous core of liposomes to protect them from enzymatic degradation as they circulate in the bloodstream.

An additional advantage of liposomes is their ability to target drugs to specific tissues in the body such as tumors. After IV administration, liposomes preferentially accumulate within tumors by what is known as the enhanced permeability and retention (EPR) effect because of their size. Tumor vasculature is typically more porous than most normal tissues of the body, which allows the permeation of colloidal sized materials. In addition, tumors typically lack significant lymphatic drainage, which results in the retention of these materials. The entrapped liposomes then slowly release the drug, resulting in a high local concentration and a low systemic exposure. This increases its effectiveness and decreases its side effects. Both *DaunoXome Lipsomal Injection*, which contains daunorubicin citrate, and *Doxil Lipsome Injection*, which contains doxorubicin HCl, are believed to operate by the EPR effect. The Doxil formulation utilizes "STEALTH" liposomes which have polyethylene glycol (PEG) derivatives attached to their surface to decrease detection by the reticuloendothelial system (RES), decrease clearance from the bloodstream, and extend circulation time. The attachment of PEG is also known as pegylation.

Liposomes dispersed in water are subject to degradation via hydrolysis of ester bonds and oxidation of unsaturated acyl chains, aggregation and fusion, as well as leakage of encapsulated drugs. Freeze-drying followed by rehydration and redispersion just prior to use is being investigated to extend their shelf life. The components of liposomes are similar to those of cell membranes. Therefore, they are nontoxic, biocompatible, and biodegradable. Liposomes have also been used as models to study the permeability of cell membranes.

MICROSPHERES—Microspheres are small, insoluble spherical particles consisting of a polymer matrix such as lactic/glycolic acid copolymer (PLGA).[46] Microspheres of gelatin or human serum albumin have been prepared in fairly narrow particle-size ranges from 10–20 nm through 45–55 μm. Drugs may be physically entrapped in the pores of the microspheres or chemically conjugated to the polymer matrix. Marketed drug products that utilize microspheres include *Lupron Depot for Suspension*, which is administered monthly by intramuscular injection and slowly releases leuprolide acetate, and *Nutropin Depot for Injectable Suspension*, which is administered 1–2× per month by subcutaneous injection and slowly releases somatropin of rDNA origin. In addition, microspheres have been labeled with a variety of β- and γ-emitting radionuclides such as ^{131}I, ^{99m}Tc, ^{113m}In, or ^{51}Cr. Such products have been used to scan the heart, brain, liver, urogenital and gastrointestinal tracts, and in pulmonary perfusion and inhalation studies.[45]

NANOPARTICLES—Nanoparticles are described in the chapter by Kreuter[42] as solid spherical polymeric particles ranging in size from 10 to 1000 nm (1 μm). The therapeutic agents are either adsorbed onto the nanoparticles, dissolved or dispersed throughout them, attached to their matrices by primary valences, trapped, or encapsulated. This definition of nanoparticles includes latexes, pseudolatexes, and even small microspheres, because it is not always easy to ascertain whether the particles consist of a solid, monolithic matrix or a shell, and whether the active ingredients are distributed throughout the particle or adsorbed onto its surface.

Polymeric nanoparticles are normally prepared in aqueous solutions of the drugs to be incorporated. Drugs having low water solubility may be solubilized by micelles. The most widely used technique is emulsion polymerization. It produces particles with controlled and fairly uniform sizes. Alternatively, preformed polymers are dissolved in a water-immiscible, low-boiling solvent, to which the drug is added, followed by emulsification in water, and finally heating to boil off the solvent. Another method is to dissolve the preformed polymers plus drugs in alcohol or acetone, and the solution is stirred into water.

In another approach, the water-soluble proteins gelatin and albumin are dissolved in water, the drugs are added, the pH is adjusted to the isoelectric point, and the proteins plus drugs are salted out with Na_2SO_4, $(NH_4)_2SO_4$ or alcohol. The coacervates are hardened by crosslinking with glutaraldehyde, and the particles are separated from the ice-cold suspension and dried. Intravenous suspensions require colloidal particles with sizes $<1\mu m$ in order to avoid blocking capillary blood vessels.

Nanoparticles of polymethacrylic acid esters, such as methyl and 2-hydroxyethyl, undergo very slow biodegradation. Polyalkylcyanoacrylate nanoparticles are more readily biodegraded. Aqueous dispersions of nanoparticles are far more stable than those of liposomes. Moreover, they can be spray-dried or freeze-dried and reconstituted much more successfully. Any surfactants present in the dried powders aid redispersion of the nanoparticles in saline.

Like liposomes, intravenously injected nanoparticles are readily taken up by the RES phagocytic cells of the liver, spleen, and lungs. Also like liposomes, surface modification may extend the blood circulation time of nanoparticles or target them to specific tissues.

DRUG-POLYMER CONJUGATES—Polymers have also been used to produce soluble drug-polymer conjugates, which are formed by chemical reactions to produce covalent bonds between a drug and a polymeric molecule.[47] These polymer conjugates include synthetic polymers as well as biological polymers such as globular and fibrous proteins, antibodies and polysaccharides. For example, *Mylotarg for Injection* (gemtuzumab ozogamicin) consists of a conjugate between an IgG monoclonal antibody and calicheamicin, a chemotherapeutic agent. These conjugates are administered by IV infusion and the antibody targets the CD33 antigen found on the surface of leukemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells. The antibody-drug conjugate is believed to have a lysomotropic mechanism of action, ie, the antibody-antigen complex is internalized into the cell through endocytosis and entrapped within endosomal compartments. These endosomes merge with primary lysosomes to form secondary lysosomes, where the drug-antibody bonds are presumably broken by the acidic environment or cleaved by certain lysosomal enzymes. Once cleaved from the antibody, the drug is able to diffuse out of the lysosome and exert its pharmacological effect.

In-111 and Y-90 Zevalin consists of a conjugate between an ibritumoab antibody (a murine IgG) and either an indium-111 or yttrium-90 radioisotope. These conjugates are administered by IV infusion and attach to the CD20 antigen found on the surface of normal and malignant B-lymphocytes. However, the antibody-antigen complex is not internalized. The attachment of the antibody induces cell apoptosis and the close proximity of the radioisotope creates free radicals that damage nearby cells. *PEG-Intron Powder for Injection* also consists of a conjugate. In this case, interferon α-2b is conjugated with a PEG derivative. The conjugates are injected subcutaneously. The PEG derivative prevents detection by the RES and, therefore, decreases the clearance of interferon α-2b from the body.

The actively targeted conjugates described above may be contrasted to passively targeted macromolecular conjugates for solid tumor tissue. Passively targeted macromolecular conjugates have shown preferential accumulation in solid tumors because of the EPR effect. The preferential accumulation reduces systemic toxicity by reducing damage to non-cancerous organs. In addition, the EPR effect is more effective for macromolecules greater than 40 kDa but negligible for smaller molecules that are cleared more rapidly from the tumor interstitium.[48,49] These macromolecular conjugates have also demonstrated the potential to overcome drug resistance. The large conjugate can be taken up into cells by endocytosis, bypassing a drug resistance mechanism of deficient drug transport.[50] This uptake process may also avoid ATP-driven efflux pumps for the free drug[51] as well as block overexpression of these pumps.[52]

A doxorubicin-HPMA [N-(2-hydroxypropyl) methacrylamide] conjugate has been studied in phase I clinical trials. The maximum tolerated dose of this conjugate is several times higher than that of the free drug. This observation was ascribed to the EPR effect.[53] A methotrexate-albumin conjugate was investigated to overcome the short *in vivo* half-life and low tumor accumulation rates of the free drug in phase I and II clinical trials in Germany.[54,55] A camptothecin PEG conjugate has been evaluated in a phase II clinical trial.[56] Other macromolecular drug conjugates under investigation include ampoly(styrene-*co*-maleic acid-half-*n*-butylate)-conjugated neocarzinostatin,[57] dextran-mitomycin C,[58] and gelatin-methotrexate.[59]

Excipients

Most of the excipients, adjuvants or non-therapeutic ingredients of dosage forms listed below are monographs in the NF or USP. Colloids are also used as pharmaceutical excipients for a variety of purposes including thickening agents. Colloidal thickening agents or viscosity builders belong to four chemical categories. *Semi-synthetic cellulose derivatives* include methylcellulose, carboxymethylcellulose sodium, hydroxypropyl methylcellulose, and hydroxypropyl cellulose. *Natural polymers* include acacia, tragacanth, xanthan gum, sodium alginate, and carrageenan. *Synthetic polymers* include carbomer, a co-polymer of acrylic acid; poloxamer, a block copolymer of ethylene oxide and propylene oxide; polyvinyl alcohol; and povidone (polyvinylpyrrolidone). *Particulate colloids* include bentonite, colloidal silicon dioxide, and microcrystalline cellulose. These viscosity builders may be used to decrease the dissolution rate of controlled release dosage forms, to decrease the sedimentation or creaming rates of dispersed systems, to improve the taste-masking abilities of liquid vehicles, and to provide consistency to ointments. Many of the water-soluble viscosity builders mentioned above are surface-active and are also used as emulsifying and suspending agents. Even particulate colloids are used to stabilize emulsions and suspensions.

Colloidal silicon dioxide is a white powder consisting of submicroscopic spherical particles of fairly uniform size in the range of 5–50 nm or higher. It is used to thicken liquid dosage forms and in tablets. The surface of colloidal silicon dioxide particles contains siloxane (Si-O-Si) and silanol (Si-OH) groups. When colloidal silicon dioxide powder is dispersed in nonpolar liquids, the particles tend to adhere to one another through hydrogen bonds between these surface groups. The spherical particles of finer grade colloidal silicon dioxide are linked together into short chain-like aggregates as shown in Figure 21-4. This creates loose three-dimensional networks that increase the viscosity of the liquid vehicles even at levels as low as a few percent. The hydrogen-bonded structures are torn apart by stirring but rebuilt while at rest, conferring a thixotropic nature to the thickened liquids.

Aerosil 200 is the grade most widely used as a pharmaceutical adjuvant. Its primary spheres, which are extensively sintered together, have an average diameter of 12 nm. At levels of 8 to 10%, it thickens liquids of low polarity such as vegetable and mineral oils to the consistency of ointments, imparting considerable yield values to them. Hydrogen-bonding liquids such as alcohols and water solvate the silica spheres, thereby reducing the hydrogen bonding between particles. Therefore, the higher silica levels of 12–18% or more are required to gel these solvents.

The grades that consist of relatively large and unattached spherical particles, such as those in Figure 21-3, are less efficient thickening agents because they lack the high specific surface area and asymmetry of the finer grades. The consistency of ointments thickened with colloidal silicon dioxide is not appreciably reduced at higher temperatures. Incorporation of colloidal silicon dioxide into ointments and pastes, such as those of zinc oxide, also reduces the syneresis or *bleeding* of the liquid vehicles.

Colloidal silicon dioxide is also used in dry dosage forms. The spherical particles are nonporous and have a density of 2.13 g/cm^3. However, the bulk density of their powder is a mere 0.05 g/cm^3. Because the powder is extremely light, it is frequently used to increase the fluffiness or bulk volume of powder formulations. In addition, the high porosity of colloidal silica enables it to absorb a variety of liquids from fluid fragrances to viscous tars, transforming them into free-flowing powders that can be incorporated into tablets or capsules. The porosity in colloidal silicon dioxide is due entirely to the enormous void space between the particles, which themselves are solid. When these ultrafine particles are incorporated at levels as low as 0.1–0.5% into a powder consisting of coarse particles or granules, they coat the surface of the granules and act as tiny ball bearings and spacers. This improves the flowability of the powder and eliminates caking, which is important in tableting. In addition, colloidal silicon dioxide is used to improve tablet disintegration. It is also used as a glidant and as a moisture absorber.

Microcrystalline cellulose is manufactured by controlled hydrolysis of purified native cellulose, which dissolves the amor-

phous matrix but leaves the crystallites intact. The needle or rod-shaped crystallites act as suspending agents in water, producing thixotropic structured vehicles. At concentrations of about 15%, the cellulose microcrystals gel water to an ointment consistency by swelling and producing a continuous network of rods that extends throughout the entire vehicle. Attraction between the elongated particles is presumably due to flocculation in the secondary minimum. Treatment of the microcrystalline mass with sodium carboxymethylcellulose facilitates its disintegration into primary needle-shaped particles and enhances their thickening action.

Gelatinous precipitates of inorganic hydrophilic compounds such as *aluminum hydroxide gel, aluminum phosphate gel,* and *magnesium hydroxide* consist of coarse flocs produced by the agglomeration of colloidal particles formed in the initial stage of precipitation. They possess large internal surface areas, which is one of the reasons why the first two are used as substrates for adsorbed vaccines and toxoids. *Alumina and magnesia oral suspensions*, a mixture of gelatinous precipitated aluminum and magnesium hydroxides, as well as aluminum hydroxide gel, are used as antacids.

Gelation is used to manufacture the following suppository bases: glycerinated gelatin suppositories; glycerin suppositories (in which glycerin is solidified with sodium stearate that crystallizes out as a network of needles upon cooling the hot solution); and polyethylene glycol suppositories (in which low molecular-weight liquid PEGs, such as PEG 400, are stiffened by high molecular-weight PEGs such as 3350 or 4000, which are waxy solids). A pharmaceutical application of gelation in a nonaqueous medium is the manufacture of *Plastibase* or *Jelene* (*Squibb*), which is prepared using 5% of a low-molecular-weight polyethylene and 95% of mineral oil. The polymer is soluble in mineral oil above 90°C, which is close to its melting point. When the solution is cooled below 90°C, the polymer precipitates and causes gelation. The mineral oil is immobilized in the network of entangled, adhering, insoluble polyethylene chains, which probably even associate into small crystalline regions. Unlike petrolatum, this gel can be heated to about 60°C without any substantial loss in consistency.

Crospovidone and croscarmellose sodium are crosslinked povidone and carboxymethylcellulose sodium, respectively. These crosslinked polymers swell rapidly and extensively in aqueous media and, therefore, are frequently used as tablet disintegrants. Starch performs the same function; its major constituent, amylopectin, is highly branched and insoluble in water but swells considerably. Because crosslinked hydrophilic polymers swell extensively without dissolution, they are also used as matrices for controlled-release dosage forms.

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CHAPTER 22

Coarse Dispersions

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This chapter includes the formation of suspensions and emulsions and the factors that influence their stability and performance as dosage forms. For the purpose of the present discussion, a dispersed system, or dispersion, will be regarded as a two-phase system in which one phase is distributed as particles or droplets in the second, or continuous, phase. In these systems, the dispersed phase frequently is referred to as the discontinuous or internal phase, and the continuous phase is called the external phase or dispersion medium. Discussion will be restricted to those solid–liquid and liquid–liquid dispersions that are of pharmaceutical significance, namely, suspensions and emulsions. However, more complicated phase systems (eg, a combination of liquid and liquid crystalline phases) can exist in emulsions. This situation will be discussed in the section dealing with emulsions.

All dispersions may be classified into three groups based on the size of the dispersed particles. Chapter 21 deals with one such group—colloidal dispersions—in which the size of the dispersed particles is in the range of approximately 1 nm to 0.5 μm. Molecular dispersions, the second group in this classification, are discussed in Chapter 20. The third group, consisting of *coarse dispersions* in which the particle size exceeds 0.5 μm, is the subject of this chapter. Knowledge of coarse dispersions is essential for the preparation of both pharmaceutical suspensions (solid–liquid dispersions) and emulsions (liquid–liquid dispersions).

THE DISPERSION STEP

The pharmaceutical formulator is concerned primarily with producing a smooth, uniform, easily flowing (pouring or spreading) suspension or emulsion in which dispersion of particles can be effected with minimum expenditure of energy.

In preparing suspensions, particle–particle attractive forces need to be overcome by the high shearing action of such devices as the colloid mill, or by use of surface-active agents. The latter greatly facilitate wetting of lyophobic powders and assist in the removal of surface air that shearing alone may not remove; thus, the clumping tendency of the particles is reduced. Moreover, lowering of the surface free energy by the adsorption of these agents directly reduces the thermodynamic driving force opposing dispersion of the particles.

In emulsification, shear rates are frequently necessary for dispersion of the internal phase into fine droplets. The shear forces are opposed by forces operating to resist distortion and subsequent breakup of the droplets. Again surface-active agents help greatly by lowering interfacial tension, which is the primary reversible component resisting droplet distortion. Surface-active agents also may play an important role in determining whether an oil-in-water (O/W) or a water-in-oil (W/O) emulsion preferentially survives the shearing action.

Once the process of dispersion begins there develops simultaneously a tendency for the system to revert to an energetically more stable state, manifested by flocculation, coalescence, sedimentation, crystal growth, and caking phenomena. If these physical changes are not inhibited or controlled, successful dispersions will not be achieved or will be lost during shelf-life.

INTERFACIAL PROPERTIES

Because suspensions and emulsions are dispersions of one phase within another, the process of dispersion creates a tremendous increase in interfacial area between the dispersed particles or droplets and the dispersion medium. When considering the interfacial properties of dispersed particles, two factors must be taken into account, regardless of whether the dispersed phase is solid or liquid. The first relates to an increase in the free energy of the surface as the particle size is reduced and the specific surface increased. The second deals with the presence of an electrical charge on the surface of the dispersed particles.

SURFACE FREE ENERGY—When solid and liquid materials are reduced in size, they tend to agglomerate or stick together. This clumping, which can occur either in an air or liquid medium, is an attempt by the particles to reduce the excess free energy of the system. The increase in surface free energy is related to the increase in surface area produced when the mean particle size is reduced. It may be expressed as

$$\Delta F = \gamma \Delta A \qquad (1)$$

where ΔF is the increase in surface free energy in ergs, ΔA is the increase in surface area in cm^2, and γ is the interfacial tension in dyne/cm, between the dispersed particle or droplet and the dispersion medium. The smaller ΔF is, the more thermodynamically stable is the suspension of particles. A reduction in ΔF is effected often by the addition of a wetting agent (discussed in Chapter 20), which is adsorbed at the interface between the particle and the vehicle, thereby reducing the interfacial tension. This causes the particles to remain dispersed and settle relatively slowly. Unfortunately, in solid–liquid suspensions, the particles can form a hard cake at the bottom of the container when they eventually settle. Such a sediment, which can be extremely difficult to redisperse, can lead to dosing errors when the product is administered to the patient.

SURFACE POTENTIAL—As discussed in Chapter 20, both attractive and repulsive forces exist between particles in a liquid medium. The balance between these opposing forces determines whether two particles approaching each other actually make contact or are repulsed at a certain distance of separation. Although much of the theoretical work on electrical surface potentials has been carried out on lyophobic colloids, the theories developed in this area have been applied to suspensions and emulsions.

SUSPENSIONS

A *pharmaceutical suspension* may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. Because some products occasionally are prepared in a dry form to be placed in suspension at the time of dispensing by the addition of an appropriate liquid vehicle, this definition is extended to include these products.

Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, instilled intranasally, inhaled into the lungs, applied to the skin as topical preparations, or used for ophthalmic purposes in the eye. They are an important class of dosage form that can offer several advantages. Suspensions offer an alternative oral dosage form for patients who cannot swallow a tablet or capsule such as pediatric and geriatric patients. Oral antibiotics, analgesic and antipyretic drugs are commonly administered as suspensions to these groups of patients. Suspensions are often used to deliver pooly water-soluble drugs that cannot be formulated as a solution. In addition, drugs that have an unpleasant taste may preferably be formulated as a suspension to reduce interaction of drug with taste receptors in the mouth. Because suspended drug must undergo a dissolution step prior to crossing biological membranes, suspensions offer a way to provide sustained release of drug by parenteral, topical, and oral routes of administration

There are certain criteria that a well-formulated suspension should meet. The dispersed particles should be of such a size that they do not settle rapidly in the container. However, in the event that sedimentation does occur, the sediment must not form a hard cake. Rather, it should be capable of redispersion with a minimum of effort on the part of the patient. Finally, the product should be easy to pour, have a pleasant taste, and be resistant to microbial attack.

The three major concerns associated with suspensions are

1. Ensuring adequate dispersion of the particles in the vehicle.
2. Minimizing settling of the dispersed particles.
3. Preventing caking of these particles when a sediment forms.

Much of the following discussion will deal with the factors that influence these processes and the ways in which settling and caking can be minimized.

FLOCCULATION AND DEFLOCCULATION—Zeta potential, φ_z, is a measurable indication of the potential existing at the surface of a particle. When φ_z is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be *deflocculated*. Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of φ_z. At some concentration of the added ion, the electrical forces of repulsion are lowered sufficiently and the forces of attraction predominate. Under these conditions the particles may approach each other more closely and form loose aggregates, termed *flocs*. Such a system is said to be *flocculated*.

Some workers restrict the term "flocculation" to the aggregation brought about by chemical bridging; aggregation involving a reduction of repulsive potential at the double layer is referred to as *coagulation*. Other workers regard flocculation as aggregation in the secondary minimum of the potential energy curve of two interacting particles and coagulation as aggregation in the primary minimum. In the present chapter, the term *flocculation* is used for all aggregation processes, irrespective of mechanism.

The continued addition of the flocculating agent can reverse the above process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anions onto positively charged, deflocculated particles in suspension will lead to flocculation. The addition of more anions eventually can generate a net negative charge on the particles. When this has achieved the required magnitude, deflocculation may occur again. The only difference from the starting system is that the net charge on the particles in their deflocculated state is negative rather than positive. Some of the major differences between suspensions of flocculated and deflocculated particles are presented in Table 22-1.

FLOCCULATION KINETICS—The rate at which flocculation occurs is a consideration in the stability of suspended dispersions. Whether flocculation is judged to be rapid or slow depends on the presence of a repulsive barrier between adjacent particles. In the absence of such a barrier, and for a monodispersed system, rapid flocculation occurs at a rate given by the Smoluchowski equation

$$\delta N/\delta t = -4\pi DRN^2 \qquad (2)$$

where $\delta N/\delta t$ is the disappearance rate of particles/mL, R is the distance between the centers of the two particles in contact, N is the number of particles per mL, and D is the diffusion coefficient. Under these conditions the rate is proportional to the square of the particle concentration. The presence or absence of an energy barrier is influenced strongly by the type and concentration of any electrolyte present. When an energy barrier does exist between adjacent particles, the flocculation rate likely will be much smaller than predicted by Equation 2.

SETTLING AND ITS CONTROL

To control the settling of dispersed material in suspension, the pharmacist must be aware of those physical factors that will af-

Table 22-1. Relative Properties of Flocculated and Deflocculated Particles in Suspension

DEFLOCCULATED	FLOCCULATED
1. Particles exist in suspension as separate entities.	1. Particles form loose aggregates.
2. Rate of sedimentation is slow, as each particle settles separately and particle size is minimal.	2. Rate of sedimentation is high, as particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	3. A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed that is difficult, if not impossible, to redisperse.	4. The sediment is packed loosely and possesses a scaffold-like structure. Particles do not bond tightly to each other, and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.
5. The suspension has a pleasing appearance, as the suspended material remains suspended for a relatively long time. The supernate also remains cloudy, even when settling is apparent.	5. The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.

fect the rate of sedimentation of particles under ideal and nonideal conditions. Also important are the various coefficients used to express the amount of flocculation in the system and the effect flocculation will have on the structure and volume of the sediment.

Sedimentation Rate

The rate at which particles in a suspension sediment is related to their size and density and the viscosity of the suspension medium. Brownian movement may exert a significant effect, as will the absence or presence of flocculation in the system.

STOKES' LAW—The velocity of sedimentation of a uniform collection of spherical particles is governed by *Stokes' law,* expressed as

$$v = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta} \qquad (3)$$

where v is the terminal velocity in cm/sec, r is the radius of the particles in cm, ρ_1 and ρ_2 are the densities (g/cm^3) of the dispersed phase and the dispersion medium, respectively, g is the acceleration due to gravity (980.7 cm/sec^2), and η is the Newtonian viscosity of the dispersion medium in poises (g/cm sec). Stokes' law holds only if the downward motion of the particles is not sufficiently rapid to cause turbulence. Micelles and small phospholipid vesicles do not settle unless they are subjected to centrifugation.

While conditions in a pharmaceutical suspension are not in strict accord with those laid down for Stokes' law, Equation 3 provides those factors that can be expected to influence the rate of settling. Thus, sedimentation velocity will be reduced by decreasing the particle size, provided that the particles are kept in a deflocculated state. The rate of sedimentation will be an inverse function of the viscosity of the dispersion medium.

However, too high a viscosity is undesirable, especially if the suspending medium is Newtonian rather than shear-thinning (see Chapter 23), because it then becomes difficult to redisperse material that has settled. It also may be inconvenient to remove a viscous suspension from its container. When the size of particles undergoing sedimentation is reduced to approximately 2 μm, random Brownian movement is observed and the rate of sedimentation departs markedly from the theoretical predictions of Stokes' law. The actual size at which Brownian movement becomes significant depends on the density of the particle as well as the viscosity of the dispersion medium.

EFFECT OF FLOCCULATION—In a deflocculated system containing a distribution of particle sizes, the larger particles naturally settle faster than the smaller particles. The very small particles remain suspended for a considerable length of time, with the result that no distinct boundary is formed between the supernatant and the sediment. Even when a sediment becomes discernible, the supernatant remains cloudy.

When the same system is flocculated (in a manner to be discussed later), two effects are immediately apparent. First, the flocs tend to fall together, so a distinct boundary between the sediment and the supernatant is readily observed; second, the supernatant is clear, showing that the very fine particles have been incorporated into the flocs. The initial rate of settling in flocculated systems is determined by the size of the flocs and the porosity of the aggregated mass. Under these circumstances it is perhaps better to use the term *subsidence,* rather than sedimentation.

Quantitative Expressions of Sedimentation and Flocculation

Frequently, the pharmacist needs to assess a formulation in terms of the amount of flocculation in the suspension and compare this with that found in other formulations. The two parameters commonly used for this purpose are outlined below.

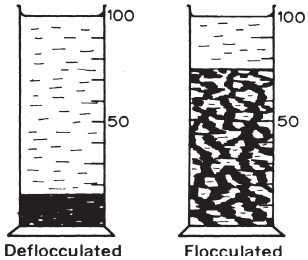


Figure 22-1. Sedimentation parameters of suspensions. Deflocculated suspension: $F\infty = 0.15$. Flocculated suspension: $F = 0.75$; $\beta = 5.0$.

SEDIMENTATION VOLUME—The *sedimentation volume, F,* is the ratio of the equilibrium volume of the sediment, V_u, to the total volume of the suspension, V_0. Thus,

$$F = V_u/V_o \qquad (4)$$

As the volume of suspension that appears occupied by the sediment increases, the value of F, which normally ranges from nearly 0 to 1, increases. In the system where $F = 0.75$, for example, 75% of the total volume in the container is apparently occupied by the loose, porous flocs forming the sediment. This is illustrated in Figure 22-1. When $F = 1$, no sediment is apparent even though the system is flocculated. This is the ideal suspension for, under these conditions, no sedimentation will occur. Caking also will be absent. Furthermore, the suspension is esthetically pleasing, there being no visible, clear supernatant.

DEGREE OF FLOCCULATION—A better parameter for comparing flocculated systems is the *degree of flocculation,* β, which relates the sedimentation volume of the flocculated suspension, F, to the sedimentation volume of the suspension when deflocculated, $F\infty$. It is expressed as

$$\beta = F/F_\infty \qquad (5)$$

The degree of flocculation is, therefore, an expression of the increased sediment volume resulting from flocculation. If, for example, β has a value of 5.0 (see Fig 22-1), this means that the volume of sediment in the flocculated system is five times that in the deflocculated state. If a second flocculated formulation results in a value for β of say 6.5, this latter suspension obviously is preferred, if the aim is to produce as flocculated a product as possible. As the degree of flocculation in the system decreases, β approaches unity, the theoretical minimum value.

FORMULATION OF SUSPENSIONS

The formulation of a suspension possessing optimal physical stability depends on whether the particles in suspension are to be flocculated or to remain deflocculated. One approach involves use of a structured vehicle to keep deflocculated particles in suspension; a second depends on controlled flocculation as a means of preventing cake formation. A third, a combination of the two previous methods, results in a product with optimum stability. The various schemes are illustrated in Figure 22-2.

DISPERSION OF PARTICLES—The dispersion step has been discussed earlier in this chapter. Surface-active agents commonly are used as wetting agents; maximum efficiency is obtained when the HLB value lies within the range of 7 to 9. A concentrated solution of the wetting agent in the vehicle may be used to prepare a slurry of the powder; this is diluted with the required amount of vehicle. Alcohol and glycerin may be used sometimes in the initial stages to disperse the particles, thereby allowing the vehicle to penetrate the powder mass.

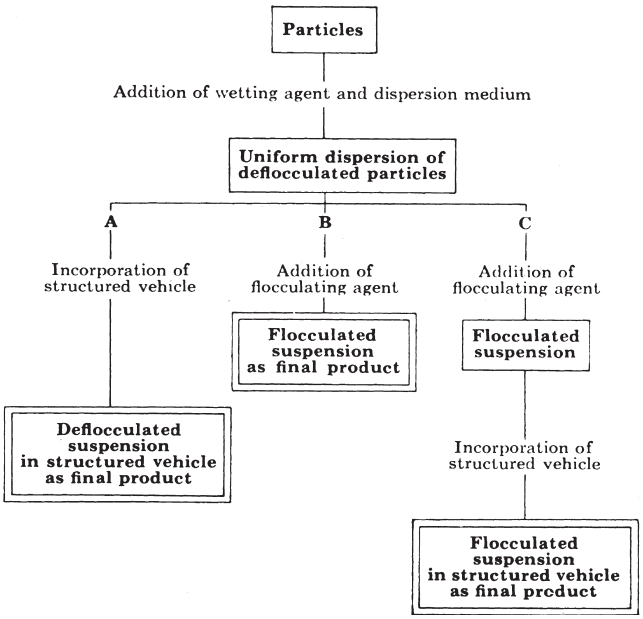


Figure 22-2. Alternative approaches to the formulation of suspensions.

Only the minimum amount of wetting agent should be used, compatible with producing an adequate dispersion of the particles. Excessive amounts may lead to foaming or impart an undesirable taste or odor to the product. Invariably, as a result of wetting, the dispersed particles in the vehicle are deflocculated.

STRUCTURED VEHICLES—*Structured vehicles* are generally aqueous solutions of polymeric materials, such as the hydrocolloids, that are usually negatively charged in aqueous solution. Typical examples are methylcellulose, carboxymethylcellulose, bentonite, and carbomer. The concentration employed will depend on the consistency desired for the suspension that, in turn, will relate to the size and density of the suspended particles. They function as viscosity-imparting suspending agents and, as such, reduce the rate of sedimentation of dispersed particles.

The rheological properties of suspending agents are considered elsewhere (Chapter 23). Ideally, these form pseudo-plastic or plastic systems that undergo shear-thinning. Some degree of thixotropy is also desirable. Non-Newtonian materials of this type are preferred over Newtonian systems because, if the particles eventually settle to the bottom of the container, their redispersion is facilitated by the vehicle thinning when shaken. When the shaking is discontinued, the vehicle regains its original consistency, and the redispersed particles are held suspended. This process of redispersion, facilitated by a shear-thinning vehicle, presupposes that the deflocculated particles have not yet formed a cake. If sedimentation and packing have proceeded to the point where considerable caking has occurred, redispersion is virtually impossible.

CONTROLLED FLOCCULATION—When using the controlled flocculation approach (see Fig 22-2*B* and *C*), the formulator takes the deflocculated, wetted dispersion of particles and attempts to bring about flocculation by the addition of a flocculating agent; most commonly, these are electrolytes, polymers, or surfactants. The aim is to *control* flocculation by adding that amount of flocculating agent that results in the maximum sedimentation volume.

FLOCCULATION USING ELECTROLYTES—*Electrolytes* are probably the most widely used flocculating agents. They act by reducing the electrical forces of repulsion between particles, thereby allowing the particles to form the loose flocs so characteristic of a flocculated suspension. As the ability of particles to come together and form a floc depends on their surface charge, zeta potential measurements on the suspension, as an electrolyte is added, provide valuable information as to the extent of flocculation in the system.

This principle is illustrated by reference to the following example, taken from the work of Haines and Martin.[2] Particles of sulfamerazine in water bear a negative charge. The serial addition of a suitable electrolyte, such as aluminum chloride, causes a progressive reduction in the zeta potential of the particles. This is due to the preferential adsorption of the trivalent aluminum cation. Eventually, the zeta potential will reach zero and then become positive as the addition of $AlCl_3$ is continued.

If sedimentation studies are run simultaneously on suspensions containing the same range of $AlCl_3$ concentrations, a relationship is observed (Fig 22-3) between the sedimentation volume F, the presence or absence of caking, and the zeta potential of the particles. To obtain a flocculated, noncaking suspension with the maximum sedimentation volume, the zeta potential must be controlled so as to lie within a certain range (generally less than 25 mV). This is achieved by the judicious use of an electrolyte. A comparable situation is observed when a negative ion such as PO_4^{3-} is added to a suspension of positively charged particles such as bismuth subnitrate.

Work by Matthews and Rhodes[3–5] involving both experimental and theoretical studies has confirmed the formulation principles proposed by Martin and Haines. The suspensions used by Matthews and Rhodes contained 2.5% *w/v* of griseofulvin as a fine powder together with the anionic surfactant sodium dioxyethylated dodecyl sulfate (10^{-3} mcolar) as a wetting agent. Increasing concentrations of aluminum chloride were added and the sedimentation height (equivalent to the sedimentation volume, see Chapter 21) and the zeta potential recorded. Flocculation occurred when a concentration of 10^{-3} molar aluminum chloride was reached. At this point the zeta potential had fallen from −46.4 to −17.0 mV. Further reduction of the zeta potential, to −4.5 mV by use of 10^{-2} molar aluminum chloride did not increase sedimentation height, in agreement with the principles shown in Figure 22-3.

Matthews and Rhodes then went on to show, by computer analysis, that the DLVO theory (see Chapter 21) predicted the results obtained—namely, that the griseofulvin suspensions under investigation would remain deflocculated when the concentration of aluminum chloride was 10^{-4} molar or less. Only at concentrations in the range of 10^{-3} to 10^{-2} molar aluminum

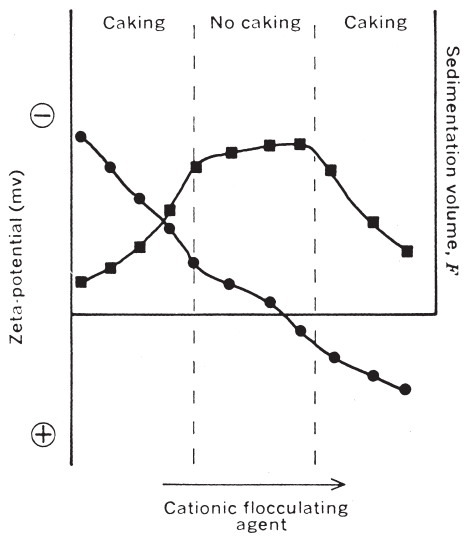


Figure 22-3. Typical relationship between caking, zeta potential, and sedimentation volume, as a positively charged flocculating agent is added to a suspension of negatively charged particles. ●: zeta potential. ■: sedimentation volume.

chloride did the theoretical plots show deep primary minima, indicative of flocculation. These occurred at a distance of separation between particles of approximately 50 Å, which led Matthews and Rhodes to conclude that coagulation had taken place in the primary minimum.

Schneider et al[6] have published details of a laboratory investigation (suitable for undergraduates) that combines calculations based on the DLVO theory carried out with an interactive computer program with actual sedimentation experiments performed on simple systems.

FLOCCULATION BY POLYMERS—*Polymers* can play an important role as flocculating agents in pharmaceutical suspensions. As such, polymers can have an advantage over ionic flocculating agents in that they are less sensitive to added electrolytes. This leads to a greater flexibility in the use of additives such as preservatives, flavoring, and coloring agents that might be needed for the formulation.

The effectiveness of a polymer as a stabilizing agent for suspensions primarily depends on the affinity of the polymer for the particle surface as well as the charge, size, and orientation of the polymer molecule in the continuous phase. Many pharmaceutically useful polymers contain polar functional groups that are separated by a hydrocarbon backbone. As a result of this structure, a polymer molecule may adsorb to particle surfaces while maintaining a degree of interaction with the solvent. As observed with ionic flocculating agents, polymers can produce both flocculated and deflocculated suspensions. It is believed that the primary mechanism by which polymers act as flocculants is due to the bridging of the polymer between the surfaces of different particles. The effect can be highly concentration dependent as illustrated in Figure 22-4. The effect has been interpreted as follows.

At very low concentrations of polymer, a large number of sites on the surface of the dispersed solid are available for adsorption of polymer. Bridging between particles occurs as a result of the simultaneous adsorption of a polymer molecule onto the surfaces of different particles. At very low polymer concentrations, the number of particle–particle bridges is relatively low. At somewhat higher concentrations of polymer, sufficient binding sites are still available on the particles, permitting additional interparticle attachments to form. It is these intermediate concentrations that result in optimum flocculation and sedimentation volume. At high concentrations of polymer, complete coverage of the particle surface with polymer occurs and insufficient binding sites remain on the particles to permit interparticle bridging. In this case, the degree of flocculation is low, but the close association of individual particles is inhibited by a phenomenon known as steric stabilization. In general, *steric stabilization* refers to the ability of adsorbed polymers to prevent close approach and cohesion of dispersed particles due to the fact that the mixing of polymers adsorbed at the particle surfaces is energetically unfavorable. Suspensions formulated with relatively high concentrations of polymer would be deflocculated and therefore tend to have small sedimentation volumes.

Flocculation using polymers may be influenced by the length of time and magnitude of mixing during the formulation process. In some cases, gentle mixing could result in a flocculated suspension; however, continued or more vigorous mixing could result in reorientation of the polymer at the particle surface with fewer interparticle bridges formed. The opposite phenomenon may also occur. Polymers are also frequently used to produce structured vehicles with relatively high viscosity. This effect may overshadow any effect on flocculation and is typically considered the most important use for pharmaceutical polymers in suspensions. Practical considerations in the formulation of suspensions using polymers have been presented by Scheer.[7]

The sedimentation volume achieved by addition of polymeric flocculating agents may or may not agree with DLVO theory. For example, Kellaway and Najib[8] found that sulfadimidine suspensions stabilized with the anionic polymer sodium carboxymethylcellulose obeyed the expected relationship between electrophoretic mobility, a measurement that is proportional to zeta potential, and to sedimentation volume in agreement with Figure 22-3. However, stabilization of the suspension with the nonionic polymer polyvinylpyrrolidone (PVP) did not obey the expected relationship between electrophoretic mobility and sedimentation volume. At high concentrations of PVP, particles had a low zeta potential, but contrary to the predictions of Figure 22-3 a low sedimentation volume was observed. Although adsorption of the polymer reduced the charge at the plane of shear, flocculation did not occur. This is believed to be due to steric stabilization of the particles at high concentrations of PVP with few interparticle bonds resulting in a low degree of flocculation.

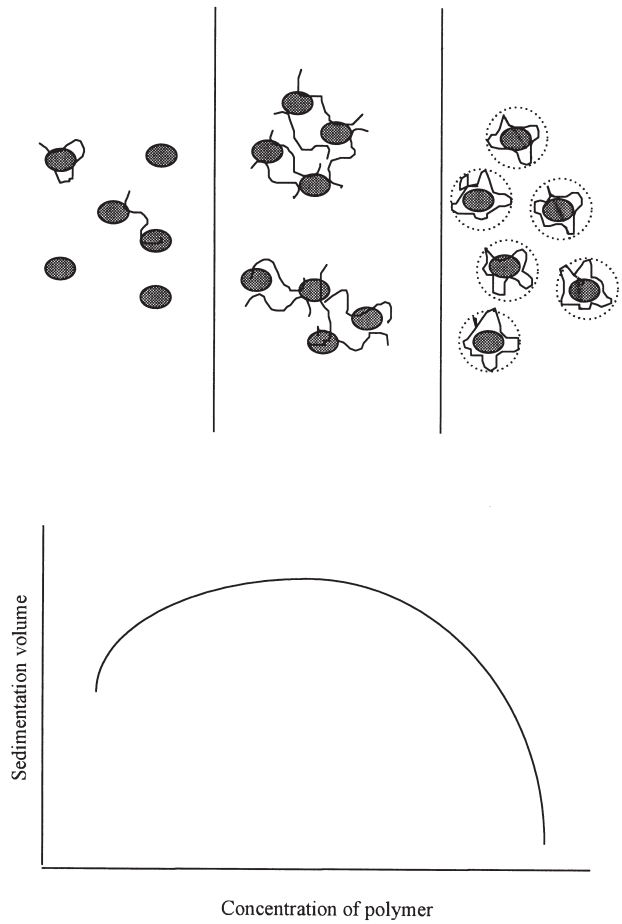


Figure 22-4. Flocculation by hydrophilic polymers. Optimal degree of flocculation and sedimentation volume occurs when a large number of interparticle bridges are formed. High concentrations of polymer result in a deflocculated suspension via steric repulsion.

The conformation of the polymers in the continuous phase may also have an effect on the degree of flocculation. At concentrations where flocculation occurs, polymers that have a linear conformation in the continuous phase will generally be more effective flocculants than polymers that are coiled in the continuous phase.

In some situations, a combination of polymeric and ionic flocculating agents have been used. In general, the sensitivity of the dispersed solid to flocculation by added electrolyte is enhanced by the presence of the polymer.

Table 22-2 contains a list of suspending agents that have been used in the formulation of pharmaceutical suspensions. Many of these can serve dual functions as flocculating/stabilizing and viscosity enhancing agents.

FLOCCULATION USING DETERGENTS—Both ionic and nonionic *detergents* can be used to produce flocculation in suspensions. Ionic detergents can produce flocculation in a

Table 22-2. Suspending Agents Used in the Formulation of Pharmaceutical Suspensions

TYPE OF POLYMER	EXAMPLES	STRUCTURE	COMMERCIAL NAMES
Cellulose derivatives			
Anionic	Carboxymethylcellulose (CMC)	Cellulose ether	
	Microcrystalline cellulose blends	Crystalline cellulose + cellulose ether	Avicel
Nonionic	Methylcellulose (MC)	Cellulose ether	Methocel, Metocel, Tylopur, Culminol, Celocol, Walsroder
	Ethylcellulose (EC)		EC - Ethocel
	Hydroxyethylcellulose (HEC)		HEC - Natrasol, Cellocize, Bermocol, Tylose, Blanose
	Hydroxypropylcellulose (HPC)		HPC - Klucel, Lacrisert
	Hydroxypropylmethylcellulose (HPMC)		HPMC - Methocel, Methlose, Pharmacoat, Culminol, Tylose, Celocol
Natural polymers			
Anionic	Alginates, carageenan, xanthan gum, acacia, tragacanth	Polysaccharide	
Nonionic	Locust bean gum, guar gum	Polysaccharide	
Synthetic polymers			
Anionic	Carbomers	Crosslinked polyacrylate	Carbopol
Nonionic	Polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) poloxamer		Plasdone, Povidone, Kollidon
Clays	Magnesium aluminum silicate (Veegum), bentonite	Hydrated aluminum silicate	
	Hectorite	Magnesium hectorite	

manner that is similar to other electrolytes; they can reduce the zeta potential of the dispersed particles. Nonionic detergents have also been observed to reduce the zeta potential of dispersed particles. Both flocculation and deflocculation can occur. Relatively high concentrations of nonionic detergents can form a hydrated layer around particles that can lead to deflocculation via a mechanism that is similar to steric stabilization described for polymers. Alternatively, some liquid detergents can induce flocculation through the formation of liquid bridges between particles. High-molecular-weight detergents would be expected to behave similarly to polymers with regard to their action as a flocculant or stabilizer of suspensions.

FLOCCULATION IN STRUCTURED VEHICLES—The ideal formulation for a suspension would seem to be when flocculated particles are supported in a structured vehicle. As shown in Figure 22-2 (under *C*), the process involves dispersion of the particles and their subsequent flocculation. Finally, a lyophilic polymer is added to form the structured vehicle. In developing the formulation, care must be taken to ensure the absence of any incompatibility between the flocculating agent and the polymer used for the structured vehicle. A limitation is that virtually all the structured vehicles in common use are hydrophilic colloids and carry a negative charge. This means that an incompatibility arises if the charge on the particles is originally negative. Flocculation in this instance requires the addition of a positively charged flocculating agent or ion; in the presence of such a material, the negatively charged suspending agent may coagulate and lose its suspendability. This situation does not arise with particles that bear a positive charge, as the negative flocculating agent that the formulator must employ is compatible with the similarly charged suspending agent.

A method that can be used to circumvent incompatibilities between an anionic suspending agent and a cationic flocculating agent is to reverse the charge on the particle through the use of a positively charged surface active material such as gelatin. Adsorption of gelatin to the surface of a negatively charged particle can reverse the particle charge when the continuous phase is adjusted to a relatively low pH. This may permit flocculation to be achieved with an anionic flocculating agent such as citrate ion or phosphate ion. Addition of these flocculating agents would be compatible with polymeric suspending agents that largely consist of molecules of anionic charge. Martin *et al*[9] have suggested that this effect can also be achieved using surface active amines, provided their toxicity does not prevent their use.

PARTICLE SIZE AND DISTRIBUTION—Particle size is an important consideration for the physical stability of a suspension. As predicted by Stokes' law, particles of small diameter tend to settle more slowly compared to larger particles; however, small particles will have an increased tendency to cake upon settling if they are not flocculated. In addition, particle–particle interactions can also have a significant effect on suspension stability. For suspensions with a relatively high percentage of solids, interparticle interactions may produce more viscous or thixotropic dispersions. Smaller particles will have a high surface area/weight ratio that favors interactions between the particles and may produce desirable rheological characteristics.

In addition to the effects on the physical properties of a suspension, particle size has important implications on the biopharmaceutical performance of the drug. Aqueous suspensions can effectively serve as a means to deliver poorly water-soluble drugs by the enteral, parenteral, and topical routes. For drugs whose solubility in water is low, the dissolution rate of the drug particles may be a primary factor that limits absorption of the drug. In these cases, the rate and extent of absorption of the drug may be enhanced through the use of small particles. Small particles dissolve faster than larger particles due to the increased surface area per unit weight of drug of the former. Lastly, the uniformity of dosing over the life of the product will be enhanced by ensuring that a relatively small particle size is achieved. This is especially true for suspensions whose individual doses are withdrawn from a larger container, such as suspensions for oral use. Additional information on the bioavailability of drug from suspensions is presented at the end of this chapter.

As most pharmaceutical powders are polydipserse rather than monodisperse, the distribution of particle sizes may also play an important role in the physical stability of a suspension. A relatively narrow distribution of particle sizes is desirable for good stability. A narrow particle size distribution provides a more uniform settling rate and allows for better predictability of suspension properties from batch to batch of finished suspension. In addition, the phenomenon of Ostwald ripening will be minimized when the distribution of particles is narrow. *Ostwald ripening* is the phenomenon in which larger particles grow in size due to the dissolution of smaller particles. This phenomenon could result in pharmaceutically unstable suspensions (caking) and alter the bioavailability of the product through an alteration in the dissolution rate. The use of an appropriate polymer with an affinity for the surface of the dispersed solid reduces or eliminates crystallization in suspensions that may occur due to Ostwald ripening or dissolution/crystallization phenomenon caused by temperature fluctuations. This effect occurs at concentrations of polymer that provide complete surface coverage of the particles. Thus, a hydrophilic colloid, such as a cellulose derivative, with high affinity for the particle surface is often added initially to the suspension formulation to provide a protective action.

In flocculated suspensions, a narrow distribution of particles also tends to result in floccules with a more opened structure. If a flocculated suspension is prepared using a powder with a wide distribution of particles, the floccules would consist of links between larger particles with small particles filling the voids created by the interparticle links between larger particles. This would create a floccule that is more dense compared to the more open structure that would be expected from a floccule composed of particles of more uniform size. The more opened floc structure is desirable, as it may exhibit thixotropic properties in addition to a large sedimentation volume.

NONAQUEOUS SUSPENSIONS—Although most pharmaceutical suspensions have a primarily aqueous continuous phase, formulation of a drug in a nonaqueous continuous phase is occasionally required. Suspension of a water-soluble drug in a nonaqueous vehicle may provide a means to prepare a liquid formulation of a drug that has poor long-term stability in aqueous solution. Dispersions of drugs in oleaginous vehicles can also provide a sustained release form of drug as observed with certain depot injections and topical products.

Aerosols represent another important class of nonaqueous suspensions. The physical stability of suspended drugs in nonaqueous propellents for aerosol products can have a significant impact on the uniformity of dose and operation of the aerosol system. Caking of the suspended particles can cause clogging of the various mechanical components of the aerosol system.

According to Coulomb's law, the force between two charges is inversely proportional to the dielectric constant of the medium between the charges:

$$f \propto \frac{q_1 q_2}{Dx} \tag{6}$$

where f is the force between the particles, q_1 and q_2 are the charges on the particles, D is the dielectric constant, and x is the distance between the charges.

In general, most nonaqueous pharmaceutical liquids have a dielectric constant that is lower than water. This would result in a greater attraction between ions or particles of opposite charge and greater repulsion between ions or particles of similar charge. The effect of a continuous phase of low dielectric constant can therefore affect a suspension formulation in different ways. The use of added electrolytes will be less useful due to their low degree of ionization and poor solubility in some nonaqueous media. In addition, the density of charges on the particle surfaces will be reduced, but repulsion between particles may be facilitated. The result is that controlled flocculation using electrolytes is difficult to achieve as with aqueous suspensions, and caking may occur upon settling. Thus, alternate means of producing pharmaceutically acceptable suspensions must be employed.

Nonionic surfactants of low HLB values can be used to improve the physical stability of the suspensions. Stearic and other aliphatic acids and stearate salts, particularly aluminum monostearate, have been used as suspending agents. These materials increase the viscosity of the oil and produce a structured medium that can hinder the settling of drug particles. Alternatively, thickening agents such as Avicel, colloidal silicon dioxide, and long-chain alcohols can be used to reduce the sedimentation rate in nonaqueous suspensions.

Few studies have been performed to predict formulation and physical stability of drugs in nonaqueous suspensions. Parsons *et al*[10] found that the suspension properties of a number of solids in a nonaqueous aerosol propellant depended on the surface properties of the solids. Solids that had relatively polar surfaces tended to aggregate to larger extents than solids with relatively nonpolar surfaces. The moisture content of the dispersed solid and continuous phase may also play an important role on the aggregation of the solid. Adsorbed moisture on the dispersed solid may help to create a liquid bridge between particles when dispersed in certain nonaqueous solvents. If carefully controlled, this could provide a means to obtain some degree of flocculation in certain nonaqueous vehicles. Examples are discussed by Hiestand.[1]

CHEMICAL STABILITY OF SUSPENSIONS—Particles that are completely insoluble in a liquid vehicle are unlikely to undergo most chemical reactions leading to degradation. However, most drugs in suspension have a finite solubility, even though this may be of the order of fractions of a microgram per milliliter. As a result, the material in solution may be susceptible to degradation. However, Tingstad *et al*[11] developed a simplified method for determining the stability of drugs in suspension. The approach is based on the assumptions that

1. Degradation takes place only in the solution and is first order.
2. The effect of temperature on drug solubility and reaction rate conforms with classical theory.
3. Dissolution is not rate-limiting on degradation.

PREPARATION OF SUSPENSIONS—The small-scale preparation of suspensions may be undertaken readily by the practicing pharmacist with the minimum of equipment. The initial dispersion of the particles is best carried out by trituration in a mortar, the wetting agent being added in small increments to the powder. Once the particles have been wetted adequately, the slurry may be transferred to the final container. The next step depends on whether the deflocculated particles are to be suspended in a structured vehicle, flocculated, or flocculated and then suspended. Regardless of which of the alternative procedures outlined in Figure 22-2 is employed, the various manipulations can be carried out easily in the bottle, especially if an aqueous solution of the suspending agent has been prepared beforehand.

For detailed discussion of the methods used in the large-scale production of suspensions, see the relevant section in Chapter 39.

EMULSIONS

An *emulsion* is a dispersed system containing at least two immiscible liquid phases. The majority of conventional emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1 to 100 μm. As with suspensions, emulsions are thermodynamically unstable as a result of the excess free energy associated with the surface of the droplets. The dispersed droplets, therefore, strive to come together and reduce the surface area. In addition to this flocculation effect, also observed

with suspensions, the dispersed particles can coalesce, or fuse, and this can result in the eventual destruction of the emulsion. To minimize this effect, a third component, the *emulsifying agent,* is added to the system to improve its stability. The choice of emulsifying agent is critical to the preparation of an emulsion possessing optimum stability. The efficiency of present-day emulsifiers permits the preparation of emulsions that are stable for many months and even years, even though they are thermodynamically unstable.

In recent years, it has been recognized that complex multiple-phase combinations can exist in emulsions. Thus, liquid crystalline phases and gel structures can form from the combination of the basic three-component mixture of water, oil, and surfactant (emulsifying agent). Often, these structures confer significant stability to the emulsion and therefore are to be desired. Such multiple-phase emulsions and their stability have been reviewed by Eccleston.[12]

Emulsions are widely used in pharmacy and medicine, and emulsified materials can possess advantages not observed in formulations in other dosage forms. For example, certain medicinal agents that have an objectionable taste have been made more palatable for oral administration when formulated in an emulsion. The principles of emulsification have been applied extensively in the formulation of dermatological creams and lotions. Intravenous emulsions of contrast media have been developed to assist the physician in undertaking x-ray examinations of the body organs while exposing the patient to the minimum of radiation. Considerable attention has been directed towards the use of sterile, stable intravenous emulsions containing fat, carbohydrate, and vitamins all in one preparation. Such products are administered to patients unable to assimilate these vital materials by the normal oral route. Emulsions are also used to deliver nutrients via the enteral route in the form of nutritional supplements. More recently, emulsions have been used to deliver poorly water-soluble drugs, such as general anesthetics and anti-cancer compounds, via the intravenous route.

Emulsions offer potential in the design of systems capable of giving controlled rates of drug release and affording protection to drugs susceptible to oxidation or hydrolysis. There is still a need for well-characterized dermatologic products with reproducible properties, regardless of whether these products are antibacterial, sustained-release, protective, or emollient lotions, creams, or ointments. In addition, emulsions may provide a useful way to deliver poorly water-soluble drugs via enteral and parenteral routes. The principle of emulsification is also involved in an increasing number of aerosol products.

The pharmacist must be familiar with the types of emulsions and the properties and theories underlying their preparation and stability; such is the purpose of the remainder of this chapter. Microemulsions, which can be regarded as isotropic, swollen micellar systems are discussed in Chapter 39.

EMULSION TYPE AND MEANS OF DETECTION

A stable emulsion must contain at least three components: the *dispersed phase,* the *dispersion medium,* and the *emulsifying agent.* Invariably, one of the two immiscible liquids is aqueous, and the second is an oil. Whether the aqueous or the oil phase becomes the dispersed phase depends primarily on the emulsifying agent used and the relative amounts of the two liquid phases. Hence, an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is termed an *oil-in-water* (O/W) *emulsion.* When water is the dispersed phase and an oil the dispersion medium, the emulsion is of the *water-in-oil* (W/O) type. Most pharmaceutical emulsions designed for oral administration are of the O/W type; emulsified lotions and creams are either O/W or W/O, depending on their use. Butter and salad creams are W/O emulsions.

So-called *multiple emulsions* have been developed with a view to delaying the release of an active ingredient. In these types of emulsions three phases are present: the emulsion has the form W/O/W or O/W/O. In these "emulsions within emulsions," any drug present in the innermost phase must now cross two phase boundaries to reach the external, continuous phase.

It is important for pharmacists to know the type of emulsion they have prepared or are dealing with, because this can affect its properties and performance. Unfortunately, the several methods available can give incorrect results, so the type of emulsion determined by one method should always be confirmed by means of a second method.

DILUTION TEST—The dilution method depends on the fact that an O/W emulsion can be diluted with water and a W/O emulsion with oil. When oil is added to an O/W emulsion or water to a W/O emulsion, the additive is not incorporated into the emulsion and separation is apparent. The test is greatly improved if the addition of the water or oil is observed microscopically.

CONDUCTIVITY TEST—An emulsion in which the continuous phase is aqueous can be expected to possess a much higher conductivity than an emulsion in which the continuous phase is an oil. Accordingly, it frequently happens that when a pair of electrodes, connected to a lamp and an electrical source, are dipped into an O/W emulsion, the lamp lights because of the passage of a current between the two electrodes. If the lamp does not light, it is assumed that the system is W/O.

DYE-SOLUBILITY TEST—The knowledge that a water-soluble dye will dissolve in the aqueous phase of an emulsion while an oil-soluble dye will be taken up by the oil phase provides a third means of determining emulsion type. Thus, if microscopic examination shows that a water-soluble dye has been taken up by the continuous phase, we are dealing with an O/W emulsion. If the dye has not stained the continuous phase, the test is repeated using a small amount of an oil-soluble dye. Coloring of the continuous phase confirms that the emulsion is of the W/O type.

FORMATION AND BREAKDOWN OF DISPERSED LIQUID DROPLETS

An emulsion exists as the result of two competing processes: the dispersion of one liquid throughout another as droplets, and the combination of these droplets to reform the initial bulk liquids. The first process increases the free energy of the system, while the second works to reduce the free energy. Accordingly, the second process is spontaneous and continues until breakdown is complete—that is, until the bulk phases are reformed.

It is of little use to form a well-dispersed emulsion if it quickly breaks down. Similarly, unless adequate attention is given to achieving an optimum dispersion during preparation, the stability of an emulsion system may be compromised from the start. Dispersion is brought about by well-designed and well-operated machinery, capable of producing droplets in a relatively short period of time. Such equipment is discussed in Chapter 39. The reversal back to the bulk phases is minimized by using those parameters that influence the stability of the emulsion once it is formed.

DISPERSION PROCESS TO FORM DROPLETS—Consider two immiscible liquid phases in a test tube. To disperse one liquid as droplets within the other, the interface between the two liquids must be disturbed and expanded to a sufficient degree so that "fingers" or threads of one liquid pass into the second liquid, and *vice versa*. These threads are unstable, and become varicosed or beaded. The beads separate and become spherical, as illustrated in Figure 22-5. Depending on the agitation or the shear rate used, larger droplets are also deformed to give small threads, which in turn produce smaller drops.

The time of agitation is important. Thus, the mean size of droplets decreases rapidly in the first few seconds of agitation. The limiting size range is generally reached within 1 to 5 min, and results from the number of droplets coalescing being equivalent to the number of new droplets being formed. It is uneconomical to continue agitation any further.

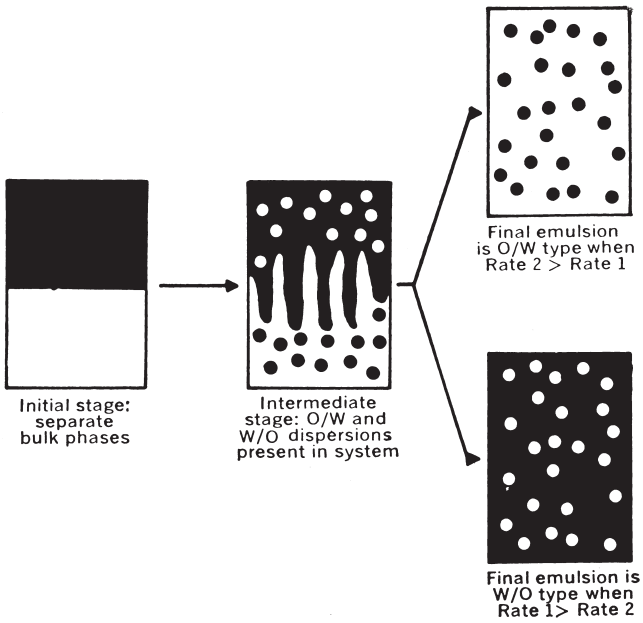


Figure 22-5. Effect of rate of coalescence on emulsion type. Rate 1: O/W coalescence rate. Rate 2: W/O coalescence rate. ●: oil. ○: water. For an explanation of Rates 1 and 2, refer to the discussion of Davies on page 329 of *Proceedings of the International Congress on Surface Activity*, 2nd ed. London: Butterworth/Academic, 1957.

The liquids may be agitated or sheared by several means. *Shaking* is employed commonly, especially when the components are of low viscosity. Intermittent shaking is frequently more efficient than continual shaking, possibly because the short time interval between shakes allows the thread that is forced across the interface time to break down into drops that are then isolated in the opposite phase. Continuous, rapid agitation tends to hinder this breakdown to form drops. A mortar and pestle is employed frequently in the extemporaneous preparation of emulsions. It is not a very efficient technique and is not used on a large scale. Improved dispersions are achieved by the use of high-speed mixers, blenders, colloid mills, or homogenizers. Ultrasonic techniques also have been employed and are described in Chapter 39.

The phenomenon of *spontaneous emulsification,* as the name implies, occurs without any external agitation. There is, however, an internal agitation arising from certain physicochemical processes that affect the interface between the two bulk liquids. For a description of this process, see Davies and Rideal in the bibliography.

COALESCENCE OF DROPLETS—*Coalescence* is a process distinct from flocculation (aggregation), which commonly precedes it. Flocculation is the clumping together of particles, but coalescence is the fusing of the agglomerates into a larger drop, or drops. Coalescence usually is rapid when two immiscible liquids are shaken together, as there is no large energy barrier to prevent fusion of drops and reformation of the original bulk phases. When an emulsifying agent is added to the system, flocculation still may occur but coalescence is reduced to an extent depending on the efficacy of the emulsifying agent to form a stable, coherent interfacial film. It is therefore possible to prepare emulsions that are flocculated yet do not coalesce. In addition to the interfacial film around the droplets acting as a mechanical barrier, the drops also are prevented from coalescing by the presence of a thin layer of continuous phase between particles clumped together. Davies[13] showed the importance of coalescence rates in determining emulsion type; this work is discussed in more detail on page 329.

EMULSIFYING AGENT

The process of coalescence can be reduced to insignificant levels by the addition of a third component—the emulsifying agent or *emulsifier.* The choice of emulsifying agent is frequently critical in developing a successful emulsion, and the pharmacist should be aware of

- The desirable properties of emulsifying agents.
- How different emulsifiers act to optimize emulsion stability.
- How the type and physical properties of the emulsion can be affected by the emulsifying agent.

Desirable Properties

Some of the desirable properties of an emulsifying agent are that it should:

1. Be surface active and reduce surface tension to below 10 dynes/cm.
2. Be adsorbed quickly around the dispersed drops as a condensed, nonadherent film that will prevent coalescence.
3. Impart to the droplets an adequate electrical potential so that mutual repulsion occurs.
4. Increase the viscosity of the emulsion.
5. Be effective in a reasonably low concentration.

Not all emulsifying agents possess these properties to the same degree; in fact, not every good emulsifier necessarily possesses all these properties. Further, there is no one ideal emulsifying agent because the desirable properties of an emulsifier depend, in part, on the properties of the two immiscible phases in the particular system under consideration.

INTERFACIAL TENSION—Lowering of interfacial tension is one way in which the increased surface free energy associated with the formation of droplets, and hence surface area, in an emulsion can be reduced (Equation 1). Assuming the droplets to be spherical, it can be shown that

$$\Delta F = \frac{6\gamma V}{d} \tag{7}$$

where V is the volume of dispersed phase in milliliters, and d is the mean diameter of the particles. To disperse 100 mL of oil as 1-μm (10^{-4}-cm) droplets in water when $\gamma_{O/W} = 50$ dynes/cm, requires an energy input of

$$\Delta F = \frac{6 \times 50 \times 100}{1 \times 10^{-4}} = 30 \times 10^{7} \text{ ergs}$$

$$= 30 \text{ joules or } 30/4.184 = 7.2 \text{ cal}$$

In the above example the addition of an emulsifier that will reduce γ from 50 to 5 dynes/cm will reduce the surface free energy from 7.2 to around 0.7 cal. Likewise, if the interfacial tension is reduced to 0.5 dynes/cm (a common occurrence), the original surface free energy is reduced a hundredfold. Such a reduction can help to maintain the surface area generated during the dispersion process.

FILM FORMATION—The major requirement of a potential emulsifying agent is that it readily form a *film* around each droplet of dispersed material. The main purpose of this film—which can be a monolayer, a multilayer, or a collection of small particles adsorbed at the interface—is to form a barrier that prevents the coalescence of droplets that come into contact with one another. For the film to be an efficient barrier, it should possess some degree of surface elasticity and should not thin out and rupture when sandwiched between two droplets. If broken, the film should have the capacity to reform rapidly.

ELECTRICAL POTENTIAL—The origin of an electrical potential at the surface of a droplet has been discussed earlier in the chapter. Insofar as emulsions are concerned, the presence of a well-developed charge on the droplet surface is signif-

icant in promoting stability by causing repulsion between approaching drops. This potential is likely to be greater when an ionized emulsifying agent is employed. Electrical potential has been shown to be a significant factor for maintaining the stability of intravenous fat emulsions that are stabilized with lecithin.

CONCENTRATION OF EMULSIFIER—The main objective of an emulsifying agent is to form a condensed film around the droplets of the dispersed phase. An inadequate concentration will do little to prevent coalescence. Increasing the emulsifier concentration above an optimum level achieves little in terms of increased stability. In practice the aim is to use the minimum amount consistent with producing a satisfactory emulsion.

It frequently helps to have some idea of the amount of emulsifier required to form a condensed film, one molecule thick, around each droplet. Suppose we wish to emulsify 50 g of an oil, density = 1.0, in 50 g of water. The desired particle diameter is 1 μm. Thus,

Particle diameter = 1 μm = 1×10^{-4} cm
Volume of particle = $(\pi d^3/6) = 0.524 \times 10^{-12}$ cm^3
Total number of particles in 50 g = $(50/0.524 \times 10^{-12}) = 95.5 \times 10^{12}$
Surface area of each particle = $\pi d^2 = 3.142 \times 10^{-8}$ cm^2
Total surface area = $3.142 \times 10^{-8} \times 95.5 \times 10^{12} = 300 \times 10^4$ cm^2

If the area each molecule occupies at the oil–water interface is 30 Å^2 (30×10^{-16} cm^2), we require

$$\frac{300 \times 10^4}{30 \times 10^{16}} = 1 \times 10^{21} \text{ molecules}$$

A typical emulsifying agent might have a molecular weight of 1000. Thus, the required weight is

$$\frac{1000 \times 10^{21}}{6.023 \times 10^{23}} = 1.66 \text{ g}$$

To emulsify 10 g of oil would require 0.33 g of the emulsifying agent.

While the approach is an oversimplification of the problem, it does at least allow the formulator to make a reasonable estimate of the required concentration of emulsifier.

EMULSION RHEOLOGY—The emulsifying agent and other components of an emulsion can affect the rheologic behavior of an emulsion in several ways, as summarized in Table 22-3.[14] It should be borne in mind that the droplets of the internal phase are deformable under shear and that the adsorbed layer of emulsifier affects the interactions between adjacent droplets and also between a droplet and the continuous phase. The means by which the rheological behavior of emulsions can be controlled have been discussed by Rogers.[15]

Table 22-3. Factors Influencing Emulsion Viscosity

1. Internal phase
   a. Volume concentration (φ); hydrodynamic interaction between globules; flocculation, leading to formation of globule aggregates.
   b. Viscosity (η_1); deformation of globules in shear.
   c. Globule size, and size distribution, technique used to prepare emulsion; interfacial tension between the two liquid phases: globule behavior in shear; interaction with continuous phase; globule interaction.
   d. Chemical constitution.
2. Continuous phase
   a. Viscosity (η_0), and other rheological properties.
   b. Chemical constitution, polarity, pH; potential energy of interaction between globules.
   c. Electrolyte concentration if polar medium.
3. Emulsifying agent
   a. Chemical constitution; potential energy of interaction between globules.
   b. Concentration, and solubility in internal and continuous phases; emulsion type; emulsion inversion; solubilization of liquid phases in micelles.
   c. Thickness of film adsorbed around globules, and its rheological properties, deformation of globules in shear; fluid circulation within globules.
   d. Electroviscous effect.
4. Additional stabilizing agents
   a. Pigments, hydrocolloids, hydrous oxides.
   b. Effect on rheological properties of liquid phases, and interfacial boundary region.

From Davies JT, Rideal EK. *Interfacial Phenomena.* New York: Academic Press, 1961, Chap 8.

Mechanism of Action

Emulsifying agents may be classified in accordance with the type of film they form at the interface between the two phases.

MONOMOLECULAR FILMS—Those surface-active agents that are capable of stabilizing an emulsion do so by forming a monolayer of adsorbed molecules or ions at the oil–water interface (Fig 22-6). In accordance with Gibbs' law (Chapter 20) the presence of an interfacial excess necessitates a reduction in interfacial tension. This results in a more stable emulsion because of a proportional reduction in the surface free energy. Of itself, this reduction is probably not the main factor promoting stability. More significant is the fact that the droplets are surrounded now by a coherent monolayer that prevents coalescence between approaching droplets. If the emulsifier forming the monolayer is ionized, the presence of strongly charged and mutually repelling droplets increases the stability of the system. With un-ionized, nonionic surface-active agents, the particles may still carry a charge; this arises from adsorption of a specific ion or ions from solution.

MULTIMOLECULAR FILMS—Hydrated lyophilic colloids form multimolecular films around droplets of dispersed oil (see Fig 22-6). The use of these agents has declined in recent years because of the large number of synthetic surface-active agents available that possess well-marked emulsifying properties. Although these hydrophilic colloids are adsorbed at an interface (and can be regarded therefore as surface active), they do not cause an appreciable lowering in surface tension. Rather, their efficiency depends on their ability to form strong coherent multimolecular films. These act as a coating around the droplets and render them highly resistant to coalescence, even in the absence of a well-developed surface potential. Furthermore, any hydrocolloid not adsorbed at the interface increases the viscosity of the continuous aqueous phase; this enhances emulsion stability.

SOLID PARTICLE FILMS—Small solid particles that are wetted to some degree by both aqueous and nonaqueous liquid phases act as emulsifying agents. If the particles are too hydrophilic, they remain in the aqueous phase; if too hydrophobic, they are dispersed completely in the oil phase. A second requirement is that the particles are small in relation to the droplets of the dispersed phase (see Fig 22-6).

Chemical Types

Emulsifying agents also may be classified in terms of their chemical structure; there is some correlation between this classification and that based on the mechanism of action. For example, the majority of emulsifiers forming monomolecular films are synthetic, organic materials. Most of the emulsifiers that form multimolecular films are obtained from natural sources and are organic. A third group is composed of solid particles, invariably inorganic, that form films composed of finely divided solid particles.

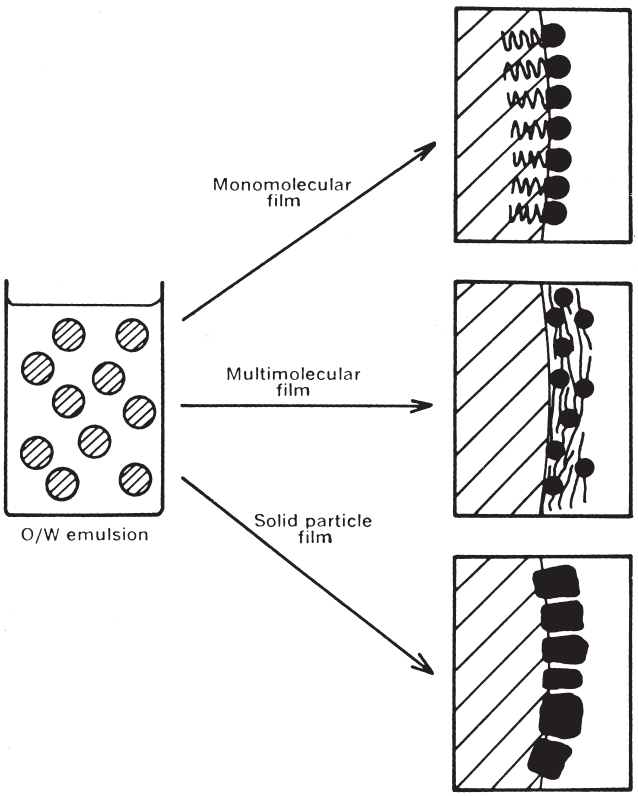


Figure 22-6. Types of films formed by emulsifying agents at the oil–water interface. Orientations are shown for O/W emulsions. ▨: oil. □: water.

Accordingly, the classification, adopted divides emulsifying agents into *synthetic, natural,* and *finely dispersed solids* (Table 22-4). A fourth group, the *auxiliary materials* (Table 22-5) are weak emulsifiers. The list of agents is not meant to be exhaustive, but rather merely illustrates the various types available.

SYNTHETIC EMULSIFYING AGENTS—Synthetic emulsifying agents, a group of surface-active agents that act as emulsifiers, may be subdivided into anionic, cationic, and nonionic, depending on the charge possessed by the surfactant.

Anionics—In the anionic subgroup, the surfactant ion bears a negative charge. The potassium, sodium, and ammonium salts of lauric and oleic acid are soluble in water and are good O/W emulsifying agents. They do, however, have a disagreeable taste and are irritating to the gastrointestinal (GI) tract; this limits them to emulsions prepared for external use. Potassium laurate, a typical example, has the structure

$$CH_3(CH_2)_{10}COO^-K^+$$

Solutions of *alkali soaps* have a high pH; they start to precipitate out of solution below pH 10 because the un- ionized fatty acid is now formed, and this has a low aqueous solubility. Further, the free fatty acid is ineffective as an emulsifier, so emulsions formed from alkali soaps are not stable at pH values less than about 10.

The calcium, magnesium, and aluminum salts of fatty acids, often termed the *metallic soaps,* are water insoluble and result in W/O emulsions.

Another class of soaps are salts formed from a fatty acid and an organic amine such as triethanolamine. These O/W emulsifiers also are limited to external preparations, but their alkalinity is considerably less than that of the alkali soaps and they are active as emulsifiers down to around pH 8. These agents are less irritating than the alkali soaps.

Sulfated alcohols are neutralized sulfuric acid esters of such fatty alcohols as lauryl and cetyl alcohol. These compounds are an important group of pharmaceutical surfactants. They are used chiefly as wetting agents, although they do have some value as emulsifiers, particularly when used in conjunction with an auxiliary agent.

Sulfonates—Sulfonates are a class of compounds in which the sulfur atom is connected directly to the carbon atom, giving the general formula

$$CH_3(CH_2)_nCH_2SO_3^-Na^+$$

A frequently used compound is sodium lauryl sulfate. Sulfonates have a higher tolerance to calcium ions and do not hydrolyze as readily as the sulfates. A widely used surfactant of this type is dioctyl sodium sulfosuccinate.

Cationics—The surface activity in the cationic group resides in the positively charged cation. These compounds have marked bactericidal properties. This makes them desirable in emulsified anti-infective products such as skin lotions and creams. The pH of an emulsion prepared with a cationic emulsifier lies in the pH 4 to 6 ranges. Because this includes the normal pH of the skin, cationic emulsifiers are advantageous in this regard also.

Cationic agents are weak emulsifiers and generally are formulated with a stabilizing or auxiliary emulsifying agent such as cetostearyl alcohol. The only group of cationic agents used extensively as emulsifying agents are the quaternary ammonium compounds. An example is cetyltrimethyl-ammonium bromide.

$$CH_3(CH_2)_{14}CH_2N^+(CH_3)_3\ Br^-$$

Cationic emulsifiers should not be used in the same formulation with anionic emulsifiers because they will interact. The incompatibility

Table 22-4. Classification of Emulsifying Agents

TYPE	TYPE OF FILM		EXAMPLES
Synthetic (surface-active agents)	Monomolecular	*Anionic*	*Cationic*
		Soaps	Quaternary ammonium compounds
		Potassium laurate	Cetyltrimethyllammonium bromide
		Triethanolamine stearate	Lauryldimethylbenzylammonium chloride
		Sulfates	*Nonionic*
		Sodium lauryl sulfate	Polyoxyethylene fatty alcohol ethers
		Alkyl polyoxyethylene sulfates	Sorbitan fatty acid esters
		Sulfonates	Polyoxyethylene sorbitan fatty acid esters
		Dioctyl sodium sulfosuccinate	Polyoxyethylene polyoxypropylene block copolymers (poloxamers)
			Lanolin alcohols and ethoxylated lalnolin alcohols
Natural	Multimolecular	*Hydrophilic colloids*	
		Acacia	
		Gelatin	
	Monomolecular	Lecithin	
		Cholesterol	
Finely divided solids	Solid particle	*Colloidal clays*	
		Bentonite	
		Veegum	
		Metallic hydroxides	
		Magnesium hydroxide	

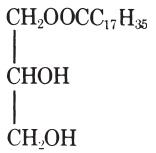
Table 22-5. Auxiliary Emulsifying Agents

PRODUCT	SOURCE AND COMPOSITION	PRINCIPAL USE
Cetyl alcohol	Chiefly $C_{16}H_{33}OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Glyceryl monosterate	$C_{17}H_{35}COOCH_2CHOHCH_2OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Methylcellulose	Series of methyl ethers of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Sodium carboxymethylcellulose	Sodium salt of the carboxymethyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions
Stearic acid	A mixture of solid acids from fats, chiefly stearic and palmitic	Lipophilic thickening agent and stabilizer for O/W lotions and ointments. Forms a true emulsifier when reacted with an alkali

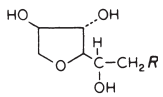
may not be immediately apparent as a precipitate, but virtually all of the desired antibacterial activity will generally have been lost.

Nonionics—Nonionics, undissociated surfactants, find widespread use as emulsifying agents when they possess the proper balance of hydrophilic and lipophilic groups within the molecule. Their popularity is based on the fact that, unlike the anionic and cationic types, nonionic emulsifiers are not susceptible to pH changes and the presence of electrolytes. The number of nonionic agents available is legion; the most frequently used are the glyceryl esters, polyoxyethylene glycol esters and ethers, and the sorbitan fatty acid esters and their polyoxyethylene derivatives. More recently, the polyoxyethylene/polyoxypropylene block copolymers have become popular surfactants and emulsifying agents.

A glyceryl ester, such as glyceryl monostearate, is too lipophilic to serve as a good emulsifier; it is used widely as an auxiliary agent (see Table 22-5) and has the structure

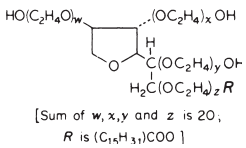


Sorbitan fatty acid esters, such as sorbitan monopalmitate



[*R* is $(C_{15}H_{31})COO$]

are nonionic oil-soluble emulsifiers that promote W/O emulsions. The polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monopalmitate

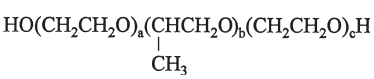


[Sum of *w*, *x*, *y* and *z* is 20; *R* is $(C_{15}H_{31})COO$]

are hydrophilic water-soluble derivatives that favor O/W emulsions.

Polyoxyethylene glycol esters, such as the monostearate, $C_{17}H_{35}COO(CH_2OCH_2)_nH$, also are used widely.

Polyoxyethylene/polyoxypropylene block copolymers



also known as *poloxamers* consist of combined chains of oxyethylene with oxypropylene where the oxyethylene portion imparts hydrophilicity and the oxypropylene portion imparts lipophilicity. The molecules are synthesized as long segments of the hydrophilic portions combined with long segments of the hydrophobic portions, with each portion referred to as a *block*. This organization produces hydrophilic and hydrophobic domains that impart the surface active character to these agents. Poloxamers have been used in the formulation of intravenous emulsions and can impart structure to vehicles and interfacial films that can protect the dispersed phase against coalescence. The polymeric nature of these surfactants protects emulsions against coalescence via steric stabilization at the droplet interface.

Very frequently, the best results are obtained from blends of nonionic emulsifiers. Thus, an O/W emulsifier customarily will be used in an emulsion with a W/O emulsifier. When blended properly, the nonionics produce fine-textured stable emulsions.

NATURAL EMULSIFYING AGENTS—Of the numerous emulsifying agents derived from natural (ie, plant and animal) sources, consideration will be given only to acacia, gelatin, lecithin, and cholesterol. Many other natural materials are only sufficiently active to function as auxiliary emulsifying agents or stabilizers.

Acacia is a carbohydrate gum that is soluble in water and forms O/W emulsions. Emulsions prepared with acacia are stable over a wide pH range. Because it is a carbohydrate it is necessary to preserve acacia emulsions against microbial attack by the use of a suitable preservative.

Gelatin, a protein, has been used for many years as an emulsifying agent. Gelatin can have two isoelectric points, depending on the method of preparation. So-called Type A gelatin, derived from an acid-treated precursor, has an isoelectric point of between pH 7 and 9. Type B gelatin, obtained from an alkali-treated precursor, has an isoelectric point of approximately pH 5. Type A gelatin acts best as an emulsifier around pH 3, where it is positively charged; on the other hand, Type B gelatin is best used around pH 8, where it is negatively charged. The question as to whether the gelatin is positively or negatively charged is fundamental to the stability of the emulsion when other charged emulsifying agents are present. To avoid an incompatibility, all emulsifying agents should carry the same sign. Thus, if gums (such as tragacanth, acacia, or agar) that are negatively charged are to be used with gelatin, then Type B material should be used at an alkaline pH. Under these conditions the gelatin is similarly negatively charged.

Lecithin is an emulsifier obtained from both plant (eg, soybean) and animal (eg, egg yolk) sources and is composed of various phosphatides. The primary component of most lecithins is phosphatidylcholine and the term "lecithin" is often used to describe purified samples of phosphatidylcholine. Frequently, lecithins that are used as emulsifiers also contain mixtures of phosphatides, including phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, and phosphatidic acid in addition to phosphatidylcholine. Although phosphatidylcholine is a zwitterionic compound, the presence of other phosphatides such as phosphatidylinositol and phosphatidic acid, as well as small quantities of lysophosphatides, result in an emulsifier that imparts a net negative charge to dispersed particles.

Lecithin can be an excellent emulsifier for naturally occurring oils such as soy, corn, or safflower. Highly stable O/W emulsions can be formed with these oils. Purified lecithins from soy or egg yolk are the principal emulsifiers for intravenous fat emulsions. Lecithin provides stable emulsions with droplet sizes of less than 1 μm in diameter. It is critical that a small, uniform particle size be maintained in these emulsions to eliminate the risks of fat embolism after intravenous injection. The

excellent stability observed with these emulsions may be the result of the large negative zeta potential that results from the small quantity of charged lipids present in lecithin as well as the ability of the lecithin to form mesophases resembling liposomes. During manufacture of the emulsions, homogenization produces small droplets that are surrounded by concentric layers of phospholipids. The latter may form a protective layer that prevents coalescence of the droplets. As an emulsifier, lecithin produces the best results at a pH of around 8.

As with any natural product, the content of lecithins will vary from source to source and their emulsifying properties and toxicity may also vary. For highly critical applications, such as intravenous emulsions, the source and composition of the lecithin must be carefully controlled and monitored.

Cholesterol is a major constituent of wool alcohols, obtained by the saponification and fractionation of wool fat. It is cholesterol that gives wool fat its capacity to absorb water and form a W/O emulsion.

FINELY DISPERSED SOLIDS—Finely dispersed solids are emulsifiers that form particulate films around the dispersed droplets, producing emulsions that are coarse-grained but have considerable physical stability. It appears possible that any solid can act as an emulsifying agent of this type, provided it is reduced to a sufficiently fine powder. In practice, the group of compounds used most frequently are the colloidal clays.

Bentonite is a white to gray, odorless and tasteless powder that swells in the presence of water to form a translucent suspension with a pH of about 9. Depending on the sequence of mixing it is possible to prepare both O/W and W/O emulsions. When an O/W emulsion is desired, the bentonite is first dispersed in water and allowed to hydrate so as to form a magma. The oil phase is then added gradually with constant titration. Because the aqueous phase is always in excess, the O/W emulsion type is favored. To prepare a W/O emulsion, the bentonite is first dispersed in oil; the water is then added gradually.

Although *Veegum* is used as a solid particle emulsifying agent, it is employed most extensively as a stabilizer in cosmetic lotions and creams. Concentrations of less than 1% Veegum will stabilize an emulsion containing anionic or nonionic emulsifying agents.

AUXILIARY EMULSIFYING AGENTS—Auxiliary emulsifying agents include those compounds that are normally incapable themselves of forming stable emulsions. Their main value lies in their ability to function as thickening agents and thereby help stabilize the emulsion. Agents in common use are listed in Table 22-5. Auxiliary emulsifying agents that are amphiphilic in nature are, in some cases, capable of forming gel or liquid crystalline phases with the primary emulsifying agent when combined with water and oil. This type of behavior may help to stabilize emulsions due to an increased viscosity, as observed in topical creams. Alternatively, gel or liquid crystalline phases may prevent coalescence by reducing van der Waals forces between particles or by providing a physical barrier between approaching particles of the internal phase. This latter effect is thought to be an important function in phospholipid-stabilized emulsions that must maintain a low viscosity to permit administration via the intravenous route. Additional information is provided by Eccleston.[12]

Emulsifying Agents and Emulsion Type

For a molecule, ion, colloid, or particle to be active as an emulsifying agent, it must have some affinity for the interface between the dispersed phase and the dispersion medium. With the monolayer and multilayer films, the emulsifier is in solution, and therefore it must be soluble to some extent in one or both of the phases. At the same time it must not be overly soluble in either phase; otherwise, it will remain in the bulk of that phase and not be adsorbed at the interface. This balanced affinity for the two phases also must be evident with finely divided solid particles used as emulsifying agents. If their affinity, as evidenced by the degree to which they are wetted, is either predominantly hydrophilic or hydrophobic, they will not function as effective wetting agents.

Table 22-6. Relationship between HLB Range and Surfactant Application

HLB RANGE	USE
0–3	Antifoaming agents
4–6	W/O emulsifying agents
7–9	Wetting agents
8–18	O/W emulsifying agents
13–15	Detergents
10–18	Solubilizing agents

The great majority of the work on the relation between emulsifier and emulsion type has been concerned with surface-active agents that form interfacial monolayers. Thus, the present discussion will concentrate on this class of agents.

HYDROPHILE–LIPOPHILE BALANCE—As the emulsifier becomes more hydrophilic, its solubility in water increases and the formation of an O/W emulsion is favored. Conversely, W/O emulsions are favored with the more lipophilic emulsifiers. This led to the concept that the type of emulsion is related to the balance between hydrophilic and lipophilic solution tendencies of the surface-active emulsifying agent.

Griffin[16] developed a scale based on the balance between these two opposing tendencies. This so-called *HLB scale* is a numerical scale, extending from 1 to approximately 50. The more hydrophilic surfactants have high HLB numbers (in excess of 10), whereas surfactants with HLB numbers from 1 to 10 are considered to be lipophilic. Surfactants with a proper balance in their hydrophilic and lipophilic affinities are effective emulsifying agents because they concentrate at the oil–water interface. The relationship between HLB values and the application of the surface-active agent is shown in Table 22-6. Some commonly used emulsifiers and their HLB numbers are listed in Table 22-7. The utility of the HLB system in rationalizing the choice of emulsifying agents when formulating an emulsion will be discussed in a later section.

RATE OF COALESCENCE AND EMULSION TYPE—Davies[13] indicated that the type of emulsion produced in systems prepared by shaking is controlled by the relative coalescence rates of oil droplets dispersed in the oil. Thus, when a

Table 22-7. Approximate HLB Values for a Number of Emulsifying Agents

GENERIC OR CHEMICAL NAME	HLB	WATER DISPERSIBILITY
Sorbitan trioleate	1.8	No dispersion
Sucrose distearate	3.0	
Propylene glycol monostearate	3.4	
Glycerol monostearate (non–self-emulsifying)	3.8	Poor dispersion
Propylene glycol monolaurate	4.5	
Sorbitan monostearate	4.7	
Glycerol monostearate (self-emulsifying)	5.5	
Sorbitan monolaurate	8.6	Milky dispersion
Polyoxyethylene-4-lauryl ether	9.5	
Polyethylene glycol 400 monostearate	11.6	Translucent to clear
Polyoxyethylene-4-sorbitan monolaurate	13.3	Clear solution
Sucrose stearate	14.5	
Polyoxyethylene-20-sorbitan monopalmitate	15.6	
Polyoxyethylene-40-stearate	16.9	
Sodium oleate	18.0	
Sodium lauryl sulfate	40.0	

mixture of oil and water is shaken together with an emulsifying agent, a multiple dispersion is produced initially that contains oil dispersed in water and water dispersed in oil (see Fig 22-5).The type of the final emulsion that results depends on whether the water or the oil droplets coalesce more rapidly. If the O/W coalescence rate (Rate 1) is much greater than W/O coalescence rate (Rate 2), a W/O emulsion is formed because the dispersed water droplets are more stable than the dispersed oil droplets. Conversely, if Rate 2 is significantly faster than Rate 1, the final emulsion is an O/W dispersion because the oil droplets are more stable.

According to Davies,[13] the rate at which oil globules coalesce when dispersed in water is given by the expression

$$\text{Rate 1} = C_1 e^{-W1/RT} \quad (8)$$

The term C_1 is a collision factor that is directly proportional to the phase volume of the oil relative to the water, and is an inverse function of the viscosity of the continuous phase (water). W_1 defines an energy barrier made up of several contributing factors that must be overcome before coalescence can take place. First, it depends on the electrical potential of the dispersed oil droplets, as this affects repulsion. Second, with an O/W emulsion, the hydrated layer surrounding the polar portion of emulsifying agent must be broken down before coalescence can occur. This hydrated layer is probably around 1 nm thick with a consistency of butter. Finally, the total energy barrier depends on the fraction of the interface covered by the emulsifying agent.

Equation 9 describes the rate of coalescence of water globules dispersed in oil:

$$\text{Rate 2} = C_2 e^{-W2/RT} \quad (9)$$

Here, the collision factor C_2 is a function of the water–oil phase volume ratio divided by the viscosity of the oil phase. The energy barrier W_2 is, as before, related to the fraction of the interface covered by the surface-active agent. Another contributing factor is the number of—CH_2—groups in the emulsifying agent; the longer the alkyl chain of the emulsifier, the greater the gap that has to be bridged if one water droplet is to combine with a second drop.

Davies[13] showed that the HLB concept is related to the distribution characteristics of the emulsifying agent between the two immiscible phases. An emulsifier with an HLB of less than 7 will be preferentially soluble in the oil phase and will favor formation of a W/O emulsion. Surfactants with an HLB value in excess of 7 will be distributed in favor of the aqueous phase and will promote O/W emulsions.

PREPARATION OF EMULSIONS

Several factors must be taken into account in the successful preparation and formulation of emulsified products. Usually, the type of emulsion (ie, O/W or W/O) is specified; if not, it probably will be implied from the anticipated use of the product. The formulator's attention is focused primarily on the selection of the emulsifying agent, or agents, necessary to achieve a satisfactory product. No incompatibilities should occur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the product should be prepared in such a way as not to prejudice the formulation.

Selection of Emulsifying Agents

The selection of the emulsifying agent or agents is of prime importance in the successful formulation of an emulsion. The pharmacist must ensure that, in addition to its emulsifying properties, the material chosen is nontoxic and that the taste, odor, and chemical stability are compatible with the product. Thus, an emulsifying agent that is entirely suitable for inclusion in a skin cream may be unacceptable in the formulation of an oral preparation due to its potential toxicity. This consideration is most important when formulating intravenous emulsions.

THE HLB SYSTEM—With the increasing number of available emulsifiers, particularly the nonionics, the selection of emulsifiers for a product was essentially a trial-and-error procedure. Fortunately, the work of Griffin[16,17] provided a logical means of selecting emulsifying agents. Griffin's method, based on the balance between the hydrophilic and lipophilic portions of the emulsifying agent, is now widely used and has come to be known as the HLB system. It is used most in the rational selection of combinations of nonionic emulsifiers, and we shall limit our discussion accordingly.

As shown in Table 22-6, if an O/W emulsion is required, the formulator should use emulsifiers with an HLB in the range of 8 to 18. Emulsifiers with HLB values in the range of 4 to 6 are given consideration when a W/O emulsion is desired. Some typical examples are given in Table 22-7.

Another factor is the presence or absence of any polarity in the material being emulsified, because this will affect the polarity required in the emulsifier. Again, as a result of extensive experimentation, Griffin evolved a series of "required HLB" values—that is, the HLB value required by a particular material if it is to be emulsified effectively. Some values for oils and related materials are contained in Table 22-8. Naturally, the required HLB value differs depending on whether the final emulsion is O/W or W/O.

Fundamental to the utility of the HLB concept is the fact that the HLB values are algebraically additive. Thus, by using a low HLB surfactant with one having a high HLB it is possible to prepare blends having HLB values intermediate between those of the two individual emulsifiers. The following formula serves as an example.

O/W Emulsion

Liquid petrolatum (Required HLB 10.5)	50 g
Emulsifying agents	5 g
Sorbitan monooleate (HLB 4.3)	
Polyoxyethylene 20 sorbitan monoleate (HLB 15.0)	
Water, qs	100 g

By simple algebra it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of polyoxyethylene 20 sorbitan monooleate will result in a mixed emulsifying agent having the required HLB of 10.5. Because the formula calls for 5 g, the required weights are 2.1 and 2.9 g, respectively. The oil-soluble sorbitan monooleate is dissolved in the oil and heated to 75°; the water-soluble polyoxyethylene 20 sorbitan monooleate is added to the aqueous phase that is heated to 70°. At this point the oil phase is mixed with the aqueous phase and the whole is stirred continuously until cool.

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. Table 22-9 shows the various proportions required, using other pairs of emulsifying agents,

Table 22-8. Required HLB Values for Some Common Emulsion Ingredients

SUBSTANCE	W/O	O/W
Acid, stearic	—	17.0
Alcohol, cetyl	—	13.0
Lanolin, anhydrous	8	15.0
Oil, cottonseed	—	7.5
Mineral oil, light	4	10–12.0
Mineral oil, heavy	4	10.5
Wax, beeswax	5	10–16.0
Microcrystalline	—	9.5
Paraffin	—	9.0

to form a blend of HLB 10.5. When carrying out preliminary investigations with a particular material to be emulsified, it is advisable to try several pairs of emulsifying agents. Based on an evaluation of the emulsions produced, it becomes possible to choose the best combination.

Occasionally, the required HLB of the oil may not be known, in which case it becomes necessary to determine this parameter. Various blends are prepared to give a wide range of HLB mixtures and emulsions are prepared in a standardized manner. The HLB of the blend used to emulsify the best product, selected on the basis of physical stability, is taken to be the required HLB of the oil. The experiment should be repeated using another combination of emulsifiers to confirm the value of the required HLB of the oil to within, say, ± 1 HLB unit.

There are methods for finding the HLB value of a new surface-active agent. Griffin[17] developed simple equations that can be used to obtain an estimate with certain compounds. It has been shown that the ability of a compound to spread at a surface is related to its HLB. In another approach a linear relation between HLB and the logarithm of the dielectric constant for a number of nonionic surfactants has been observed.

An interesting approach, developed by Davies,[13] is related to his studies on the relative rates of coalescence of O/W and W/O emulsions. According to Davies, hydrophilic groups on the surfactant molecule make a positive contribution to the HLB number, whereas lipophilic groups exert a negative effect. Davies calculated these contributions and termed them HLB Group Numbers (Table 22-10). Provided the molecular structure of the surfactant is known, one simply adds the various group numbers in accordance with the following formula:

$$\text{HLB} = \sum(\text{hydrophilic group numbers}) - m(\text{group number/—CH}_2\text{—group}) + 7$$

where m is the number of —CH_2— groups present in the surfactant. Poor agreement is found between the HLB values calculated by the use of group numbers and the HLB values obtained using the simple equations developed by Griffin. However, the student should realize that the absolute HLB values per se are of limited significance. The utility of the HLB approach (using values calculated by either Griffin's or Davies' equations) is to

1. Provide the formulator with an idea of the relative balance of hydrophilicity and lipophilicity in a particular surfactant.
2. Relate that surfactant's emulsifying and solubilizing properties to other surfactants. The formulator still needs to confirm experimentally that a particular formulation will produce a stable emulsion.

Later, Davies and Rideal[18] attempted to relate HLB to the C_{water}/C_{oil} partition coefficient and found good agreement for a series of sorbitan surfactants. Schott showed, however, that the method does not apply to polyoxyethylated octylphenol surfactants. Schott concluded that "so far, the search for a universal correlation between HLB and another property of the surfactant that could be determined more readily than HLB has not been successful."[19]

Table 22-9. Nonionic Blends Having HLB Values of 10.5

SURFACTANT BLEND	HLB	REQUIRED AMOUNTS (%) TO GIVE HLB = 10.5
Sorbitan tristearate	2.1	34.4
Polyoxyethylene 20 sorbitan monostearate	14.9	65.6
Sorbitan monopalmitate	6.7	57.3
Polyoxyethylene 20 sorbitan monopalmitate	15.6	42.7
Sorbitan sesquioleate	3.7	48.5
Polyoxyethylene lauryl ether	16.9	51.5

Table 22-10. HLB Group Numbers

	GROUP NUMBER
Hydrophilic groups	
—$SO_4^-Na^+$	38.7
—COO^-K^+	21.1
—COO^-Na^+	19.1
N (tertiary amine)	9.4
Ester (sorbitan ring)	6.8
Ester (free)	2.4
—COOH	2.1
Hydroxyl (free)	1.9
—O—	1.3
Hydroxyl (sorbitan ring)	0.5
Lipophilic groups	
—CH—	
—CH_2—	
CH_3—	−0.475
=CH—	
Derived groups	
—(CH_2—CH_2—O)—	+0.33
—(CH_2—CH_2—CH_2—O)—	−0.15

From Wedderburn DL. In: *Advances in Pharmaceutical Sciences*, vol 1. London: Academic Press, 1964, p 195.

The HLB system gives no information as to the *amount* of emulsifier required. Having once determined the correct blend, the formulator must prepare another series of emulsions, all at the same HLB, but containing increasing concentrations of the emulsifier blend. Usually, the minimum concentration giving the desired degree of physical stability is chosen.

When varying the amounts of emulsifier in an emulsion it is useful to consider the use of a phase diagram to select the proper ratio of oil/water/surfactant. The use of the phase diagram to aid in the formulation of emulsions has been discussed by Swarbrick.[20] This approach can provide a systematic way to optimize an emulsion formulation and help to identify the existence of liquid crystalline phases that, when present in an emulsion formulation, can enhance the stability. Because liquid crystals exhibit birefringence, observation of prototype emulsions under polarized light microscopy can be a useful tool to identify combinations of water–oil and emulsifier that produce liquid crystals. It should be noted that liquid crystals are often formed when relatively high concentrations (eg, 20% or more) of surfactant are used in a formulation. The toxicity of the emulsifier for the intended use (eg, topical, oral, or parenteral) must be considered in addition to the physical characteristics.

MIXED EMULSIFYING AGENTS—Emulsifying agents are frequently used in combination because a better emulsion usually is obtained. This enhancement may be due to several reasons, one or more of which may be operative in any one system. Thus, the use of a blend or mixture of emulsifiers may

1. Produce the required hydrophile–lipophile balance in the emulsifier.
2. Enhance the stability and cohesiveness of the interfacial film.
3. Affect the consistency and feel of the product.

The first point has been considered in detail in the previous discussion of the HLB system.

With regard to the second point, Schulman and Cockbain in 1940 showed that combinations of certain amphiphiles formed stable films at the air–water interface. It was postulated that the complex formed by these two materials (one, oil-soluble; the other, water-soluble) at the air–water interface was also present at the O/W interface. This interfacial complex was held to be responsible for the improved stability. For example, sodium cetyl sulfate, a moderately good O/W emulsifier, and elaidyl alcohol or cholesterol, both stabilizers for W/O emulsions, show evidence of an interaction at the air–water interface. Furthermore, an O/W emulsion prepared with sodium cetyl sulfate and

elaidyl alcohol is much more stable than an emulsion prepared with sodium cetyl sulfate alone.

Elaidyl alcohol is the *trans* isomer. When oleyl alcohol, the *cis* isomer, is used with sodium cetyl sulfate, there is no evidence of complex formation at the air–water interface. Significantly, this combination does not produce a stable O/W emulsion either. Such a finding strongly suggests that a high degree of molecular alignment is necessary at the O/W interface to form a stable emulsion. This high degree of molecular alignment may be a prerequisite event for the formation of lamellar liquid crystalline or gel phases. As illustrated in Figure 22-7, the combination of certain long chain acids and alcohols with water can result in the formation of micelles and liquid crystals. It has also been observed that when liquid crystals or gels form in an emulsion, increased stability is generally observed. As discussed previously, gel or liquid crystalline phases can have an important effect in inhibiting coalescence in emulsions.

When using combinations of emulsifiers, care must be taken to ensure their compatibility, as charged emulsifying agents of opposite sign are likely to interact and coagulate when mixed.

STERIC STABILIZATION—Many useful nonionic surfactants consist of hydrophobic portions composed of fatty acids or other lipophilic organic compounds and hydrophilic portions composed of polyoxyethylene chains. When used to prepare O/W emulsions, the oxyethylene chains protrude into the aqueous side of the O/W interface while the hydrophobic portion of the emulsifier will be primarily located in the oil side. As in the case of suspensions, approaching oil droplets will be influenced by van der Waals attractive forces as well as repulsive forces. For an emulsion that is stabilized by a non-ionic surfactant, the repulsive forces consist of electrostatic and non-electrostatic forces. The electrostatic repulsive forces are similar to those discussed for suspensions and depend largely upon the zeta potential of the oil droplets.

Non-electrostatic forces may also arise from a phenomenon that is frequently described as *steric stabilization.* This effect has been explained as follows. First, as emulsion droplets approach, the adsorbed layers of surfactant on each droplet begin to mix. The hydrophilic oxyethylene chains behave as soluble polymers; as their concentration increases in the region of interfacial mixing, segments of the polymers from separate droplets compete for water molecules. This results in restricted movement of the polymer chains or a loss of entropy. Likewise, a positive heat of solution (enthalpy) may result from the mixing of the polymers in the interfaces. The loss of entropy and/or increase in enthalpy results in an increase in the free energy of mixing, meaning that spontaneous mixing in the interfacial region is not favorable. The particles will tend to separate in order to reverse the temporary increase in the free energy of mixing.

An additional effect that causes repulsion of the droplets may be a result of the increased osmotic pressure that results in the area of contact between the two emulsion droplets. The concentration of oxyethylene groups in the region of overlap between the two droplets increases, necessitating an influx of water into the region. This increase in osmotic pressure has the effect of forcing the droplets apart. Thus, in addition to their favorable effect of reducing interfacial tension, nonionic surfactants that possess long, hydrophilic chains provide additional emulsion stabilization via the energetically unfavorable result of mixing of polymer chains at the droplet–droplet interface.

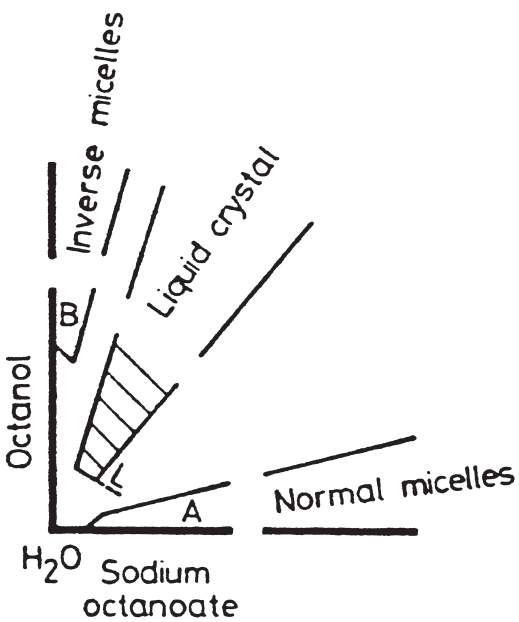


Figure 22-7. Phase diagram illustrating the formation of micellar and liquid crystalline phases in mixtures of a long-chain alcohol, long-chain acid, and water. Compositions that form the lamellar liquid crystalline phase can provide enhanced emulsion stability. (From Friberg S, Larson K. In: Brown GH, ed. *Advances in Liquid Crystals*, vol 2. New York: Academic Press, 1976, p 173.)

Method of Preparation

Different methods are employed, depending on the type of emulsifying agent used and the scale of manufacture. Traditionally, the mortar and pestle was used for the small scale preparation of emulsions stabilized by the presence of such agents as acacia and tragacanth. However, the use of these agents has declined drastically in recent years; as a result, the use of the mortar and pestle has declined as well. (Refer to the 18th edition of this text, page 306, for details of the mortar and pestle method.)

An increasing number of emulsions are being formulated with synthetic emulsifying agents, especially of the nonionic type. The components in such a formulation are separated into those that are oil-soluble and those that are water-soluble. These are dissolved in their respective solvents by heating to about 70° to 75°. When solution is complete, the two phases are mixed and the product is stirred until cool. This method, which requires nothing more than two beakers, a thermometer, and a source of heat, is necessarily used in the preparation of emulsions containing waxes and other high-melting-point materials that must be melted before they can be dispersed in the emulsion. The relatively simple methodology involved in the use of synthetic surfactant-type emulsifiers is one factor that has led to their widespread use in emulsion preparation. This, in turn, has led to a decline in the use of the natural emulsifying agents.

With hand homogenizers, an initial rough emulsion is formed by trituration in a mortar or shaking in a bottle. The rough emulsion then is passed several times through the homogenizer. A reduction in particle size is achieved as the material is forced through a narrow aperture under pressure. A satisfactory product invariably results from the use of a hand homogenizer and overcomes any deficiencies in technique. Should the homogenizer fail to produce an adequate product, the formulation, rather than the technique, should be suspected.

For a discussion of the techniques and equipment used in the large-scale manufacture of emulsions, see Chapter 39.

STABILITY OF EMULSIONS

Several criteria must be met in a well-formulated emulsion. Probably the most important and most readily apparent requirement is that the emulsion possess adequate physical stability; without this, any emulsion soon will revert back to two

separate bulk phases. In addition, if the emulsified product is to have some antimicrobial activity (eg, a medicated lotion), care must be taken to ensure that the formulation possesses the required degree of activity. Frequently, a compound exhibits a lower antimicrobial activity in an emulsion than, say, in a solution. Generally, this is because of partitioning effects between the oil and water phases, which cause a lowering of the *effective* concentration of the active agent. Partitioning has also to be taken into account when considering preservatives to prevent microbiological spoilage of emulsions. Finally, the chemical stability of the various components of the emulsion should receive some attention, as such materials may be more prone to degradation in the emulsified state than when they exist as a bulk phase.

In the present discussion, detailed consideration will be limited to the question of physical stability. Reviews of this topic have been published by Garrett[21] and Kitchener and Mussellwhite.[22] For information on the effect that emulsification can have on the biologic activity and chemical stability of materials in emulsions, see Wedderburn,[23] Burt[24] and Swarbrick.[20]

The theories of emulsion stability have been discussed by Eccleston[25] in an attempt to understand the situation in both a simple O/W emulsion and complex commercial systems. A recent review by the same author[12] has discussed the stability of multiple phase emulsions and the role of bilayer gels and liquid crystalline phases on the physical stability of these systems.

The three major phenomena associated with physical stability are

1. The upward or downward movement of dispersed droplets relative to the continuous phase, termed *creaming* or *sedimentation,* respectively.
2. The *aggregation* and possible *coalescence* of the dispersed droplets to reform the separate, bulk phases.
3. *Inversion,* in which an O/W emulsion inverts to become a W/O emulsion and *vice versa*.

CREAMING AND SEDIMENTATION—*Creaming* is the upward movement of dispersed droplets relative to the continuous phase; *sedimentation,* the reverse process, is the downward movement of particles. In any emulsion one process or the other takes place, depending on the densities of the disperse and continuous phases. This is undesirable in a pharmaceutical product where homogeneity is essential for the administration of the correct and uniform dose. Furthermore, creaming, or sedimentation, brings the particles closer together and may facilitate the more serious problem of coalescence.

The rate at which a spherical droplet or particle sediments in a liquid is governed by Stokes' law (Equation 3). Other equations have been developed for bulk systems, but Stokes' equation is still useful because it points out the factors that influence the rate of sedimentation or creaming. These are the diameter of the suspended droplets, the viscosity of the suspending medium, and the difference in densities between the dispersed phase and the dispersion medium.

Usually, only the use of the first two factors is feasible in affecting creaming or sedimentation. Reduction of particle size contributes greatly toward overcoming or minimizing creaming, because the rate of movement is a square-root function of the particle diameter. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm. The most frequently used approach is to raise the viscosity of the continuous phase, although this can be done only to the extent that the emulsion still can be removed readily from its container and spread or administered conveniently.

AGGREGATION AND COALESCENCE—Even though creaming and sedimentation are undesirable, they do not necessarily result in the breakdown of the emulsion, as the dispersed droplets retain their individuality. Furthermore, the droplets can be redispersed with mild agitation. More serious to the stability of an emulsion are the processes of aggregation and coalescence. In *aggregation* (flocculation) the dispersed droplets come together but do not fuse. *Coalescence,* the complete fusion of droplets, leads to a decrease in the number of droplets and the ultimate separation of the two immiscible phases. Aggregation precedes coalescence in emulsions; however, coalescence does not necessarily follow from aggregation. Aggregation is, to some extent, reversible. Although it is not as serious as coalescence, it will accelerate creaming or sedimentation, because the aggregate behaves as a single drop.

Aggregation is related to the electrical potential on the droplets, but coalescence depends on the structural properties of the interfacial film. As discussed previously, it has been recognized that combinations of emulsifiers produce more stable emulsions than a single emulsifier alone. One reason for this synergy, as suggested by Shulman and Cockbain, is that appropriate combinations of surfactants form densely packed complex films at the oil–water interface. Additional beneficial effects of mixed emulsifier films could result from an increase in viscosity of the interfacial emulsifier film. A viscous interfacial film could enhance emulsion stability because thinning of the film at the points of droplet to droplet contact would be inhibited. An additional explanation for the beneficial effect of mixed-film emulsifiers suggests that appropriate mixtures of surfactants provide a more elastic interfacial film. A more elastic interfacial film would resist rupture upon collision of emulsion droplets.

It has also been observed that when emulsifiers are combined in certain concentrations and proportions, liquid crystalline phases can be formed. The preparation of emulsions with surfactants that form liquid crystalline states can have greater stability against coalescence compared to emulsions that are formulated in the absence of liquid crystalline states. Friberg and Larson[26] have explained the enhanced stability of emulsions due to liquid crystals in terms of a reduced van der Waals attraction between emulsion droplets. Such an effect depends upon the formation of layers or lamellae around the emulsion droplets. Each layer of liquid crystal contributes to a further reduction in the van der Waals attractive force.

An additional effect of liquid crystals may be related to the high viscosity that often is observed upon their formation. Liquid crystals possess a viscosity that is on the order of 100-fold greater than most oil–water interfaces. The high viscosity may result in reduced rates of coalescence. A key factor that may be important for the stabilizing effect of liquid crystals is the location of the liquid crystalline phase in relation to the dispersed droplets. To effectively inhibit coalescence, the liquid crystals should concentrate at the interface between the droplet and the continuous phase. This may not occur with all oil–water–surfactant combinations.

Particle-size analysis can reveal the tendency of an emulsion to aggregate and coalesce long before any visible signs of instability are apparent. The methods available have been reviewed by Groves and Freshwater.[27]

INVERSION—An emulsion is said to *invert* when it changes from an O/W to a W/O emulsion, or *vice versa*. Inversion sometimes can be brought about by the addition of an electrolyte or by changing the phase-volume ratio. For example, an O/W emulsion having sodium stearate as the emulsifier can be inverted by the addition of calcium chloride, because the calcium stearate formed is a lipophilic emulsifier and favors the formation of a W/O product.

Inversion often can be seen when an emulsion, prepared by heating and mixing the two phases, is being cooled. This takes place presumably because of the temperature-dependent changes in the solubilities of the emulsifying agents. The phase inversion temperature (PIT) of nonionic surfactants has been shown by Shinoda and Kunieda[28] to be influenced by the HLB number of the surfactant—the higher the PIT value, the greater the resistance to inversion.

Apart from work on PIT values, little quantitative work has been carried out on the process of inversion; nevertheless, it would appear that the effect can be minimized by using the proper emulsifying agent in an adequate concentration. Wherever possible, the volume of the dispersed phase should not exceed 50% of the total volume of the emulsion.

BIOAVAILABILITY FROM COARSE DISPERSIONS

All dosage forms must be capable of releasing the drug in a known and consistent manner following administration to the patient. Both the rate and extent of release are important. Ideally, the extent of release should approach 100%, while the rate of release should reflect the desired properties of the dosage form. For example, with products designed to have a rapid onset of activity, the release of drug should be immediate. With a long-acting product, the release should take place over several hours or days, depending on the type of product used. The rate and extent of drug release should be reproducible from batch to batch of the product, and should not change during shelf-life.

The principles on which biopharmaceutics is based are dealt with in some detail in Chapters 57 to 59. Although most published work in this area has been concerned with the bioavailability of solid dosage forms administered by the oral route, the rate and extent of release from both suspensions and emulsions are also important and so must be considered in some detail.

BIOAVAILABILITY FROM SUSPENSIONS—Suspensions of a drug may be expected to demonstrate improved bioavailability compared to the same drug formulated as a tablet or capsule. This is because the suspension already contains discrete drug particles, whereas tablet dosage forms must invariably undergo disintegration in order to maximize the necessary dissolution process. Frequently, antacid suspensions are perceived as being more rapid in action and therefore more effective than an equivalent dose in the form of tablets. Bates et al[29] observed that a suspension of salicylamide was more rapidly bioavailable, at least during the first hour following administration, than two different tablet forms of the drug; this study was also able to demonstrate a correlation between the initial *in vitro* dissolution rates for the several dosage forms studied and the initial rates of *in vivo* absorption. A similar argument can be developed for hard gelatin capsules, where the shell must rupture or dissolve before drug particles are released and can begin the dissolution process. Such was observed by Antal et al[30] in a study of the bioavailability of several doxycycline products, including a suspension and hard gelatin capsules. Sansom et al[31] found that mean plasma phenytoin levels were higher after the administration of a suspension than when an equivalent dose was given as either tablets or capsules. It was suggested that this might have been due to the suspension having a smaller particle size.

In common with other products in which the drug is present in the form of solid particles, the rate of dissolution, and thus potentially the bioavailability of the drug in a suspension, can be affected by such factors as particle size and shape, surface characteristics, and polymorphism. Strum *et al*[32] conducted a comparative bioavailability study involving two commercial brands of sulfamethiazole suspension (Product A and Product B). Following administration of the products to 12 normal individuals and blood samples taken at predetermined times over a period of 10 hr, the Strum study found no statistically significant difference in the extent of drug absorption from the two suspensions. The absorption rate, however, differed, and from *in vitro* studies it was concluded that product A dissolved faster than Product B, and that the former contained more particles of smaller size than the latter, differences that may be responsible for the more rapid dissolution of particles in Product A. Product A also provided higher serum levels during *in vivo* tests 0.5 hr after administration. The results showed that the rate of absorption of sulfamethiazole from a suspension depended on the rate of dissolution of the suspended particles, which in turn was related to particle size. Previous studies[33,34] had shown the need to determine the dissolution rate of suspensions to gain information as to the bioavailability of drugs from this type of dosage form.

The viscosity of the vehicle used to suspend the particles has been found to have an effect on the rate of absorption of nitrofurantoin but not the total bioavailability. Thus Soci and Parrott[35] were able to maintain a clinically acceptable urinary nitrofurantoin concentration for an additional 2 hr by increasing the viscosity of the vehicle.

BIOAVAILABILITY FROM EMULSIONS—There are indications that improved bioavailability may result when a poorly absorbed drug is formulated as an orally administered emulsion. However, little research appears to have been done to directly compare emulsions and other dosage forms such as suspensions, tablets, and capsules; thus, it is not possible to draw unequivocal conclusions as to advantages of emulsions. If a drug with low aqueous solubility can be formulated so as to be in solution in the oil phase of an emulsion, its bioavailability may be enhanced. It must be recognized, however, that the drug in such a system has several barriers to pass before it arrives at the mucosal surface of the GI tract.

For example, with an O/W emulsion, the drug must diffuse through the oil globule and then pass across the oil–water interface. This may be a difficult process, depending on the characteristics of the interfacial film formed by the emulsifying agent. In spite of this potential drawback, Wagner *et al*[36] found that indoxole, a nonsteroidal anti-inflammatory agent, was significantly more bioavailable in an O/W emulsion than in either a suspension or a hard gelatin capsule. Bates and Sequeira[37] found significant increases in maximum plasma levels and total bioavailability of micronized griseofulvin when formulated in a corn O/W emulsion. In this case, however, the enhanced effect was not due to emulsification of the drug in the oil phase *per se*, but more probably because of the linoleic and oleic acids present having a specific effect on GI motility.

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CHAPTER 23

Rheology

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Rheology is the branch of physics that deals with deformation, including flow, of matter. Although this definition was proposed in 1929, the recognition of rheological phenomena dates back to antiquity.[1] The earliest application of rheology (*ca* 1600 BCE) is associated with the Egyptian Amenemhet who made a 7° correction to the drainage angle of a water clock in order to account for the temperature dependent variation in water flow during the course of a day. Archimedes's claim (*ca* 250 BCE)—"Give me but one firm spot on which to stand, and I will move the earth."—was based on the application of solid mechanics, the oldest branch of the physical sciences.[1]

Reiner[2] describes a simple mechanical experiment in which he lets three different materials—a pencil, a ball of plasticine, and a known mass of water—fall from some height onto the surface of a table. Newton's second law tells us that $F = m \cdot a$, where F is the force acting upon each of these materials of mass m, and a is the acceleration of the center of mass of each material. Since F is proportional to m, a is the same for each of these materials. Consequently, these three bodies fall towards the table in exactly the same manner. Their material differences do not become apparent until they reach the table top. At that point, the pencil rebounds somewhat, the plasticine stays put, and the water spreads over the tabletop and, on reaching the edge, flows off. These very different outcomes—which mechanics is unable to explain—are the focus of rheology.

The ubiquity of rheological phenomena in pharmacy is evident in the levigation or mixing of ointments on slabs, the use of a mortar and pestle to prepare suspensions and emulsions, the flow of emulsions through colloid mills and pumps, the use of roller mills for compacting powders or processing ointments, and the mechanical properties of glass or plastic containers and of rubber or polymeric closures. Squeezing ointments, creams, or toothpaste from a collapsible tube, spreading lotion on the skin, or spraying liquids from atomizers or aerosol cans all involve rheological phenomena. The fluidity of solutions to be injected by syringe or infused intravenously, the flexibility of tubing used in catheters, and the strength of sutures and ligatures are important rheological properties. Drug release from dosage forms and delivery systems is often controlled or modulated by the rheological properties of the formulation matrix. Although at a molecular level, diffusion is governed, in part, by the rheological behavior of the environment. Rheological principles govern the circulation of blood and lymph through capillaries and large vessels, the flow of mucus, the transit of the luminal contents through the gastrointestinal tract, the bending of bones, the stretching of cartilage, and the contraction of muscles.

The fundamentals of rheology are presented in the following section in the sequence that underscores their temporal recognition and application in pharmacy rather than their historic development in physics.

FUNDAMENTALS

The jargon of rheology can be problematic for the uninitiated. For example, as Scott Blair[3] notes, *stress* and *strain*, in everyday English, have virtually the same meaning. Rheologists, however, use the word *stress* to refer to a system of forces, whether applied in a *compressive*, *extensional*, or *shear* mode, and *strain*, to a change in size or shape.

Rheological principles stem from two fundamental laws derived in the late 17th century: Robert Hooke's law of elasticity (*ca* 1676) and Isaac Newton's law of flow (1687). The corresponding equations, which embody these laws, characterize Hookean and Newtonian materials, respectively. When a force is applied to a body, the two rheological extremes of behavior are the pure elastic deformation of a Hookean solid and the pure viscous flow of a Newtonian liquid. Pure (ideal) elasticity means that the body returns to its original form once the stress is removed, while pure (ideal) viscosity means that the liquid flows even under the smallest stress and does not return to its original shape or form once the stress is removed[4]. The resistance to deformation, or flow, is described by the modulus of elasticity or Young's modulus, E, for an elastic body undergoing extension, and by η, the coefficient of viscosity for a liquid.

Elastic deformation of solids is described by Hooke's law,

$$dl = \frac{\sigma}{E}, \tag{1}$$

where dl is the elastic deformation or extension in length l caused by the application of stress σ. This is illustrated in Figure 23-1.

Viscous deformation, i.e. viscous flow, occurs in accordance with Newton's law,

$$\sigma = \eta\dot{\gamma} \tag{2}$$

wherein the applied stress σ results in flow with a velocity gradient, $\dot{\gamma}$ or rate of shear. The proportionality constant η is termed *viscosity*, while its reciprocal is called *fluidity*. Viscosity has also been described as the *internal friction* in the fluid as it corresponds to the resistance of the fluid to the relative motion of adjacent layers of liquid. This is illustrated in Figure 23-2.

Imagine a liquid contained between two very large, parallel plates as being divided into a stack of very thin, parallel layers much like a deck of cards, as shown in Figure 23-2. Shear is applied to the liquid by pulling or pushing the top plate with a constant force F per unit area A, ie F/A, or σ, while holding the bottom plate stationary. The top liquid layer, in contact with the moving plate, adheres to it and moves with the same velocity as the plate. The second layer, adjacent to the top one, is dragged

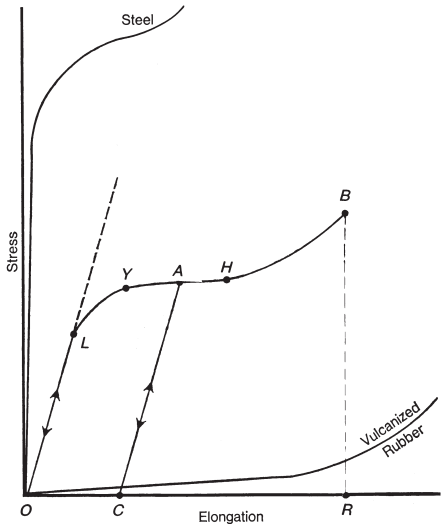

Figure 23-1. Elastic deformation in accordance with Hooke's Law.

along by friction, but its velocity is reduced somewhat by the resistance of the layers beneath it. Each layer is pulled forward by the layer moving above it but is held back by the layer underneath it, over which it moves and which it drags along. The farther the liquid layers are from the moving plate, the smaller their velocities. The bottom layer adheres to the stationary plate and has zero velocity. Thus, the velocity of the liquid layers increases in the direction x perpendicular to the direction of flow y. The *shear strain* or deformation in shear, γ, is the displacement y divided by the height, x, of the sheared or deformed portion of the liquid, as shown in Figure 23-2. It equals the tangent of the displacement angle θ that, at low θ values, is approximately equal to θ expressed in radians: $\gamma = \frac{y}{x} = \tan\theta \cong \theta$.

In due time, all layers except the bottom one undergo infinite deformation. What distinguishes one liquid from another is the rate at which the deformation increases with time. This is called the *rate of* (deformation in) *shear*, $\dot{\gamma}$ or $d\gamma/dt$, the derivative of γ with respect to time, t. An equivalent definition for $\dot{\gamma}$ is the *velocity gradient,* ie, the rate at which the velocity, v, changes with the distance, x, perpendicular to the direction of flow:

$$\dot{\gamma} = \frac{d\gamma}{dt} = \frac{dv}{dx} \qquad (3)$$

The rate of shear or velocity gradient, $\dot{\gamma}$ indicates how fast the liquid flows when a shear stress is applied to it. Its unit according to both definitions is s^{-1}, since γ is dimensionless, velocity is expressed in m/sec, and x in m.

It should be noted that the symbols used in the past in the pharmaceutical literature for the rate of shear, D, and for the shearing stress, τ, have been replaced by $\dot{\gamma}$ and σ, respectively, in accordance with more widely accepted nomenclature recommendations.[5,6]

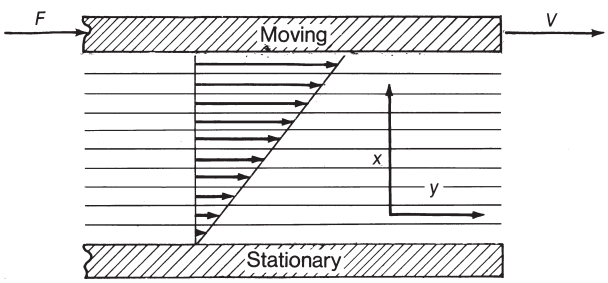

Figure 23-2. Laminar flow of a liquid contained between two parallel plates.

Table 23-1. Approximate Shear Rates for Pharmaceutical Operations

OPERATION	RATE OF SHEAR, S^{-1}
Pouring from a bottle	50
Spreading lotion on skin	400–1000
Levigating ointment on slab with spatula	400–1000
Injecting through hypodermic syringe	4,000
Dispensing nasal spray from plastic squeeze bottle	20,000
Processing in colloid mill	10^5–10^6

Characteristic shear rates for pharmacy-related activities are listed in Table 23-1. Even for a given process, the shear rate can vary within wide limits, depending on the scale of the process and the processing rate. Thus, when a lotion is rubbed into the skin, if the hand (moving surface) slides across the skin (stationary surface) with a velocity $v = 45$ cm/s and if the thickness of the lotion film is $x = 0.05$ cm, then, according to Equation 3, the rate of shear is $\dot{\gamma} = (45 \text{ cm/s})/(0.05 \text{ cm}) = 900 \text{ s}^{-1}$. For a given force and a constant viscosity, the rate of shear is uniform throughout the layer of lotion.

The flow of liquids by parallel layers moving past each other and dragging adjacent layers along (as in Fig 23-2) is called *laminar* or *streamline flow*. At higher velocities and/or if the plates have rough surfaces, eddies or swirls develop whereby mass transfer occurs from one layer or lamina to another. Theoretically, this complex phenomenon—referred to as *turbulent flow*—may be described by a set of partial differential equations, known as the Navier-Stokes equations, which govern fluids in motion. However, explicit solutions of these nonlinear equations, originally derived in the 1840s on the basis of laws of conservation of mass, momentum, and energy, remain elusive.

From a historic rheological viewpoint, deformation of matter was first described in ideal terms. Precise differentiations were made among perfect, rigid *Euclidean* bodies (solids), ideal *Hookean* elastic solids, *Pascalian*, or inviscid, liquids, and *Newtonian* liquids. For ideal Euclidean solids, only mass (or density) is relevant; rigid bodies do not undergo deformation under stress. When stress is applied to an ideal Hookean elastic solid, the deformation induced is fully recovered when the stress is removed. Inviscid liquids exhibit no resistance to flow when stressed, whereas Newtonian liquids undergo flow at a rate that is proportional to the stress applied.

Unfortunately, most solids and fluids encountered in pharmacy do not exhibit ideal behavior consistent with the classical models that evolved with Hooke, Pascal, or Newton. By the 19th century, evidence for more complex, nonideal rheological behavior began to accumulate and the clear-cut dividing line between Hookean or elastic solids and Newtonian or viscous liquids became increasingly blurred. Some systems that behave as elastic solids when subjected to small stresses, or to moderate stresses of short duration, will undergo permanent deformation, resembling very viscous liquids, if the stresses are larger and/or applied for longer periods of time. For many materials, the temporal dependence of their rheological properties necessitates careful consideration of their handling prior to and during the process of rheological evaluation. Nonetheless, an understanding of ideal rheological behavior is necessary before deviations from ideality can be considered.

Elastic Solids

In the stretching or extension of an elastic solid, the deformation is said to be in tension. The deformation or strain of the stretched body, or its elongation, is the difference between its

Table 23-2. Values of Modulus of Elasticity[a] of Representative Solids of Pharmaceutical or Biomedical Interest

MATERIAL	YOUNG'S MODULUS (DYNES/CM^2)
Steel	2.2×10^{12}
Glass	6×10^{11}
Potassium chloride	2.3×10^{11}
Silk, viscose rayon	1.5×10^{11}
Microcrystalline cellulose	1.3×10^{11}
Polystyrene	3.4×10^{10}
Polyethylene (low density)	2.4×10^{9}
Rubber (vulcanized)	2×10^{7}
Tooth enamel	4.7×10^{11}
Bone	2.2×10^{11}
Tendon	1.3×10^{9}
Muscle	6×10^{6}
Soft tissue	7.5×10^{4}
Gelatin gels	
10% solids	2.4×10^{5}
20% solids	1.0×10^{6}
30% solids	1.5×10^{6}

[a]At room temperature.

length while under tension, l_s and its original length, l, which is equal to the length after the stress is released, expressed as a fraction of the original length, namely, $(l_s - l)/l$. Other modes of deformation are by bending or flexure, torsion, compression and shear.

For an ideal elastic solid, Hooke's law (Equation 1) states that the stress is directly proportional to the strain. This relationship is obeyed by real solids at moderate stresses and strains sustained for short periods of time. The *modulus of elasticity* or *Young's modulus, E*, is a measure of the stiffness, hardness, or resistance to elongation. There is also a modulus of shear or rigidity and a compression or bulk modulus. *Tensile compliance* is the reciprocal of Young's modulus, or the ratio of strain to stress.

In the CGS system, the units of stress are dynes/cm^2 or, since force = mass × acceleration, (g-cm/sec^2)/cm^2 = g/(cm sec^2). To convert dynes/cm^2 to the SI unit, Newton/m^2 or Pascal, divide by 10. Since strain is dimensionless, Young's modulus has the same dimensions as stress. Modulus values for a range of solids of pharmaceutical or biomedical interest are listed in Table 23-2.

Figure 23-3 shows representative stress-strain curves in tension, also called load-elongation curves. The cross-sectional area, A, of the solid becomes smaller as it is stretched. Therefore, to calculate the actual or true tensile stresses, the forces are divided by A_s, the cross-sectional area at each appropriate elongation. Stress-strain curves often are plotted with the strain or extension, the dependent variable, on the abscissa while consistency or flow curves (see below) usually are plotted with stress, the independent variable, on the abscissa. The practice followed here is to plot stress on the ordinate for both stress-strain and consistency curves, in order to make modulus and viscosity, respectively, the slopes of these curves.

The characteristic portions in the representative stress-strain curve *OLYAHB* in Figure 23-3 are as follows. Hooke's law of proportionality between stress and strain is obeyed throughout the linear portion *OL*. The elastic modulus of the solid is the slope of *OL* or the tangent of the angle *LOC*. The material behaves elastically up to the yield point *Y*, where the stress is called *yield stress*. When stresses below the yield stress are applied to the sample and then released, it stretches and contracts along the same curve *OLY*.

Beyond *Y*, the material behaves as a *plastic*, rather than as an elastic solid. Along the (nearly) horizontal portion *YAH*, the material is ductile; it flows or creeps under practically constant stress like a viscous liquid. If the stress is released at *A*, the sample retracts along *AC*. The nonrecoverable deformation *OC* is called *permanent set*. Many materials undergoing such "cold flow" are strengthened by some change in structure, causing an upturn *HB* in the stress-strain curve. This is called work (or strain) hardening. It may result from the elimination of flaws, from a reduction in crystal size as in the case of metals, or from reversible crystallization on stretching, as in the case of homo polymer elastomers.

At *B*, the sample ruptures; *R* is the elongation at the break or the ultimate elongation, and the stress corresponding to *B* is the ultimate strength or tensile strength. These values, as well as the load-elongation curve beyond *Y*, depend on the rate at which the sample is stretched.

The area *OLYAHBRCO* under the stress-strain curve is the energy or work required to break or rupture the material. It measures its toughness or brittleness. Glass is hard because of its high elastic modulus. Owing to the absence of a yield point and to a very low elongation to break, it is brittle as opposed to steel, which undergoes work hardening, has a high elongation to break, and is tough. Plastics are medium-hard or soft. Those that exhibit comparatively high elongations at break, like polyethylene but unlike polystyrene, are tough. Vulcanized rubbers are tough even though they are soft (low elastic modulus) because their elongation to break is very high, namely, 600–800%.

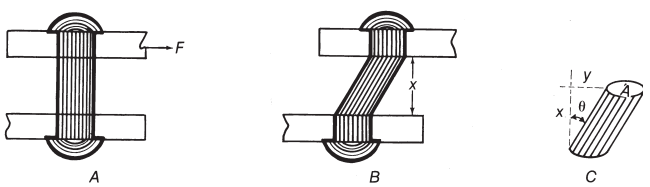

Figure 23-3. Stress-strain curves in tension. Loads or tensile stresses are corrected for actual cross-sectional areas.

Newtonian Fluids

The viscosity of simple liquids, ie, pure liquids consisting of small molecules and solutions where solute and solvent are small molecules, depends only on composition, temperature, and pressure. It increases moderately with increasing pressure and markedly with decreasing temperature. For solutions of solid solutes, the viscosity usually increases with concentration. Simple liquids follow Newton's law (Equation 2) of direct proportionality between shear stress and rate of shear, so that their viscosity is independent of the shear stress or the rate of shear. Their flow behavior is thus referred to as *Newtonian*. Representative Newtonian viscosities are listed in Table 23-3.

Table 23-3. Newtonian Viscosities and Activation Energies for Viscous Flow[a]

MATERIAL	TEMPERATURE (°C)	VISCOSITY (POISE)	ACTIVATION ENERGY FOR VISCOUS FLOW (KCAL/MOLE)
Water	20	0.0100	4.2
	50	0.0055	3.4
	99	0.0028	2.8
Ethanol			
Absolute	20	0.0120	3.3
	50	0.0070	3.3
40% *w/w*	20	0.0291	6.8
	50	0.0113	5.3
Ethyl ether	20	0.0024	1.65
Glycerin			
Anhydrous	20	15.00	12.5
95% *w/w*	20	5.45	10.6

[a]At 1 atm pressure.

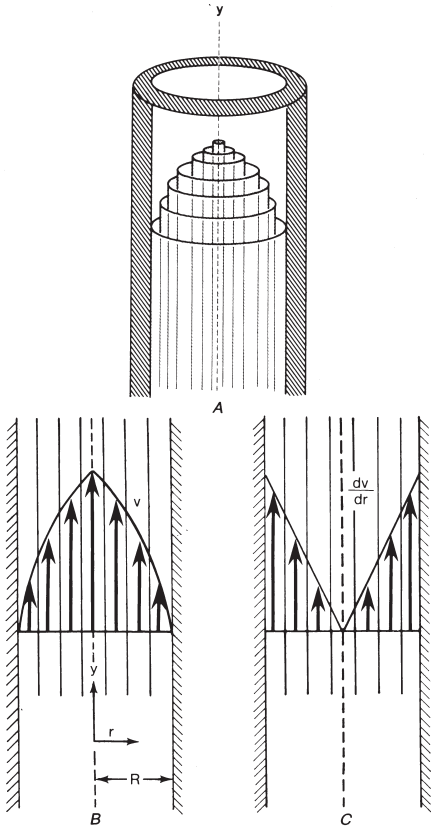

Figure 23-4. Laminar flow of a liquid through a cylindrical duct. **A.** Three-dimensional view of telescoping layers. **B.** Cross-section showing radial distribution of velocity. **C.** Cross-section showing radial distribution of velocity gradient.

Fluid flow through cylindrical pipes or capillaries is laminar, ie, Newtonian, at low velocities, for small tube radii, or for liquids of high viscosity. The liquid layers are very thin cylinders concentric with the duct[2]. During flow, they telescope past one another as shown in Figure 23-4*A*. The arrows in Figure 23-4*B* represent the velocity v of the individual cylindrical layers of radius r; v is maximal in the center of the tube and decreases in the radial direction, ie, in the direction r (previously x) perpendicular to the direction of flow y. The velocity is zero in the outermost liquid layer adjacent to and adhering to the wall, whose radius is equal to the inside radius of the tube R. In the center of the tube, where v is maximum, the velocity gradient $dv/dr = \dot{\gamma}$ is zero. This is shown in Figure 23-4*C*, where the arrows represent $\dot{\gamma}$ and the velocity gradient is maximum at the wall.

If V is the volume of liquid flowing through a cylindrical tube of radius R in time t, the volumetric flow rate is V/t, and the shear rate at the wall is

$$\dot{\gamma}_{wall} = \frac{4}{\pi R^3}(V/t) \tag{4}$$

The shear stress is zero in the center of the tube and maximum at the wall:

$$\sigma_{wall} = \frac{R\Delta P}{2l} \tag{5}$$

The liquid flows through the tube due to pressure, either caused by its own weight (hydrostatic) or produced by a pump. This pressure exceeds the innate viscous friction of the liquid and is converted into heat. The pressure drop, ΔP, along a length l of the tube is the difference between the pressure at the beginning and at the end of the tube.

As viscosity is shear stress divided by rate of shear, and as both vary in the x-direction perpendicular to the direction of flow, both must be evaluated at the same location. Using the values at the wall of a cylindrical tube, dividing Equation 5 by Equation 4, and rearranging gives

$$\frac{V}{t} = \frac{R^4\Delta P}{8l\eta} \tag{6}$$

This is Poiseuille's law, found experimentally by this French physician while studying the flow of liquids through capillary tubes representative of blood vessels. [The poise is also named in his honor.]

In the human body, the pumping action of the heart supplies the driving pressure for the flow of blood, which is the difference between the arterial and venous pressure. Digitalis glycosides increase the force of contraction of the heart muscle and make the heart a more efficient pump. This increases ΔP and, hence, the rate of flow of blood V/t. Vasodilator drugs like nitroglycerin or hydralazine hydrochloride increase the radius of blood vessels by relaxing the vascular smooth muscles. Since the flow rate varies with the fourth power of the radius of the blood vessel, a mere 5% increase in radius causes a 22% increase in the flow rate at constant blood pressure, because $(1.05)^4 = 1.22$.

Plots of shear stress (on the y-axis) as a function of the rate of shear (on the x-axis) are referred to as flow curves or rheograms. The rheograms of typical Newtonian liquids, like those of Figure 23-5, are straight lines going through the origin. Viscosity is the slope of such a line or the tangent of the angle it makes with the horizontal axis. Of the two liquids shown in Figure 23-5, A has a higher viscosity than B because $\alpha > \beta$, so that $\eta_A (= \tan\alpha) > \eta_B (= \tan\beta$; $\eta_A = \sigma_2/\dot{\gamma}_2 = \sigma_1/\dot{\gamma}_1$ and $\eta_B = \sigma_1/\dot{\gamma}_3 = \sigma_3/\dot{\gamma}_2$. A given shear stress, σ_1, produces a greater rate of shear, $\dot{\gamma}_3$, in the more fluid Liquid B than $\dot{\gamma}_1$ in the more viscous Liquid A. Alternatively, to produce a given rate of shear, $\dot{\gamma}_2$, in the two liquids requires a higher shear stress, σ_2, for the more viscous Liquid A than σ_3 for the more fluid Liquid B.

In the CGS system, viscosity is defined as the tangential force per unit area, in dynes/cm^2, required to maintain a difference in velocity of 1 cm/s between two parallel layers of liquid 1 cm apart. Its unit is therefore dynes/cm^2-sec^{-1} or g/cm-s, which is called a *poise.* Because many common liquids including water have viscosities of the order of 1/100 of a poise, their viscosity is often expressed in *centipoise.* In the SI system, the unit of viscosity is Newton/m^2-s^{-1} or Pascal•s, which equals 10 poise. Typical Newtonian viscosities are listed in Table 23-3.

The variation of viscosity with temperature often is described by an *Arrhenius equation:*

$$\eta = Ae^{E_a/RT} \quad \text{or} \quad \ln\eta = \ln A + \frac{E_a}{RT} \tag{7}$$

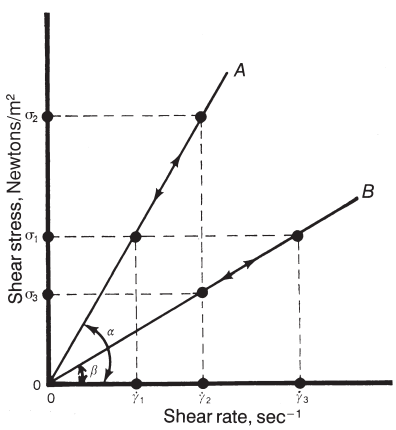

Figure 23-5. Rheograms or flow curves of two Newtonian liquids.

where A and E_a are constants, T is the absolute temperature and R is the molar gas constant. Values of E_a, the *activation energy* for viscous flow, are listed in Table 23-3. Large values of E_a indicate that the viscosity decreases substantially with rising temperature. According to Equation 7, plots of ln η as a function of the reciprocal of the absolute temperature should be straight lines with slopes of E_a /R. For associated, eg, hydrogen-bonded, liquids such plots are often somewhat curved.

According to Eyring's "*hole theory,*" liquids contain vacancies or holes that are essential to flow. The activation energy is used largely to form these holes.[7] E_a is about 1/3 to 1/4 of the latent heat of vaporization for nonassociated liquids.

Non-Newtonian Fluids

Fluids that do not obey Newton's law (Equation 2) are described as *non-Newtonian fluids*. The rheological behavior of non-Newtonian fluids may be characterized either as time-*independent* or time-*dependent* non-Newtonian fluids.

TIME-INDEPENDENT NON-NEWTONIAN FLUIDS— *Shear-thinning fluids.* Many colloidal systems, especially polymer solutions and flocculated solid/liquid dispersions, become more fluid the faster they are stirred. This *shear-thinning* behavior is often referred to as *pseudoplasticity*, but the latter term is outdated and potentially misleading. Shear-thinning behavior is an example of non-Newtonian flow because the viscosity, at constant temperature and composition, is not constant as required by Newton's law of viscous flow (Equation 2), but decreases with increasing shear. As the increase in shear rate is greater than the increase in the corresponding shear stress, the flow curve of Figure 23-6 is concave toward the shear-rate axis.

There is an apparent viscosity for each value of shear rate or shear stress, which can be expressed in two different ways. At point P in Figure 23-6, the apparent viscosity can be taken as the slope of the secant to the flow curve at P, or tan θ, which is the viscosity of a Newtonian liquid whose flow curve passes through P. This is equal to the ratio $\sigma_P / \dot{\gamma}_p$. The second method defines the apparent viscosity as the slope of the tangent to the flow curve at P, ie, $d\sigma_P / d\dot{\gamma}_p = \tan \phi$. Since both θ and ϕ decrease with increasing shear stress or shear rate, so does the viscosity.

The shear-thinning behavior of polymer or macromolecule solutions arises from the alignment of neighboring macromolecules and the degree of their entanglement and concomitant immobilization of solvent. In aqueous solution, for example, the flexible, thread-like macromolecules are buffeted constantly by the surrounding water molecules in thermal agitation. This causes continuous random motion of chain segments by translation and by rotation around bonds between the atoms that make up the macromolecular backbone. These thermal fluctuations result in the formation of loose, roughly spherical coils that are permeated by water. The macromolecule chains are encased

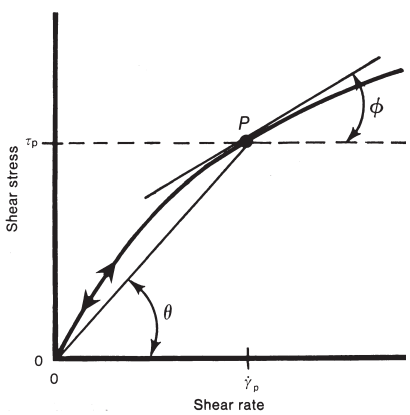

Figure 23-6. Flow curve of a shear-thinning liquid.

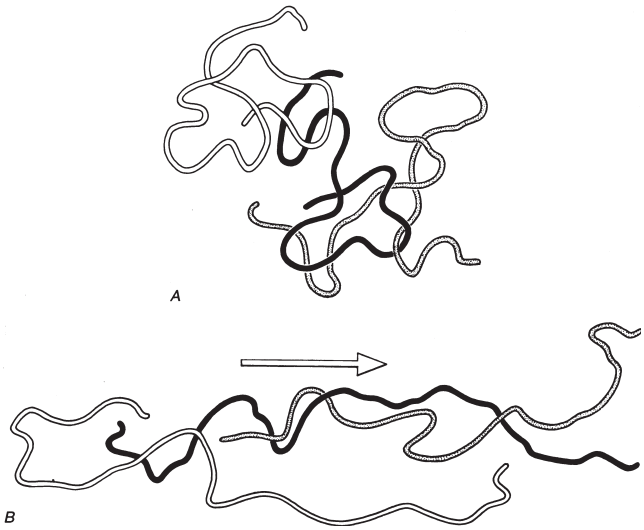

Figure 23-7. Three randomly coiled polymer chains in solution. **A.** At rest; **B.** In shear field.

in sheaths of water of hydration. Additional water is mechanically trapped inside the open coils. The coiled macromolecules, in constant segmental motion, become entangled (Figure 23-7*A*). Upon the application of shear, a unidirectional laminar motion is superimposed on the random thermal motion of the water molecules and chain segments. The randomly coiled, entangled macromolecules tend to disentangle themselves and to align themselves in the direction of flow, as shown in Figure 23-7*B*. The viscosity of the solution—its resistance to flow—depends on the size and shape of the flow units. The imposition of increasing shear in these systems enables the macromolecule "chains" to uncoil progressively and become streamlined or elongated, thereby offering less resistance to flow than the original, approximately spherical, shapes. At the same time, the amount of water trapped inside the coils and dragged along decreases. Furthermore, the chains become gradually more disentangled. Reduced entrapment of water and decreased entanglement of the macromolecules reduce the size of the flow unit, thereby reducing the viscosity. A further reduction in viscosity results from shear-induced uncoiling of the macromolecules. Thus, the apparent viscosity at a given rate of shear reflects the degree of randomization, coiling, entanglement, and alignment of the macromolecules, and the extent to which solvent molecules are associated with the macromolecules.

Dispersions of flocculated solid particles exhibit shear-thinning if the particle-particle bonds are too weak to withstand the applied shear stresses. Examples of weak interparticle bonds include weakly flocculated particles, in a secondary minimum, or electrostatically attracted lamellar clay platelets with positively charged edges and negatively charged faces that produce a "house-of-cards" structure in an aqueous suspension.

Shear progressively breaks up these aggregates at a rate that increases with increasing shear stress, releasing increasing amounts of trapped water. Brownian motion tends to rebuild the aggregates at a rate that is independent of shear. There is an average equilibrium size for the aggregates at each rate of shear that decreases with increasing shear, resulting in a decrease in the resistance to flow, or viscosity, as the shear increases.

At extremely low shear rates, well below 1 s^{-1}, the rate of disentanglement and alignment of polymer chains and the rate of breaking up of aggregates of particles under the influence of shear are negligible compared to the rate of entanglement and randomization of polymer chains and to the rate of aggregation of particles produced by Brownian motion, respectively. Hence, the flow units are neither noticeably deformed nor reduced in

size by shear, and the systems exhibit Newtonian flow, with a constant and high viscosity designated as the *lower Newtonian* or *zero-shear viscosity,* η_0.

At very high shear rates, the dissolved polymer chains are wholly disentangled and well aligned in the direction of flow, and the aggregates of particles are broken up as far as possible. There is no residual structure left which can be broken up by further increments in shear rate: The viscosity levels off at a constant value called the *upper Newtonian viscosity,* η_∞. Turbulent flow and shear-induced rupture of polymer chains may set in before the upper Newtonian regime is reached. As can be seen in Figure 23-8, η_∞ is considerably lower than η_0. The value of the non-Newtonian viscosity observed at intermediate shear rates, including those encountered in most practical situations, depends on the amount of residual structure. It is, therefore, called *structural viscosity.*

Dilatancy—In contrast to shear-thinning, *shear-thickening* or *dilatancy*, ie an increase in viscosity with increasing shear, is rare. It is shown by concentrated dispersions of particles which do not tend to aggregate or stick together, provided the amount of liquid present is not much larger than that needed to fill the voids between the particles. Sediments of suspensions from which the supernatant liquid has been decanted are sometimes dilatant. When such a concentrated suspension is poured or stirred slowly, there is just enough liquid to lubricate the slipping of one particle past another, and the viscosity is low. When stirred fast, the particles get into each other's way, block each other and bunch up rather than slipping past each other. Large voids form between the unevenly clustered particles, and as the liquid seeps into these, the suspension appears dry—as if the suspended solids had expanded or become dilated. This phenomenon, which results in progressive viscosity increases, becomes more severe with increasing shear. When high shear is followed by low shear or rest, the particles that had been crowded together separate again, the interparticle void volume decreases, and the viscosity drops as the suspension appears wet again. Wet sand offers small resistance to slow flow or penetration, but stiffens and appears dry when deformed fast.

Among the few systems reported[8] to exhibit dilatant flow are suspensions of starch in water, aqueous glycerin or ethylene glycol containing about 40–50% *v/v* starch, and concentrated suspensions of inorganic pigments in water and in nonpolar liquids with enough surfactant added to deflocculate the disperse phase completely, eg, red iron oxide (12% *v/v* in water or 18% *v/v* in carbon tetrachloride), zinc oxide (30% *v/v* in water or 33% *v/v* in carbon tetrachloride), barium sulfate (39% *v/v* in water), and titanium dioxide (30–50% *v/v* in water).

Plasticity—Semisolids that do not flow at low shear stresses (exhibiting reversible deformation like elastic solids) but flow like liquids above their yield value (ie yield stress) are termed

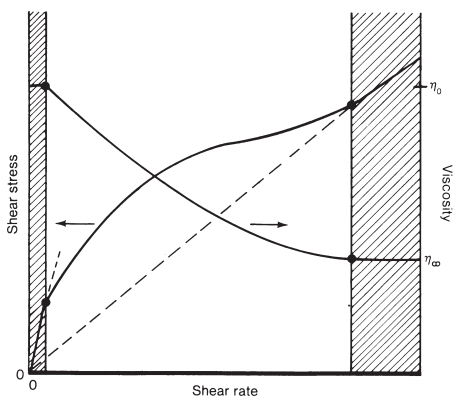

Figure 23-8. The three flow regions of a shear-thinning liquid. Shaded areas refer to lower (left) and upper (right) Newtonian regions; center area represent shear-thinning behavior.

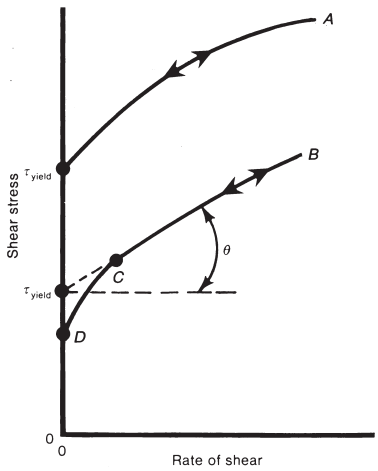

Figure 23-9. Flow curves of two plastic systems.

plastics or *Bingham bodies*. This type of rheological behavior is called *plasticity*. Plasticity is often exhibited by semisolids characterized as structured media, ie semisolids that have a *cross-linked* three-dimensional network of polymers, macromolecules, or particulates extending throughout the system.

Figure 23-9 shows the flow curves for two plastic systems. System *B* has a lower yield value than System *A* and Newtonian behavior at stresses above the yield value; BCσ_{yield} is a straight line of inclination θ, so that the *plastic viscosity* of *B,* ie, its viscosity above the yield value, is the slope of this line or tan θ:

$$\eta_{plastic} = \frac{\sigma - \sigma_{yield}}{\dot{\gamma}}. \quad (8)$$

This is equivalent to moving the origin of the flow curve from zero stress to the yield stress, and treating System *B* as a Newtonian liquid at stresses beyond. Semisolids with high yield values are described as "hard." When their plastic viscosity is high, they are described as "stiff."

Some Bingham bodies have flow curves that deviate from straight lines at stresses close to the yield stress, such as the portion *CD* in the flow curve of System *B,* where flow occurs even below the yield stress. This phenomenon is called *plug flow* because the material moves in chunks or as a plug rather than by laminar motion, often through slippage at the wall of the duct. In such cases, the yield value usually is obtained by extrapolating the linear portion *BC* to the stress axis.

System *A* is shear-thinning *above* its yield stress. This type of flow behavior is observed frequently with suspensions thickened with dissolved polymers, where the vehicle itself is shear-thinning.

TIME-DEPENDENT NON-NEWTONIAN FLUIDS—In the previous discussion, shear-thinning and plastic behavior was seen to arise from competition between the detachment of entanglement links among dissolved macromolecules or the rupturing of van der Waals links among dispersed particles by shear, and the reestablishment of such links by Brownian motion. The balance between breakdown and restoration of links shifts more and more toward breakdown as the shear increases. Reduction in interchain or interparticle links results in smaller flow units and lower apparent viscosity. It was assumed tacitly that the system adapts itself to changing shear "instantaneously," ie, so fast that by the time the instrumental conditions had been changed to higher or lower shear and readings then taken, the equilibrium between breakdown and restoration of links at the new shear already had been reached, producing flow units of the new average equilibrium size and the corresponding new apparent viscosity. Points representing pairs of $\dot{\gamma}$, σ values determined at increasing and at decreasing shear rates or shear stresses in Figures 23-5, 23-6, and 23-9 fall

on the same single curves. It is immaterial whether a given shear rate was reached by increasing or decreasing the speed of the viscometer. This is the meaning of the double arrows on these curves.

Thixotropy—If the suspension is viscous and/or the particles are large and heavy, their Brownian motion is too slow to restore the broken interparticle links "instantaneously." Likewise, the entanglements of polymer chains are slow to be reestablished by Brownian motion if their solution is viscous. If the rate of link restoration by Brownian motion is lower than the rate of link breakdown by shear, the apparent viscosity decreases even while the system is under constant shear, as the size of the particle aggregates or the extent of macromolecular entanglement is progressively reduced. Furthermore, the apparent viscosity at a given shear rate is lower if the system was stirred recently at high speeds than if that shear rate was approached from low speeds or from rest.

Materials, whose consistency depends on the duration of shear as well as on the rate of shear, are said to be thixotropic or to exhibit *thixotropy.* Their apparent viscosity depends not only on temperature, composition, and rate of shear or shear stress, but on the previous shear history and time under shear.

The extreme behavior is an isothermal, reversible sol-gel transformation produced by rest and by shear, respectively. For example, an aqueous dispersion of 8% w/w sodium bentonite sets to a gel within an hour or two after preparation when undisturbed, but flows and can be poured within many minutes after it had been stirred above the yield value. After prolonged rest it reverts to a gel as the Brownian motion rebuilds the house-of-cards structure throughout the material.

Thixotropy in a shear-thinning liquid is shown in Figure 23-10. Starting with the system at rest (at the origin *O)* and gradually increasing the speed of the viscometer produces the "up" branch *ODAB* of the flow curve. After the maximum shear rate $\dot{\gamma}_1$ and shear stress σ_3 corresponding to point *B* have been reached, the speed of the instrument is reduced. If there is not enough time for Brownian motion to regenerate completely, the structure torn down at the high speed, the liquid will be less viscous, and the "down" branch of the flow curve, *BCO,* is lower than the "up" branch. Thus, the shear stress required to maintain the rate of shear $\dot{\gamma}_2$ has been reduced from σ_1 to σ_2, and the apparent viscosity has dropped from $\sigma_1/\dot{\gamma}_2$ to $\sigma_2/\dot{\gamma}_2$. This contrasts with the flow curve of Figure 23-6, where the "up" and "down" branches coincide.

When starting from rest, if the speed is not increased all the way up to $\dot{\gamma}_1$ but only to $\dot{\gamma}_2$ corresponding to point *A* in Figure 23-10 and then decreased, the "down" branch is *AEO:* Since the maximum speed is lower than previously, less structure is broken down and the apparent viscosity is not reduced by as much.

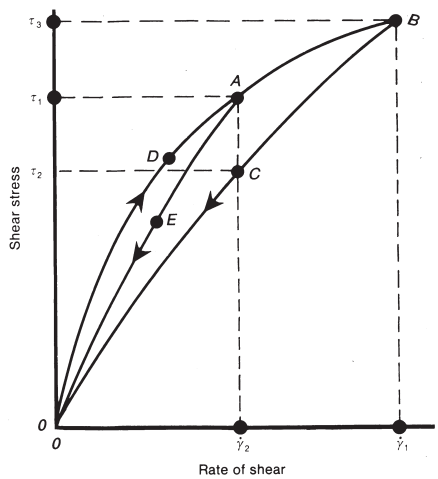

Figure 23-10. Flow curves of a shear thinning liquid exhibiting thixotropy.

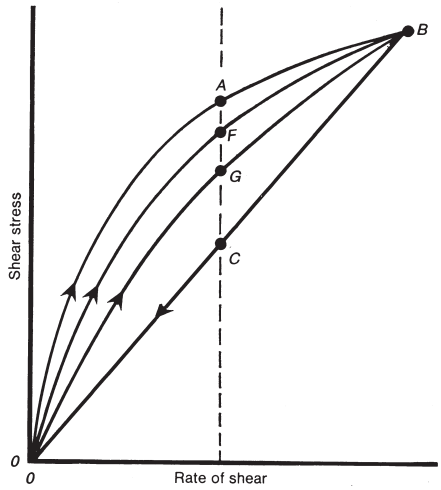

Figure 23-11. Flow curves representing successive shear cycles for a thixotropic, shear-thinning liquid.

If the liquid in the instrument is kept at rest for a sufficient time period after it was subjected to the shear cycle *ODABCO,* Brownian motion rebuilds its structure, restoring its original high consistency. Starting from rest, the flow curve is again *ODABCO.* If no rest period is allowed and the shear cycle is repeated as soon as the "down" branch is completed, the next "up" branch is below *ODAB,* say, *OFB* in Figure 23-11. A third shear cycle following immediately after the second may give the "up" branch *OGB.* The "down" branch *BCO* may be curved as in Figure 23-10 or straight as in Figure 23-11. If the buildup of structure is very slow, there may be no structure left after the third shear cycle. In that case, the "up" branch coincides with the straight "down" branch *BCO* and the liquid has become Newtonian. This is only temporary because the flow curve reverts to *OABCO* of Figure 23-11 after a prolonged rest period.

Thixotropy frequently is superimposed on plastic flow behavior. The yield value may disappear after one or more shear cycles, as in curve *C* of Figure 23-12; it may be reduced as in curve *B* (sometimes called *false body* behavior), or it may remain unaltered as in curve *A.*

The difference between the *up* and *down* branches of a flow curve illustrates a common phenomenon called *hysteresis.* The area enclosed by the two branches (eg, areas *ODAEO* and *ODABCO* in Figure 23-10) or by the two branches and the stress axis (as in Figure 23-12 *B* and *C*) is called the *hysteresis loop.* Its size is a measure of the extent of thixotropic breakdown in the structure of the system. In Figure 23-11, the areas enclosed by the two branches of the flow curves representing successive shear cycles become progressively smaller: *OABCO* > *OFBCO* > *OGBCO.* This parallels a decrease in the amount of structural breakdown of the system as each cycle leaves intact less residual structure to be broken down in the next cycle. When no structure remains, the Newtonian flow curve *OCBCO* of Figure 23-11 results. The absence of hysteresis in the flow curves of Figures 23-6 and 23-9 is due to another cause: The rebuilding of structure by Brownian motion is as fast as or faster than the shear-induced structural breakdown or the response time of the viscometer.

Thixotropy may be represented quantitatively by the area of the hysteresis loop, by a thixotropic coefficient or index (*T.I.*) at a specific $\dot{\gamma}$ for a set period of time, eg,

$$TI = \frac{\sigma\,|_{\text{before shearing}}}{\sigma\,|_{\text{after shearing at } 0.01\text{s}^{-1}}} \qquad (9)$$

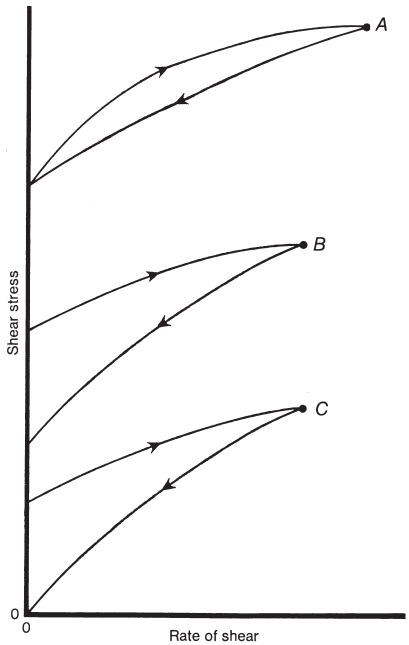

Figure 23-12. Flow curves of plastic systems exhibiting thixotropy (see text).

by shearing samples at various $\dot{\gamma}$ as a function of time and fitting all of the data to an equation of the form

$$\eta = A\dot{\gamma}^{B}t^{C} \qquad (10)$$

where *A* is a proportionality constant, and the exponents *B* and *C* are indices of shear-thinning and thixotropy, respectively. As B increases, the fluid becomes more shear-sensitive; as C increases, the fluid becomes more time-dependent.[9] A simple alternative method involves the measurement of the decay of shear stress or apparent viscosity as a function of time at a constant rate of shear. This method is illustrated in Figure 23-13. When a system is stirred at a constant shear rate, it eventually reaches constant or equilibrium values for shear stress and apparent viscosity. This is shown by the leveling off of the curve. Equilibration at a given shear rate may take half an hour or longer.

Thixotropy is particularly useful in the formulation of pharmaceutical suspensions and emulsions. These must be poured easily from containers, which implies low viscosity. Low viscosity, however, causes rapid settling of solid particles in suspensions and rapid creaming of emulsions. Solid particles that have settled out frequently stick together, producing a sediment difficult to redisperse ("caking" or "claying"). Creaming in emulsions is a first step towards coalescence. Thixotropy can be used to resolve this dilemma. A thixotropic agent such as sodium bentonite magma, other colloidal clays (magnesium bentonite, attapulgite), colloidal silicon dioxide, or microcrystalline cellulose is incorporated into the suspensions or emulsions to confer a high apparent viscosity or even a yield value. High viscosities retard sedimentation and creaming since, according to Stokes' law, the rate of sedimentation or creaming is inversely proportional to the viscosity of the medium. If the system possesses a yield value, sedimentation or creaming is prevented altogether since there is no flow below the yield stress, ie the apparent viscosity at low shear becomes infinite. When it is desired to pour some of the suspension or emulsion from its container, it is shaken well, at shear stresses considerably above the yield value. The agitation breaks down temporarily the thixotropic structure such as the house-of-cards scaffold of bentonite, reducing the yield value to zero and lowering the apparent viscosity. This makes for easy pouring. Back on the shelf, the viscosity slowly increases again and the yield value is restored as Brownian motion rebuilds the house-of-cards structure of bentonite. This prevents sedimentation and caking of the suspended particles and creaming of the emulsion droplets; the disperse particles again become trapped in the plastic matrix. The optimum flow curve for such formulations is that of Figure 23-12*C*.

Rheopexy and Negative Thixotropy—Once the links among suspended particles or the entanglements among dissolved polymer chains have been broken by shear, their restoration by Brownian motion is slow if the suspensions or solutions are viscous. In such cases slow flow, gentle agitation, or moderate and rhythmic vibration may accelerate the rebuilding of the structure, ie, the restoration of the links between particles or macromolecules by Brownian motion. Low shear rates thus hasten the reappearance of high apparent viscosities or onset of gelation in thixotropic sols. In the case of sheared dispersions of bentonite, gentle vibration or rotation of the beaker speeds up the rebuilding of the house-of-cards structure. The material's recovery of some of its presheared viscosity at a faster rate when it is gently sheared, compared to when it is allowed to stand, is called *rheopexy*. Rheopexy is not to be confused with *negative thixotropy* (ie, anti-thixotropy), which is defined as a reversible time-dependent increase in viscosity at a particular shear rate as a result of shear-induced buildup of structure over time.

VISCOELASTICITY—Normal condensed matter is either solid or liquid. The molecules of an ideal solid are fixed in place while those of an ideal liquid are mobile. *Soft condensed matter* occupies a middle ground between the solid and liquid states as it typically possesses a structure that is on a substantially larger scale than atomic or molecular dimensions, ie the *mesoscopic* scale. [*Soft condensed matter*, *soft matter*, and *nanostructured systems* are, in effect, *colloids* or *colloidal dispersions* but the latter terms are being increasingly supplanted in the scientific literature by the former terms.] As a result, the *macro*scopic rheological behavior of soft condensed matter is determined by the structure and dynamics at the mesoscopic scale and is often described as *viscoelastic* in nature. When stressed, viscoelastic materials simultaneously exhibit some of the properties of elastic solids and some of the properties of viscous liquids: some deformation occurs instantaneously upon the application of stress and continues as long as the stress is applied. Upon removal of the stress, there is partial recovery of the original shape. In effect, viscoelastic systems are capable of storing part of the deformation energy elastically and reversibly. The relative proportions of elastic deformation and viscous flow are dependent upon the duration of time that stress is applied. In effect, the rheological characterization of viscoelastic materials depends, in part, on the experimental methodology employed. One useful parameter is the dimensionless *Deborah* number, N_{De}, defined by Reiner[10] as

$$N_{De} = \frac{\lambda}{t_p} \qquad (11)$$

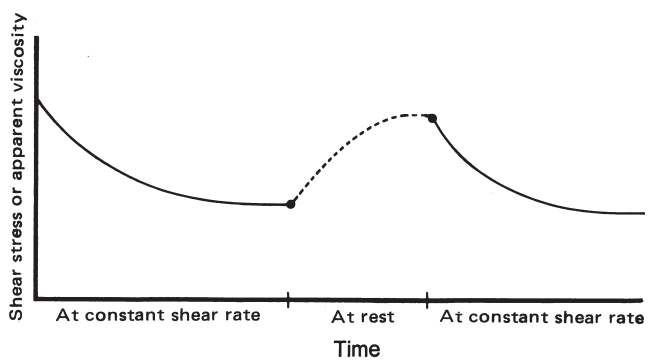

Figure 23-13. Time dependence of shear stress or of apparent viscosity of a thixotropic system.

where λ is the stress relaxation time (defined as the time required for the stress to decay to $1/e = 36.8\%$ of its initial value) and t_p is the process or observation time. When material is instantaneously deformed, the structure is perturbed as viscous flow occurs, and its microstructural elements, whether molecules or particles, are in a higher energy state. It takes some time for these molecules or particles to diffuse to a location where their energy state is equivalent to the pre-stress level.[11] The relaxation time for viscoelastic materials is of the same order of magnitude as the observation time ($N_{De} \approx 1$) while the relaxation time for a Newtonian fluid would be 0 (ie, relaxation time is instantaneous) and that for a Hookean solid would be ∞ (ie, no relaxation occurs). For nonideal materials, then, $N_{De} << 1$ are indicative of liquids and $N_{De} >> 1$, of solids.

Silicone putty (*Silly Putty*) is an example of a viscoelastic material. It has a comparatively short mean relaxation time (~1 s) at room temperature. It bounces, behaving like an elastic solid when the time of observation or of application of stress is short, but flows and shows little elasticity when slowly stretched. However, viscoelasticity is widespread even among liquids and plastic materials which seem to lack elasticity or stringiness to the touch, especially if they are tested at small deformations. Higher deformations or rates of shear approaching use conditions frequently rupture the elastic network in these materials, causing the loss of the elastic components of their rheological properties. For instance, fluid emulsions are often slightly viscoelastic at very low shear due to flocculation of the disperse droplets and interlinking of the flocs; they flow readily and lose all recovery properties under slightly higher shear.[12] Davis[13] determined the viscoelastic properties of oleaginous, emulsion, and absorption-type ointment bases by creep measurements. Radebaugh and Simonelli[14] evaluated the viscoelastic properties of powder-filled semisolids using starch dispersions in lanolin as their model. As gels, pastes, and polymer or macromolecule solutions often exhibit substantial viscoelasticity, this aspect of rheological behavior should not be ignored.

Unusual rheological phenomena associated with viscoelastic flow include the *Weissenberg effect*, in which fluid climbs up a shaft or impeller rotating in the fluid, and the *die swell effect*, wherein fluid exiting from a tube or capillary expands to two or more times the diameter of the tube. The Weissenberg effect is occasionally encountered in mixing operations while the die swell effect may be experienced during extrusion processes. Both phenomena result from the so-called *normal stress* effect in viscoelastic flow, ie the tendency of some viscoelastic fluids to flow in a direction normal to the direction of shear. Experimentally observable stresses normal to the direction of shear arise from fluid motion and the isotropic hydrostatic pressure in the system. In Newtonian fluids, the stresses generated by the flow act parallel to the direction of shear; Figure 23-14 presents a schematic view in x, y, and z coordinates of the stresses operating within a system subjected to shear.

The stresses in the system are denoted by σ_{xx}, σ_{xy}, σ_{xz}, σ_{yx}, σ_{yy}, σ_{yz}, σ_{zx}, σ_{zy}, and σ_{zz}, where the first subscript letter indicates the direction of the plane in which the shear stress lies and the second gives the direction in which it acts. The stresses $\sigma_{xx}\sigma$, σ_{yy}, and σ_{zz} are the normal stresses in the system. In a Newtonian system in simple shear in the x-direction, $\sigma_{xx} \sim \sigma_{yy} = 0$ and $\sigma_{yy} - \sigma_{zz} = 0$, $\sigma_{xy} = \sigma_{yx}$, $\sigma_{xz} = \sigma_{zx}$, $\sigma_{yz} = \sigma_{zy}$, and $\sigma_{xz} = \sigma_{yz} = 0$, so that there are only six independent stresses in the system.[15] It is customary to eliminate the isotropic pressure in the system by taking the differences between normal stresses[16]:

$$\sigma_{xx} - \sigma_{yy} = N_1 \quad \text{and} \quad \sigma_{yy} - \sigma_{zz} = N_2 \tag{12}$$

where N_1 and N_2 are the first and second normal stress differences, respectively.

In effect, stresses normal to the direction of shear are different from those in the parallel direction. Fluids that exhibit no normal stress effects but only time-independent non-Newtonian viscous flow are sometimes characterized as *generalized Newtonian fluids*. However, when normal stress effects *are* evident, the fluids are viscoelastic in nature. Another indicator of viscoelasticity related to the Deborah number, N_{De}, is the dimensionless *Weissenberg* number, N_{Wi}, that characterizes the importance of elasticity in the flow by expressing the ratio of the first elastic normal stress difference to the shear stress:

$$N_{Wi} = \frac{N_1}{\sigma}. \tag{13}$$

For Newtonian fluids, $N_{Wi} \equiv 0$; for viscoelastic fluids $N_{Wi} > 0$. In the course of addressing scale-up issues in biotechnology, Zlokarnik[17] has estimated N_{Wi} for various aqueous hydrocolloid solutions (carboxymethyl cellulose sodium, 1–2% w/v; xanthan gum, 0.05–0.2% w/v) used as model fluids in cell culture studies; typical N_{Wi} values range from 1 to 10. In effect, the substantial viscoelastic nature of these systems must not be ignored if scale-up is to be successful.

In the realm of pharmaceutical solids, plasticity and viscoelasticity are observed during the course of tableting. This is not unexpected given the conditions of extreme stress used in the compaction of compressed tablets. The viscoelastic parameters of a number of drugs and excipients have been measured, under various conditions, during the stress-unloading phase of the tablet compaction cycle in a rotary tablet press.[18,19]

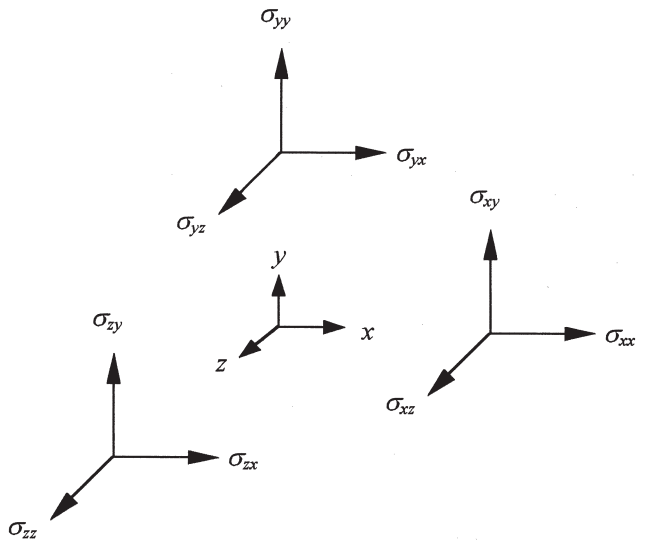

Figure 23-14. Schematic representation in x, y, and z coordinates of stresses operating within a system subjected to shear.

Rheological Models

LIQUIDS—Many liquids of pharmaceutical interest follow the empirical *power law* or *Ostwald-de Waele equation* over a wide range of shear rates, where

$$\dot{\gamma} = K\sigma^n \quad \text{or} \quad \log\dot{\gamma} = \log K + n \log \sigma \tag{14}$$

In many references in the literature, the power law is given as $\sigma = k\dot{\gamma}^n$, so that values of $n > 1$ correspond to dilatant or shear thickening behavior and values of $n < 1$ to shear-thinning behavior. Of course, for Newtonian liquids $n = 1$.

For so-called *power-law liquids*, a plot of log $\dot{\gamma}$ versus log σ yields a straight line of slope n. The power law equation has the advantage of representing flow behavior in terms of only two constants, K and n. On the other hand, it has the disadvantage of all power laws, namely, the dimensions of the intercept K

depend on the value of n, the specific shear rate at which K is evaluated, and the nature of the rheometer.[2]

For n = 1, K = 1/η, and Newton's law (Equation 2) results. Thus, the exponent, n, is an index of the deviation from Newtonian flow behavior. The more n differs from unity, the more non-Newtonian is the flow behavior, ie, the more substantial the viscosity decrease or increase with increasing shear. Among pharmaceutical liquids, the most commonly encountered deviants from time-independent Newtonian behavior are those described as *shear-thinning* fluids for which the power law exponent $n > 1$; less commonly encountered are *dilatant* fluids for which $n < 1$. Shear-thinning and dilatant liquids frequently follow this empirical *power law* or (Equation 8) over a wide range of shear rates.

OTHER EMPIRICAL EQUATIONS AND MODELS— Many empirical equations and models have been developed over the years in an effort to describe the flow behavior of non-Newtonian systems. One of the more successful relationships is the Herschel-Bulkley model,

$$\sigma = k\dot{\gamma}^n + \sigma_0 \qquad (15)$$

in which σ_0 is the yield stress and k is a consistency coefficient. For dilatant or shear thickening systems, $k > 0$, $1 < n < \infty$, and $\sigma_0 = 0$; for shear-thinning systems, $k > 0$, $0 < n < 1$, and $\sigma_0 = 0$; and, for Bingham plastics, $k > 0$, $n = 1$, and $\sigma_0 > 0$.

VISCOELASTIC MATERIALS—Viscoelastic behavior is often represented in terms of a mechanical model. Two of the basic elements used in such a model are a helical spring (which obeys Hooke's law and is characterized by a modulus *E)* and a dashpot (ie, a cylindrical container with a loosely fitting piston filled with a Newtonian liquid, characterized by its viscosity, η). When the deformation is in shear rather than in tension, Young's modulus E is replaced with the rigidity or shear modulus G. When a spring and a dashpot are connected in series, they form a Maxwell element (Figure 23-15*A*); when they are connected in parallel, they form a Voigt-Kelvin element (Figure 23-15*B*). Several Maxwell and/or Voigt-Kelvin elements can be combined in parallel and/or in series to represent the complex viscoelastic behavior of solutions and semisolids. A simple combination is Burgers' model, which consists of a Maxwell and a Voigt-Kelvin element in series (Figure 23-15*C*) and is characterized by two elastic moduli and two viscosities.

When a constant load or stress, σ_0, is applied to a Maxwell element, the elastic spring extends immediately to the recoverable strain or elongation, $\gamma_{el} = OA = \sigma_0/E$ (Figure 23-16*A*). The

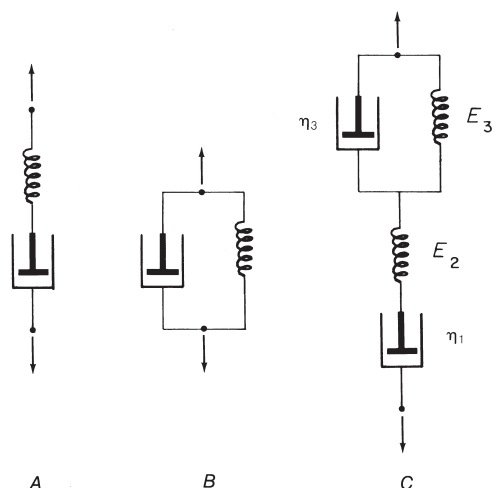

Figure 23-15. Elements of mechanical models for viscoelastic behavior. **A.** Maxwell element. **B.** Voigt-Kelvin element. **C.** Burgers' model. Arrows show applied force or load.

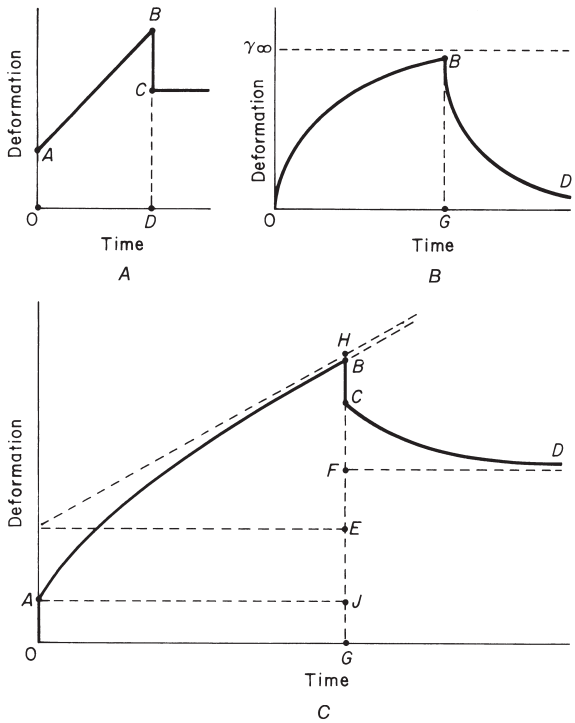

Figure 23-16. Deformation of three rheological models at constant applied stress. **A.** Maxwell element. **B.** Voigt-Kelvin element. **C.** Burgers' body.

piston in the dashpot pulls upwards gradually; this permanent deformation, γ_{vis}, is directly proportional to time, t. The two deformations are additive: $\gamma = \gamma_{el} + \gamma_{vis}$. At time D, $\gamma = BD = BC + CD = OA + CD$. When the stress is removed at time D (Point B), the spring retracts immediately and fully, and the specimen contracts from B to C by a length, $\gamma_{el} = BC = OA$. The permanent or nonrecoverable deformation, or creep, is $\gamma_{vis} = CD = \sigma_0 t/\eta$.

In plots like those of Figure 23-16, compliance (ie, strain per unit stress) often is used instead of strain. Compliance (eg, shear or tensile) is the reciprocal of modulus.

If the Maxwell element is stretched to a given deformation, γ_0, the stress required to maintain this deformation constant decreases gradually. As the piston of the dashpot is pulled gradually upwards and the dashpot extended, it increasingly relieves the stress on the spring, which gradually contracts. After a long time, as $\gamma \to \gamma_{vis}$, $\sigma \to 0$.

If the initial stress is σ_0 and the stress at time, t, is σ, the stress relaxation is

$$\sigma = \sigma_0 e^{-(Et/\eta)} = \sigma_0 e^{(-t/\theta)} \qquad (16)$$

The exponent Et/η is dimensionless and the ratio $\theta = \eta/E$, which has the dimension of time, is the relaxation time.

When a constant stress σ_0 is applied to a Voigt-Kelvin element (Figure 23-16*B*), the spring can stretch only as fast as the slow extension of the viscous dashpot permits. The greater the viscosity of the liquid in the dashpot, the greater is this retardation. The stress is shared by spring and dashpot, ie, $\sigma_0 = E\gamma + \eta\dot{\gamma}$. As σ_0 stretches the spring-dashpot assembly, the retarded elastic deformation of the specimen increases with time until, at $t = \infty$, the spring reaches the full extension corresponding to the applied stress: $\gamma_\infty = \sigma_0/E$. No additional deformation then takes place. When the stress is removed at time G, the specimen retracts fully to its original shape where $\gamma = 0$, because of the elasticity of the spring, but the motion is damped along the exponential curve BD, which is the mirror image of OB, because the plunger is pulled back only slowly to its origi-

nal position through the viscous liquid in the dashpot. A retardation time, θ_d, analogous to the relaxation time, is the time required for strain to relax to 1/*e* of its initial value when stress is removed and is defined as $\theta_d = E/\eta$. Along the retarded elastic deformation branch *OB*

$$\gamma = \frac{\sigma_0}{E}(1 - e^{-t/\theta_d}) = \gamma_\infty(1 - e^{-t/\theta_d}) \qquad (17)$$

When the stress is removed, the exponential curve *CD* is described by

$$\gamma = \frac{\sigma_0}{E} e^{-t/\theta_d} = \gamma_\infty e^{-t/\theta_d} \qquad (18)$$

Under constant load, Voigt-Kelvin elements reach a constant deformation; Maxwell elements continue to deform in creep as long as the load is applied. Upon removal of the load, Maxwell elements recover instantly, but not completely, while Voigt-Kelvin elements recover gradually, but completely. Most materials require more than one Maxwell or Voigt-Kelvin element to characterize their rheological behavior and to describe their load-deformation curves. The most suitable models frequently have a range or spectrum of relaxation or retardation times.

One simple model, whose stress-strain behavior is approximated by many viscoelastic materials, such as disperse and polymeric systems, is Burgers' body (see Figure 23-15*C*). Its creep deformation-time curve is shown in Figure 23-16*C*. The *OAB* portion of the curve, corresponding to the period when the model is under a constant stress, σ_0, consists of two segments. When the load is applied, *spring* 2 stretches instantly and the specimen is elongated from *O* to *A*. On a molecular level, this corresponds to the elastic stretching of bonds between primary structural units, such as primary particles aggregated into flocs or crystallites in a semicrystalline polymer above its glass transition temperature. If the stress is removed at *A,* the specimen would recover its original structure completely.

The second segment, *AB,* results from the combination of the recoverable deformation of *spring* 3, retarded by *dashpot* 3 which is connected in parallel, and the non-recoverable creep of *dashpot* 1. The recoverable deformation predominates in the initial, strongly curved region of *AB*. In this region, interparticle bonds break and reform. The remainder of *AB,* which approaches a straight line, represents mainly the creep of *dashpot* 1. Here, some of the bonds that break are too slow to reform within the test period. The rupture of such interparticle bonds releases some structural units, which flow past one another to produce the permanent deformation.

At time *G,* the overall deformation is the sum of the instantaneous deformation of *spring* 2 *(BC* or *AO* or *JG),* of *spring* 3 damped by *dashpot* 3 *(CF)* and of *dashpot* 1 *(HE).* The first two deformations are completely recoverable; the third is not recovered at all.

$$\gamma = BG = JG + EJ + BE = \frac{\sigma_0}{E_2} + \frac{\sigma_0}{E_3}(1 - e^{-t/\theta_d}) + \frac{\sigma_0}{\eta_1}t \qquad (19)$$

where the retardation time $\theta_d = \eta_3/E_3$.

The recovery, *BCD,* follows a pattern similar to the deformation. When the stress is removed at time *G, spring* 2 retracts instantly, and the specimen contracts along $BC = OA$. The retraction of *spring* 3 is retarded by *dashpot* 3 along *CD*. The nonrecoverable part of the deformation, due to *dashpot* 1, is represented by $FG = HE$.

DISPERSE SYSTEMS—Many pharmaceutical preparations are dispersions of solids or liquids in liquid or semisolid vehicles, and their usefulness often depends on their flow properties. Few disperse systems are Newtonian. Most exhibit non-Newtonian flow behavior, some of it time-dependent, often in conjunction with elastic deformation.

Einstein's Law of Viscosity—This is the simplest equation derived to describe the flow behavior of dispersions. Unfortunately, it applies only to Newtonian and idealized systems.

$$\eta_{sp} = \frac{\eta_{12}}{\eta_1} - 1 = \frac{\eta_{12} - \eta_1}{\eta_1} = 2.5\phi \qquad (20)$$

The Newtonian viscosities η_{12} and η_1 are those of the dispersion and of the liquid vehicle or solvent, respectively; η_{sp} represents the specific viscosity of the dispersion, ie, the increase in viscosity of the dispersion over that of the solvent, expressed as a multiple of the viscosity of the solvent; ϕ is the volume fraction of the disperse phase [Blood contains 45% *v*/*v* of red and 1% *v*/*v* of white cells; the corresponding ϕ values are 0.45 and 0.01.] The viscosity of a dispersion obeying Einstein's law depends only on the viscosity of the solvent and on the volume of solvent replaced by the disperse phase, not on the size of its particles.

Assumptions operative in Einstein's law of viscosity include negligible gravitational and inertial effects and the absence of turbulence. Particles of the dispersion are large compared to the solvent molecules (ie, the discontinuities between the solvent molecules are negligible compared to the size of the dispersed particles) but small compared to the dimensions of the viscometer (eg, gap between the coaxial cylinders or diameter of the capillary). The particles of the dispersion neither attract nor repel one another. [In reality, as most dispersions consist of particles of like charge, the viscosity of such dispersions increases due to interparticle electrostatic repulsion (the *electroviscous effect*). In aqueous dispersions, viscosity increases can be minimized by adding electrolytes.]

In addition, Einstein's law assumes that the solvent is continuous and that the particles are unsolvated, smooth, and rigid spheres (eg, glass beads, polymer latex particles, and many spores and fungi). However, emulsion droplets are deformable and the liquid inside them can circulate. This decreases the distortion of the flow pattern around the droplets and reduces the numerical constant in Equation 20 *below* 2.5. Rigid anisometric particles offer increased resistance to flow, raising the constant *above* 2.5. If the solvation layer of solvated spherical particles is included in ϕ, their dispersions may obey Equation 20. Examples of the latter are solutions of globular proteins at their isoelectric point, where their net electric charge is zero.

Furthermore, the "ideal" dispersions addressed by Einstein's law are considered to be so dilute that the distortion of the laminar streamlines of the solvent at the surface of one particle does not overlap and reinforce the distortions around its neighbors. However, at higher disperse phase concentrations, the perturbation of laminar flow produced by one particle reaches into the fields of other particles. This produces additional resistance to flow and increases η_{sp} and η_{12} above the values given by Equation 20.

Deviations from these conditions result in higher dispersion viscosities than those calculated by Einstein's law except that, when the disperse phase is fluid, the calculated viscosity is too high. An example of an extreme positive deviation is found in aqueous sodium bentonite dispersions. Their specific viscosity is about 70 times greater than that calculated from Equation 20. The particles are thin plates, deviating considerably from spherical shape. They are hydrated, and their negatively charged faces attract the positively charged edges but repel the negatively charged faces of other particles. Polymer solutions with their thread-like, highly solvated, and entangled macromolecules also deviate considerably from Einstein's law. Several variations on Einstein's law express the specific viscosity as a polynomial in ϕ thereby broadening its applicability, for example, to more concentrated dispersions.

Casson Model—One of the more successful relationships applied to dispersions with a *high* solids content is the Casson[20] model,

$$\sigma^{1/2} = k_0 + k_1 \dot{\gamma}^{1/2} \quad , \qquad (21)$$

where k_0 and k_1 are constants which depend on the properties of the dispersion medium and the disperse phase. Although the

Casson equation has been used empirically in modeling the rheological properties of a wide range of concentrated dispersions, it was originally derived from basic principles with the assumption that the disperse phase behaved as rigid rods.

Computational Rheology

Empirical relationships aside, numerical methods for the characterization of non-Newtonian flow were developed in the 1960s, but it is only relatively recently that computational rheology has emerged to address previously intractable problems such as three-dimensional transient flows of polymeric liquids, non-isothermal non-Newtonian flows, or turbulent flow of generalized Newtonian and viscoelastic materials.[21] Computer software, in consort with modern rheometer design, has also facilitated the development of more complex models of deformation and flow under flow regimes ranging from the laminar to the turbulent, even encompassing the transitional flow regime in which flow is neither completely laminar or completely turbulent. In all likelihood, the net effect of these advances is to demystify rheological principles and allow the *a priori* estimation of the mechanical properties of the living and nonliving systems with which we contend.

BIORHEOLOGY

Biorheology is the study of deformation and flow in biological systems. Biological fluids are generally both elastic and viscous. Hence they are viscoelastic materials. Biological fluids are rheologically complex due to their multicomponent nature. The altering effects of disease compound the complexity of evaluating the rheology of physiological fluids. Several journals cover issues related to rheological characterization of biological fluids and tissues and the effect of disease and drugs on these properties. These include *Biorheology*, *Journal of Biomechanics*, and *Clinical Hemorheology and Microcirculation*. It is important to understand the rheological properties of biological materials for a greater understanding of their implications in both the healthy and diseased state. Rheological parameters of biological materials are also important in successful drug delivery to the body.

Hemorheology

The main function of blood is to act as a transport medium. It transports almost everything that is essential for the various organs of the body. Blood is composed of solid particles (red cells, white cells, and platelets) suspended in a fluid medium (plasma).[22] Early investigators conceptualized blood as a viscous fluid, assuming that the viscosity controls its flow properties.[23] However, blood is not a fluid in the ordinary sense; it is a fluidized suspension of elastic cells, which characterizes its rheological behavior. Blood is a non–Newtonian fluid with viscoelastic properties. At low shear rates, blood viscosity is higher because of the tendency of erythrocytes to aggregate. At high shear rates, which are typical for the arterial side and capillaries, blood viscosity is lower and constant because of erythrocyte deformation.[22,24,25] Comprehensive studies show that the shear dependence of the viscosity of blood may be attributed exclusively to the formation or disintegration of erythrocyte aggregation. The formation of aggregates is reversible and increases at decreasing shear rates.[26–28] The Casson equation has been suggested to describe mathematically the flow curve of blood.[28] In the circulation, the rheological behavior of blood is determined by the interactions of the erythrocyte cells with the vessel walls.[22,29] When blood is allowed to flow through capillary tubes of decreasing caliber, a second non-Newtonian characteristic is observed. Below a critical vessel caliber of 1mm, blood viscosity becomes dependent upon vessel radius. Viscosity drastically decreases when the vessel caliber is approximately 12–15μm. This phenomenon is known as the *Fahraeus-Lindqvist* or *Sigma Effect*.[29,30] Three possible contributory causes are:

1. The hematocrit value is lower for blood in capillaries. For instance, blood flowing through a capillary of 50μm diameter has only 70% of the red blood cells of blood flowing through large vessels.
2. Red blood cells are biconcave discs with an average diameter (d) of 7.5μm. Their size is by no means negligible compared to the radius (R) of capillaries. This leads to a reduction in the apparent viscosity by a factor of $(1+d/R^2)$ according to the so-called *Sigma Effect*.[31]
3. The tubular pinch effect consists of an accumulation of red cells in an annular region located at a distance of about 60% of the tube radius from the tube axis during laminar flow of blood through cylindrical capillaries. Almost colorless plasma flows in the vicinity of the capillary wall. Blood flowing in the center of the tube is also deficient in red cells. This phenomenon commonly is observed when suspensions of spherical or asymmetric particles flow through ducts whose diameter is only a low multiple of the particle size.[31]

In the diameter range between 30μm and 300μm the effective blood viscosity can be predicted using the hematocrit reduction resulting from the *Fahraeus* effect.[29] The apparent viscosity can be determined in macro-viscometers.[29]

The flow properties of blood are determined by the hematocrit (Hct) value, plasma viscosity, red cell aggregation, and deformability.[22,29] The studies of blood viscosity factors present an important mechanism to better understand the pathways of cardiovascular disorders. It also allows utilization of blood viscosity tests in diagnostics, prognostic, and preventive medicine.[26] Elevated Hct levels have been associated with adverse cardiovascular outcomes including arteriosclerosis, coronary heart disease (CHD), angina pectoris, myocardial infarction, and CHD incidence.[32–34] Individuals who exercise regularly have been found to have reduced blood and plasma viscosity compared with nonexercisers.[33] On the other hand, after heavy exercise or during severe asthma attacks, serum mean lactate levels increase. In high concentrations, lactic acidosis produces erythrocyte swelling, increasing the Hct level and increasing whole-blood viscosity at high and low shear rates.[24]

Artificial Blood Substitutes (ABS) offer an alternative to blood transfusion. They have the ability to replace temporally the volume expansion and oxygen transport functions of transfused blood.[35–40] In the normal circulation system, vascular receptors have been calibrated to respond to a determined pressure and shear force exerted by normal blood. When ABS are introduced, new biorheological properties of the blood mixture can occur. Depending on the flow properties of the specific ABS, peripheral resistance of the circulatory system, and vascular receptor responses might be altered.[35] ABS can be divided in 3 classes: hemoglobin based products, perflurocarbon based products, and volume plasma expanders. Hemoglobin-based products include conjugates of hemoglobin with larger molecules (dextran or polyethyleneglycol), intramolecular cross-linked hemoglobins, polymerized hemoglobins, and liposome encapsulated hemoglobin.[37] Perfluorocarbon-based products have the ability to dissolve significant quantities of oxygen. Perfluorochemicals are immiscible with water, consequently must be emulsified before introduction to the bloodstream.[35–37] Due to the small size of the emulsion particles (<0.2μm diameter), perfluorocarbon emulsions have the ability to perfuse into smaller capillaries where red blood cells are normally unable to perfuse due to their size limitation.[38] A study of a perfluorocarbon emulsions has shown that they exhibit non-Newtonian behavior.[35] Plasma expander products are non-oxygen carriers. Their purpose is to expand the blood volume after significant blood loss. The most common gelling agents used in these products are gelatin and starch. These products are viscous in nature. Rheological behavior studies of red blood cells when in contact with various polymeric plasma expanders are ongoing[36]

Lymph

The lymphatic system drains most regions of the body. Lymph is a clear to white viscous fluid. The chemical composition of lymph is very similar to that of plasma. Generally the composition of lymph differs from plasma in the concentration of its constituents. Lymph component concentration varies as a function of body region. The major components of lymph include proteins, enzymes, lipids, electrolytes, nonelectrolytes, iron and transferrin, and coagulation factors. A large number of white blood cells are present in the lymphatic fluid. The rheological properties of lymph are more complex than those of plasma. Very little information is available with regard to the rheological properties of lymph.

Mucus

Mucus is a weak viscoelastic gel.[41] It is a translucent or opaque, gel-like, stringy, slimy secretion. A mucus covering lines all the internal tracts of the body, the respiratory tract (nose, trachea, bronchi, and bronchioles), gastrointestinal tract, and female reproductive tract. It both lubricates and protects mucosal surfaces. More than 95% of mucus is water. The other components of mucus include glycoproteins or mucins (0.5–5%), inorganic salts (1%), proteins (0.5–1%), lipids, and mucopolysaccharides.[42] The primary component of mucus, the glycoproteins, are responsible for its gelling properties. The glycoproteins within mucus covalently bind to each other through disulfide bonds. Mucus secretions that reside in different locations of the body vary with respect to their rheological properties. This variability is required such that the physiological functions of the mucus secretions can be met. The rheological properties of mucus are a function of anatomical location, and the physiological and pathological state.[43] The rheology of mucus can be affected by ion content, hydration state, and pH.

The viscosity and elasticity of mucus can be altered using mucus thinning or mucus thickening agents. Di and Trivalent cations can thicken mucus in a concentration dependent manner. Reduction of mucus viscoelasticity by mucolytic agents which split mucus glycoproteins into smaller subunits such as N-acetylcysteine, dithiothretol, bromhexine, and erdosteine has been reported.[43] Acetylcysteine is one of the sulfhydryl mucolytics that disrupt disulfide bonds in mucus.[50,51] Changes in rheological properties can also be induced by other drug substances.

EYE—Mucus is primarily produced by goblet cells in the conjunctiva. The mucus is secreted onto the surface of the conjunctiva and the upper lid distributes the mucus in a thin film over the surface of the cornea.[44] The tear film is essential to provide a perfect optical surface for the eye. It is consisted of three distinct layers:

1. Mucus layer: present on top of the epithelial cells of the cornea. It is 10 to 100 times more viscous than the aqueous layer.[45]
2. Aqueous layer: present above the mucus layer. The lacrimal glands supply it.
3. Lipid or fatty layer: that covers the aqueous layer.[46]

The whole tear fluid is considered a non-Newtonian fluid, which means that the viscosity depends on the shear rate. The greater the shear rate, the lower the viscosity. The rationale of this is that the viscosity must be high enough to allow the tear film to maintain a continuous layer, covering the exposed area of the ocular surface.[47]

The *vitreous humor* is a clear gel, which occupies the posterior compartment of the eye, located between the *crystalline lens* and the *retina* and occupying about 80% of the volume of the eyeball. Normally, it is of a very consistent thickness, or viscosity, and is crystal clear. With age, the vitreous humor changes from a gel to a liquid. As it does so, the vitreous mass gradually shrinks and collapses, separating and falling away from the *retina*.[48] Certain pathological conditions result in changes in the viscosity of intraocular fluids.

MOUTH, NOSE, AND RESPIRATORY TRACT—*Mouth*—Saliva is an exocrine secretion composed of water, bicarbonate, enzymes and mucoproteins.[25] It is produced predominantly by the salivary glands which include the parotid, submandibular, and sublingual glands. It is viscoelastic in nature. The viscosity of secretions from the parotid gland is less than the viscosity of secretions produced by the submadibular and sublingual glands. This is due to the lack of mucin in these secretions. Sublingual gland secretions contain a large amount of mucus making them very thick and viscous. In an adult the total amount of saliva produced daily is 500 to 1500 ml.[49]

Nose—Nasal secretions consist of a combination of glycoproteins, lipids, DNA, and ions in 95% water.[50] It is produced at a resting rate of 0.5 to 1mL of mucus/cm^2 mucosa over a period of 24h.[50] Mucins, a high molecular weight glycoproteins present in the nasal mucus, contain a large amount of sugar residues.[50] Due to this large amount of sugar and consequent polymerization of disulfide bonds, it is thought that mucins have a considerable influence on the rheological properties of mucus.[50–52]

Nasal mucus is thought to consist of a biphasic layer, which is a superficial gel layer that contains most of the glycoproteins overlying an aqueous layer in contact with cilia. Mucociliary transport depends on both ciliary activity and the rheological properties of nasal mucus. The nasal mucus traps and transports airbone particles and endogenous products.[50,52]

The mucus layer behaves as a non-Newtonian viscoelastic fluid. Studies have shown that the correlation between the mucociliary transport rate and the elastic modulus/dynamics viscosity change below and above the optimal viscoelasticity (close to 15 Pa/s).[50] Several methods have been developed to measure mucus viscosity including capillary viscometer (the simplest one),[53] coaxial cylinder sensor system,[54] magnetic microrheometer,[55] and controlled stress technique.[50]

Diseases and presence of drugs may alter the rheological properties of mucus. In chronic inflammation, there is a hypertrophy of the submucosal glands and an increase in the goblet cells, which results in an increase in the volume of mucus.[50] In chronic sinusitis, there is an increase in the submucosal cells, but the number of goblets cells are not significantly increased. In this case, the dynamic viscosity of the mucus was found to be 1.6 Pa/s.[50,52]

Respiratory Tract—The mucus present on the respiratory epithelium is produced by surface cells and submucosal glands. The various constituents of bronchial mucus provide a surface protective membrane. It is considered a membrane that moves. Bronchial mucus consists mainly of lipids and glycoconjugates.[56] Samples are generally difficult to analyze because are mixed with saliva and are not homogeneous. Consequently, the precise composition of bronchial mucus is not well elucidated.[56,57]

Sputum is defined as secretions from the lungs, bronchi, and trachea. Bronchial mucus samples can be collected from sputum or aspirated from fiberoptic bronchoscopy.[56] Sputum exhibits non-Newtonian rheological behavior.[57] The viscosity of sputum is influenced by the state of body hydration. Sputum produced overnight is more viscous than that produced during the day.[57]

Bronchial mucus has been shown to be shear thinning[57] Increases in bronchial mucus viscosity result in breathing difficulty. In chronic hypersecretory lung diseases, viscosity of bronchial mucus is increased. For example, lung epithelial mucus has increased viscosity in cystic fibrosis patients.[58] Patients with cystic fibrosis have a decrease in mucus water content and an increase in the DNA and total phospholipid content of mucus resulting in increase in viscosity and changes in the viscoelastic properties of the mucus.[50,54] In these cases, physiotherapies to change viscoelastic properties and improve mucus clearance have been used.[60–62]

The lung-lining layer is composed principally of phospholipids, the most prevalent being dipalmitoyl-phosphatidylcoline. This surfactant layer forms a film and spreads through the alveolar surface.[25] Evidences suggested that this lining

material is continually replenished.[25] However, the rheological properties of this fluid have not been established.[63]

GASTROINTESTINAL TRACT—A water insoluble gel layer covers the mucosal surfaces of the stomach, duodenum, and colon. Gastric mucus is a non-Newtonian substance. Mucus secretions in the gastrointestinal tract have a viscoelastic gel structure. This gel structure is of a three-dimensional arrangement comprised of both entanglement and covalent and noncovalent association of mucin. The viscosity of this mucus is affected by pH. It has been shown that the viscosity of mucus in the stomach is greater at pH 2 than that at pH 7 with a maximum in viscosity being observed at pH 3–4.[64,65] In addition the viscoelastic properties can be modified by the presence of albumin which increases the viscosity of the gel.[66] Given that this mucus is viscoelastic in nature the stress contains both a storage modulus (G')(elastic component) as well as a loss modulus (G")(viscous component). Mucus gels from the stomach have been shown to have a storage modulus value which is greater than that of the loss modulus.[67] Tan δ values (the ratio of the loss modulus to the storage modulus) obtained for gastric mucus were found to be less than 0.4, characteristic of a viscoelastic gel.[67] The mucus in the gastrointestinal tract responds to pathological and physiological changes. Various drug molecules, stresses, and disease states can result in alterations in gastric mucus visocisty. The ulcerative processes that can occur in the stomach are a result of the weakening of the normal gastric mucosal barrier.

REPRODUCTIVE TRACT SECRETIONS—*Vaginal Fluid*—Vaginal fluid is made up of a vaginal transudate, secretions from Bartholin's and Skene's glands, exfoliated epithelial cells, residual urine, and fluids from the upper reproductive tract such as cervical mucus and fluid from the uterus and endometrial tubes.[68]

Cervical Mucus—The components of cervical mucus are mucus glycoproteins, plasma proteins, other proteins (eg, lactoferrin), enzymes, amino acids, cholesterol, lipids, and a range of inorganic ions.[69] Cervical mucus exhibits non-Newtonian viscosity and is a viscoelastic, highly hydrated substance. It is produced by secreting cells within the cervical canal or cervical os. Its primary functions are protection and transport. Mucus glycoproteins interact to form a gel. There have been two models proposed for the macromolecular arrangement of mucus glycoprotein. The first is Odeblad's model, which describes the arrangement of mucus as a micellar system with associated bound water molecules.[70,71] The second model proposed by Blandau and Lee suggests that in the high viscosity phase of mucus the glycoproteins within behave as a random coil structure without crosslinking.[72,72]

A number of factors have been shown to impact the viscoelastic properties of cervical mucus. The fucose/sialic acid ratio of cervical mucins present impacts the viscoelasticity. The viscoelasticity of cervical mucus may also be altered by serum albumin, which increases mucus viscosity. The gel structure of cervical mucus is susceptible to alteration by proteolytic enzymes.[73] In a study evaluating the nonlinear viscoelastic properties of cervical mucus conducted by Tam et al, the viscosity was shown to vary from 17 to 600 poise whereas values obtained for shear modulus ranged from 20 to 250 dynes/cm^2. The relaxation times for human cervical mucus ranged from 1 to 10 seconds.[74] The viscosity of cervical mucus is hormonally regulated. The viscosity changes of cervical mucus that occur during the menstrual cycle are also the result of variation in water content. At midcycle the amount of cervical mucus increases due to estrogen-induced increases in gel hydration. Cervical mucus becomes less viscoelastic at this point, thus the penetration of spermatozoa is facilitated.[75] The transfer of spermatozoa to the uterus is highly dependent on the rheological properties of the cervical mucus. The rheological properties of cervical mucus can be used to predict ovulation. The rheology of cervical mucus is not only altered by menstrual cycle stage but also varied by pathological state. It has been shown that bacterial vaginosis organisms degrade the protective mucus gel.[76]

Semen—Semen is a semi-gelatinous cellular suspension containing spermatozoa (the male gametes) and secretions from the male reproductive accessory glands. Temporal variations exist in the rheological properties of semen. The viscous component of post ejaculatory semen can be characterized by power law model.[77] Semen exhibits pseudoplastic behavior. The viscosity of normal semen at 230 s^{-1} and 25° was found to be 4.3 ± 0.2 cp.[78]

Synovial Fluid

Fluids which lubricate and cushion the joints are known as synovial fluids. The structure of these fluids is quite complex. Synovia or synovial fluid is a clear liquid not only contained in joint cavities but also in bursae and tendon sheaths. Synovial fluid is a dialysate of blood plasma[79]and consists of electrolytes and proteins. An important component of synovial fluid is hyaluronic acid. This is the substance that is primarily responsible for this fluid's rheological properties. The consistency of synovial fluid is comparable to that of an egg white. This fluid is highly viscous and exhibits non-Newtonian behavior due primarily to the presence of hyaluronic acid. The fluid owes its viscoelastic behavior to the complex between hyaluronic acid and soluble proteins (mainly albumin). The storage modulus of healthy synovial fluid is high and decreases with age.[80]

Normal synovial fluid is a weak highly hydrated gel. Its zero shear viscosity ranges from 100 to 1000 poise. Synovial fluid is strongly pseudo plastic. At a shear rate of 100 sec^{-1}, the apparent viscosity is significantly smaller than the zero-shear viscosity. There are considerable variations between the rheological properties of normal synovial fluid from different human subjects.

The shear modulus (G) (analogous to the modulus of elasticity (E) when the deformation is in shear rather than in tension) of synovial fluid at low shear rates is surprisingly low. The combination of an extremely high zero-shear viscosity and an extremely low initial shear modulus renders their ratio, the relaxation time very long: [(126 to 300 poise)/(20 to 40 dynes/cm^2)] ≅ 3 to 10 sec.

Increasing shear affects the modulus in two opposite ways. Progressive disentanglement of the long hyaluronic acid molecules with the attached protein side chains breaks up their network and tends to lower the modulus. However, as the shear rate increases, the relaxation time cannot keep pace with it. This results in incomplete relaxation, which causes the polymer chains to stiffen and tends to increase the modulus. Consequently, the shear modulus retains a nearly constant value, ranging from 20 to 40 dynes/cm^2 between 0 and 100 sec^{-1}, and increases moderately at higher shear rates. Because increasing shear rates lower the apparent viscosity of synovial fluid strongly but leave the shear modulus nearly unchanged, they shorten the relaxation time considerably.

The rheological properties of synovial fluid are well adapted to its functions. Its very high viscosity at low or zero shear, combined with its viscoelasticity, enable it to maintain the space or clearance between articular surfaces. Its lubricity is aided by its pronounced pseudoplasticity. When a joint moves rapidly and the motion-induced shear and pressure are high, the apparent viscosity is lowered substantially and the amount of energy dissipated as heat by viscous friction is reduced commensurately. However, the amount of energy stored elastically during the loading phase of a motion cycle is nearly the same as at rest because the elastic properties of synovial fluid (eg, the elastic component of the complex viscosity and the shear modulus) undergo only small changes with increasing shear. Therefore, the lubricating film of synovial fluid between articular surfaces is squeezed out only very slowly by pressure and protects the cartilage from wear.

Because motion-induced shear lowers the apparent viscosity of synovial fluid so strongly, while leaving its shear modulus nearly constant or somewhat higher, it shortens its relaxation

times appreciably. Shorter relaxation times permit the stress-relaxation mechanisms to be carried to completion within each loading-unloading cycle during articular motion. Thus, synovial fluid can store energy elastically during each new loading phase without building up excessive peak stresses.

The rheological properties of synovial fluid are altered by disease. Although protein content in pathological synovial fluid is unaltered, joint diseases reduce the hyaluronic acid content of synovial fluid. The concentration of hyaluronic acid in normal synovial fluid ranges from 1.5 to 2.9 g/L. Hyaluronic acid concentration is reduced to levels of 1.1 to 1.4 g/L with meniscus lesions, 0.9 g/L in degenerative diseases, and to less than 0.5 g/L in inflammatory disease. This reduction in hyaluronic acid content impair the rheological/functional properties of synovial fluid. These alterations in rheological properties are not only contributable to decreased concentration of hyaluronic acid. In addition decreases in hyaluronic acid molecular weight in pathologic conditions alters synovial fluid rheological properties. Decreases in zero shear viscosity occur in diseased synovial fluid. Pathological synovial fluid is much less pseudoplastic than the normal fluid. Viscoelasticity is reduced considerably by inflammatory joint diseases. Assessment of synovial fluid rheological properties can be used as a promising diagnostic tool.

Cerebrospinal fluid

Cerebrospinal fluid is a clear fluid secreted by the choroids plexuses of the ventricles of the brain. It circulates in the space surrounding the spinal cord and brain. It serves to protect these areas from physical impact by providing a water cushion.[25] Cerebrospinal fluid is a newtonian fluid with a viscosity similar to water.[15] At 37° its viscosity lies in the range of 0.7 to 1mPa.s.[81]

RHEOLOGICAL MEASUREMENTS

A wide variety of viscometers is available commercially; they vary in regards to range of shear, sample size, ease of operation, reproducibility, and cost. It is necessary to select an instrument which provides the information desired for a specific application. Information on selected suppliers along with web sites is listed in Table 23-4. This section outlines the basic aspects of some of the more frequently used types of viscometers (rheometers).

All of the equations routinely used with viscometers yield viscosities, shear rates, and shear stresses based on the assumption that the fluid is Newtonian. The viscosity, in particular, is an apparent viscosity defined as the ratio of shear stress to shear rate. For non-Newtonian fluids and in order to compare data from one viscometer to another, the pseudo-Newtonian data must be corrected for non-Newtonian behavior.

Table 23-5. Viscometer Parameters

TYPE OF VISCOMETER	X_γ	X_σ
Flow	Time of fluid flow	Fluid density
Rotary	Rotation speed of rotating element	Torque
Falling object	Velocity of falling object	Diameter of object

One very important potential problem is measuring the apparent viscosity of a material at a single rate of shear instead of covering a wide range of shear. A Newtonian, a pseudoplastic, a plastic, and a dilatant fluid may all have the same apparent viscosity if their flow curves have a common intersection point since apparent viscosity is defined as (shear stress)/(shear rate), whereas their flow curves may demonstrate very dissimilar behavior.

Measuring the apparent viscosity over a range of shear rates but maintaining the material for only short times at each shear rate also can give misleading results by missing thixotropic or time-dependent effects. The latter usually are detected by measuring the flow curve first at increasing shear rates and, after reaching the desired maximum value, at decreasing shear rates. An alternate technique is to keep the material at a constant shear rate for a given period of time and to observe the decay, if any, of the shear stress with time.

General Viscometer Types

There are three principal methods for measuring viscosity: (1) based on the rate of flow of a liquid through an orifice or a duct of simple geometry such as a capillary viscometer, (2) based on the resistance of a rotating element in contact with or immersed in the liquid such as a concentric cylinder viscometer, and (3) based on the velocity of an object rolling or falling through the liquid under the effect of gravity (or of an air bubble rising through the liquid) such as the falling or rolling sphere viscometer.

The apparent viscosity with any viscometer can be determined following calibration of the viscometer with a standard Newtonian oil:

$$\eta = K_\eta (x_\gamma, x_\sigma) \tag{22}$$

where K_η is the viscometer constant for determining viscosity and x_γ and x_σ are experimental parameters related to shear rate and shear stress respectively. Alternately, shear rate and shear stress can be determined separately as follows:

$$\dot{\gamma} = K_\gamma x_\gamma \tag{23}$$

and

$$\sigma = K_\sigma x_\sigma \tag{24}$$

Table 23-4. Selected Viscometer Companies With Web Addresses

COMPANY	VISCOMETERS AND SERVICES	WEB ADDRESS
Brookfield Engineering	Broad Line Of Laboratory & Process Viscometers, Rheometers & Accessories For The Measurement & Control Of Viscosity	www.brookfieldengineering.com
Cannon Instrument Co.	Glass Capillary Viscometers, Automatic Viscometers, Rotational Viscometers, Special Purpose Viscometers, Viscosity Baths, Viscosity Standards	www.cannon-ins.com
Rheometric Scientific	A broad range of rheometers, controlled stress or controlled strain measurements.	www.rheosci.com
Thermo Haake	Rheometers & Viscometers Including Extension, Shear, Capillary, Rotation, Oscillation, Controlled Stress & Controlled Strain & Extrusion Capillary Rheometers	www.thermo.com
Reologica Instruments	Customized Research Rheometers, Accessories, & Measuring Systems	www.reologicainstruments.com
Gilson Company	Automatic, Brookfield, Saybolt, Kinematic, Absolute	www.globalgilson.com
Grace Instrument Co.	Extra High/Low Shear Viscometers, Rheometers	www.graceinstrument.com

where K_γ and K_σ are the viscometer constants for determining shear rate and shear stress respectively. K_γ and K_σ are related to K_η as follows:

$$K_\eta = \frac{K_\gamma}{K_\sigma} \tag{25}$$

The experimental parameters x_γ and x_σ for the three basic types of viscometers are listed in Table 23-5.

CAPILLARY VISCOMETER—The glass capillary Cannon-Fenske, Ubbelohde, and Ostwald viscometers are the most popular instruments based on the first method. The duct is a cylindrical capillary, and the driving force causing the liquid to flow through it is its weight. Thus, ΔP in Poiseuille's law (Equation 6) is replaced by the hydrostatic pressure $h\rho g$ of a liquid column of height h and density ρ; *g* is the acceleration of gravity.

$$\eta = \left(\frac{\pi R^4 hg}{8L\,V}\right)\rho t \text{ or } \eta = K\eta\rho t \tag{26}$$

therefore:

$$K_\eta = \left(\frac{\pi R^4 hg}{8L\,V}\right) \tag{27}$$

A standard volume of the liquid is transferred into the viscometer. Liquid is then drawn into the upper reservoir bulb of the instrument by suction (Figure 23-17). The efflux time, t, required for the liquid level to fall from the upper to the lower benchmark, emptying the upper reservoir, is measured with a stopwatch. The height, h, is the difference between the liquid levels in the two arms of the viscometer. The height, h, decreases as liquid flows through the capillary, but its time-averaged value is constant for a given viscometer containing a constant volume of liquid.

Calibration of the viscometer consists in determining the constant K_η experimentally with a liquid of known viscosity and density by measuring the efflux time t as described from Equation 26;

$$K_\eta = \frac{\eta}{\rho t} \tag{28}$$

The viscosity for an unknown liquid is then determined from Equation (29);

$$\eta = K_\eta \rho t \tag{29}$$

The liquid used to calibrate the viscometer should have approximately the same flow time t as the unknown, in order to minimize two corrections when using Equation (8). The major portion of the potential energy represented by the hydrostatic pressure head is dissipated in overcoming the viscous resistance against flow in the capillary tube, ie, the friction of layer slipping past concentric layer. This portion is converted into heat. However, a small portion of the potential energy is required to accelerate the liquid as it enters the capillary from the reservoir (*kinetic energy correction*). Another small amount is used up in the streamlines converging from the broad reservoir into the narrow capillary and in spreading the streamlines upon issuing from the capillary (entrance or end effects, also called the *Couette correction*). These two corrections are included experimentally in the constant K_η.

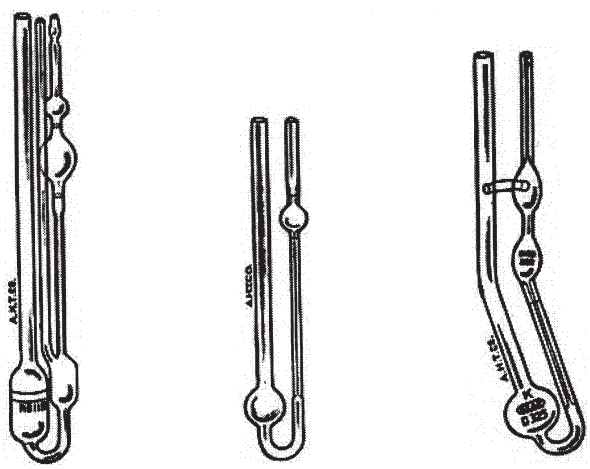

Figure 23-17. Capillary Viscometers: Ubbelohde, Ostwald, and Cannon-Fenske.

It is not necessary to evaluate K_η if the viscosity of one liquid relative to a reference liquid is sufficient. It suffices to measure the flow time t_1 for the reference liquid of known viscosity η_1 and density ρ_1, and to compare it with the flow time t_2 for the liquid of density ρ_2 whose viscosity η_2 is to be determined. The equation

$$\eta_2 = \frac{t_2\rho_2}{t_1\rho_1}\eta_1 \tag{30}$$

gives the unknown viscosity.

If the viscosity of the reference liquid is not known a relative viscosity, η_r, can be determined as defined in the following equation.

$$\eta_r = \frac{\eta_2}{\eta_1} = \frac{t_2\rho_2}{t_1\rho_1} \tag{31}$$

If the density of the liquid is not known a kinematic viscosity can be determine which is defined as the absolute viscosity divided by the fluid density as:

$$\text{kinematic viscosity} = \frac{\eta}{\rho} = K_\eta t \tag{32}$$

Kinematic viscosity has the units of stoke(s) or centistoke(s) and is not numerically or dimensionally equivalent to the viscosity in cps.

Shear rate and shear stress can be determined explicitly from Equations (23) and (24) as they apply to capillary viscometers. It can be shown that Equation (26) can be separated into shear stress and shear rate as follows:

$$\dot\gamma = \frac{4VL}{\pi R^3 t} = K_\gamma \frac{L}{t} \tag{33}$$

and

$$\sigma = \frac{hgR}{2L}\rho = K_\sigma \rho \tag{34}$$

It follows that K_γ, x_γ, K_σ, and x_σ in Equations (23) and (24) are defined as $4V/\pi R^3$, L/t, $hgR/2L$ and ρ, respectively.

It would appear that K_γ and K_σ in Equations (33) and (34) could be calculated directly since all of the parameters in their definition appear to be measurable. In reality the length of the capillary, L, cannot be measured precisely due to the corrections discussed above. Consequently, K_σ must be determined from calibration of the capillary viscometer with a Newtonian standard. This can be done conveniently by determining K_η experimentally, calculating K_γ directly from viscometer parameters, and then calculating K_σ from the relationship defined in Equation (25).

A range of shear rates and shear stresses can be obtained for a given liquid by using a series of glass capillary viscometers of different diameters since the usual glass capillary viscometer affords viscosity measurements at only one time-averaged value of shear rate. The efflux times should exceed 200 sec to minimize the kinetic energy correction and the possible error when starting and stopping the stopwatch. A range of shear

rates can be obtained with a single capillary viscometer if external pressure is applied to force the liquid through the capillary. A variety of capillary extrusion viscometers operating under pressure are commercially available.

ROTATIONAL VISCOMETERS—These instruments depend on the fact that a solid rotating body immersed in a liquid is subjected to a retarding force due to the viscous drag, which is proportional to the viscosity of the liquid. The advantages of rotational viscometers are that the shear rate can be varied over a wide range of values, and that continuous measurements at a given shear rate or shear stress can be made for extended periods of time, affording measurements of the time-dependency as well as of the shear-dependency of the viscosity.

The entire liquid sample is in shear for as long as the rotational viscometer is being operated. Its temperature rises progressively as the energy used to overcome its viscous resistance is transformed into heat; the higher the viscosity, the greater the heat buildup. Since the viscosity of liquids depends strongly on temperature, accurate temperature control is essential. Rotational viscometers have arrangements for circulating water from a constant-temperature bath past the liquid sample, eg, around the cup. In capillary viscometers, only a small portion of the test liquid is sheared at any given moment, and the measurements are intermittent. Despite the minimal heat buildup, glass capillary viscometers are also usually operated in constant-temperature baths.

In the *MacMichael* type viscometer, the outer cup is rotated at a constant though adjustable speed. The torque on the bob is measured as the deflection or twist of the torsion wire from which the bob is suspended.

In the *Stormer* type viscometer, the cup is stationary and the bob or rotor is driven by weights suspended at the end of a pulley to which the shaft of the bob is connected. The shear stress is varied by applying different weights. The shear rate is measured by the speed of rotation of the bob; the number of revolutions per minute (rpm) is determined by means of a revolution counter connected to the shaft of the bob, and a stopwatch.

In most modern rotational viscometers, the cup likewise is fixed. The bob is rotated at a constant though adjustable speed that can be varied over a wide range of rpm or shear rates. The torque on the rotating bob required to maintain a constant speed of rotation against the viscous drag of the liquid is measured with a dynamometer consisting of a torsion spring interposed between the motor and the bob. The deflection or twist of the spring generates an electric signal by means of a potentiometer. The shear stress is read as the deflection of a needle on the torque scale. Modern rotational viscometers are interfaced with computers in order to simplify data collection and interpretation.

Coaxial-Cylinder Viscometer—The geometry of a coaxial-cylinder viscometer is shown in Figure 23-18. The viscosity is calculated by means of the *Margules* equation:

$$\eta = \frac{(R_c^2 - R_b^2)}{4\pi h R_b^2 R_c^2}\left(\frac{T}{\Omega}\right) = K'_\eta\left(\frac{T}{\Omega}\right) \qquad (35)$$

where R_c and R_b are the radii of the cup and bob, respectively, h is the height of the bob immersed in the liquid, T the torque, and Ω the angular velocity of the bob in radians/sec.

The angular velocity of the bob is usually expressed in terms of rpm ($\Omega = (2\pi/60)$ rpm); torque is proportional to number of divisions, S, on the viscometer scale, ie, $T = k\,S$. These relationships are substituted into Equation (35) to give:

$$\eta = \frac{(R_c^2 - R_b^2)k}{120 h R_c^2 R_b^2}\left(\frac{S}{\text{rpm}}\right) = K_\eta\left(\frac{S}{\text{rpm}}\right) \qquad (36)$$

The calibration factor K_η, can be determined experimentally for each combination of cup and bob by means of a viscosity standard.

Equation (36) was derived for two coaxial cylinders of infinite length. The *end effect* is the traction on both end surfaces of the bob if it is completely immersed in the liquid or on its bottom surface if it is only partly immersed. Thus, h in Equations (35) and (36) is an "effective" height of the bob. One way to correct for the end effect is by adding an increment Δh to the height h of the bob to arrive at an effective height. For a partly immersed bob with a flat bottom, Δh is frequently of the order of 0.1h. The added height can be determined experimentally for each material by filling the annular gap to different depths of immersion of the bob. The ratio T/Ω is plotted against the height or depth of immersion h. The negative intercept of this usually straight line with the h axis represents Δh.

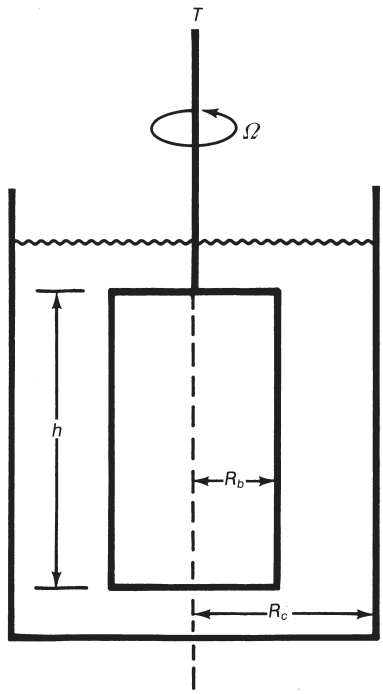

Figure 23-18. Geometry of a coaxial-cylinder (cup and bob) viscometer.

The end effect is more conveniently accounted for by calibrating the viscometer with a viscosity standard as was done with a capillary viscometer in Equation (26). However, since a rotational viscometer can be operated over a range of shear rates, the constant, K_η, is best determined from the slope of a plot of scale reading, S, vs. rpm as defined by a rearrangement of Equation (36);

$$S = \frac{\eta}{K_\eta}\,\text{rpm} \qquad (37)$$

Shear rate and shear stress can be determined explicitly from Equations (23) and (24) as they apply to a coaxial-cylinder viscometer. It can be shown that Equation (35) can be separated into shear stress and shear rate as follows;

$$\sigma = \frac{T}{2\pi R_b^2 h} = \frac{kS}{2\pi R_b^2 h} = K_\sigma\,S \qquad (38)$$

$$\dot{\gamma} = \frac{2R_c^2\Omega}{(R_c^2 - R_b^2)} = \frac{4\pi R_c^2 \text{rpm}}{60(R_c^2 - R_b^2)} = K_\gamma\,\text{rpm} \qquad (39)$$

The shear rate constant, K_γ can be calculated from viscometer parameters while the shear stress constant, K_σ, must be determined from K_η and K_γ as described in Equation (25).

Infinite Gap Viscometers—This is a type of concentric-cylinder viscometer in which the viscous traction is measured on a spindle or bob rotating in the liquid, which is contained in a beaker or similar container. The size of the container is such that $R_c^2 >> R_b^2$. The shear rate in Equation (39) is defined as:

$$\dot{\gamma} = 2\Omega = \frac{4\pi}{60}\,\text{rpm} = K_\gamma\,\text{rpm} \qquad (40)$$

while the shear stress remains as defined in Equation (38).

The viscometer spindle can be inserted not only into beakers in the laboratory but also into kettles, reactors, and mixing tanks in the plant. Thus, the viscometer can be adapted for continuous in-line viscosity measurements. A guard can be mounted around the spindle to prevent it from being deflected laterally and thereby cause misalignment of the shaft. The guard also ensures that the condition, $R_c^2 >> R_b^2$, is maintained.

Cone-and-Plate Viscometers—These instruments consist of a rotating cone with a very obtuse angle and a stationary lower flat plate. The plate is raised until the apex of the cone just touches its surface. The liquid fills the narrow triangular gap between cone and plate (Figure 23-19). Its surface tension prevents it from spreading on the plate. The plate is maintained at a constant temperature by circulating water. The cone is driven at controlled speeds that can be varied continuously. The viscous drag on the rotating cone exerts a torque on a dynamometer that is proportional to the shear stress. The angle θ formed by cone and plate is usually less than 3°, and the average gap width is less than 2 mm. An added advantage of the instrument is that sample volumes smaller than 0.5 cm^3 can be used.

For small values of θ in radians, the viscosity is determined as:

$$\eta = \frac{3\theta}{2\pi R_b^2}\left(\frac{T}{\Omega}\right) = \frac{180\,\theta\,k}{4\pi R_b^2}\left(\frac{S}{rpm}\right) = K_\eta\left(\frac{S}{rpm}\right) \qquad (41)$$

where k, S, T, and Ω are as defined previously and R_b is the maximum cone radius. Equation (41) can be expressed in terms of shear stress and shear rate as follows:

$$\sigma = \frac{3T}{2\pi R_b^2} = \frac{3k}{2\pi R_b^2}\,S = K_\sigma S \qquad (42)$$

and

$$\dot{\gamma} = \frac{\Omega}{\theta} = \frac{2\pi}{60\theta}\,rpm = K_\gamma\,rpm \qquad (43)$$

As with concentric-cylinder viscometers, K_η is determined by calibration with a viscosity standard, K_γ is calculated from viscometer parameters and K_σ is calculated from K_η and K_γ.

Parallel-Plate Viscometers—A parallel-plate or rotating-disk viscometer is similar to a cone and plate viscometer except that the rotating plate is parallel to the fixed plate. The equations are as follows where d is the distance between the plates:

$$\eta = \frac{d}{\pi R_b^4}\left(\frac{T}{\Omega}\right) = \frac{60\,d\,k}{2\pi^2 R_b^4}\left(\frac{S}{rpm}\right) = K_\eta\left(\frac{S}{rpm}\right) \qquad (44)$$

$$\sigma = \frac{T}{2\pi R_b^3} = \frac{k}{2\pi R_b^3}\,S = K_\sigma S \qquad (45)$$

$$\dot{\gamma} = \frac{R\Omega}{2d} = \frac{\pi R}{60d}\,rpm = K_\gamma\,rpm \qquad (46)$$

The constants, K_η, K_σ and K_γ are determined as described above for the cone and plate viscometer.

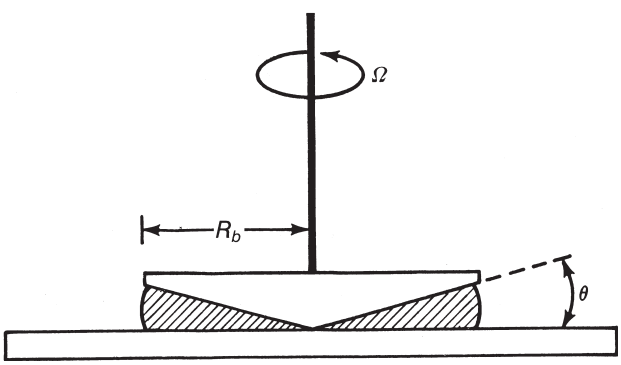

Figure 23-19. Geometry of a cone-and-plate viscometer.

FALLING BALL OR NEEDLE VISCOMETERS—With these instruments, viscosities are determined by measuring the velocity of a falling or rolling ball, a falling needle, or a rising air bubble in the liquid being studied. This method is best suited for Newtonian liquids because it measures viscosities at a single shear rate.

When a sphere of radius, R, and density, ρ_2, descends vertically through a liquid of density, ρ_1, the driving force is the effective weight of the sphere, ie, the weight of the sphere minus the weight of the liquid it displaces. It equals the volume of the sphere multiplied by the net density $\rho_2 - \rho_1$ and by the acceleration of gravity g, namely $(4\pi R^3/3)(\rho_2 - \rho_1)g$. The viscous resistance of the liquid is given by Stokes' law, namely, $6\pi\eta Rv$. When the sphere attains the terminal or constant velocity, v, (which occurs soon after it is dropped into the liquid column), the two opposing forces are equal, so that the viscosity is, in general, governed by Stokes' law:

$$\eta = \frac{2R^2(\rho_2 - \rho_1)\,g}{9v} \qquad (47)$$

When deriving his law, Stokes assumed that the velocity of sedimentation was very low and that the liquid medium extended at an infinite distance from the ball. Among the factors requiring correction, therefore, is the proximity of the wall.

The viscosity can then be determined from the following:

$$\eta = \frac{2R^2 g}{9}\left(\frac{(\rho_2 - \rho_1)}{v}\right) = K_\eta\left(\frac{(\rho_2 - \rho_1)}{v}\right) \qquad (48)$$

where v is the velocity in cm/sec of the falling, rolling, or rising object. Most viscometers of this type have a known distance marked on the instrument so that one merely measures the time for the object to move between the marks. Equation (48) then becomes:

$$\eta = \frac{2R^2 g}{L9}(\rho_2 - \rho_1)\,t = K_\eta(\rho_2 - \rho_1)\,t \qquad (49)$$

where L is the distance between the two marks on the viscometer and t is the time for the object to travel between the marks. Calibration of the viscometer involves determining K_η using a viscosity standard for each ball or object.

Shear stress and shear rate can be determined from the following:

$$\sigma = \frac{Rg}{3}(\rho_2 - \rho_1) = K_\sigma(\rho_2 - \rho_1) \qquad (50)$$

$$\dot{\gamma} = \frac{3L}{2R}\left(\frac{1}{t}\right) = K_\eta\left(\frac{1}{t}\right) \qquad (51)$$

Instead of spheres, viscosities can be obtained from the velocity of sedimentation of cylindrical metal needles with hemispherical ends falling vertically through liquids contained in glass capillaries. The latter have much larger diameters than the needles and are closed at the bottom. To make measurements at different shear rates, hollow needles are used and their densities are varied with different inserts.[50]

For very viscous liquids, values of the Newtonian or the apparent viscosity at a single shear rate can be measured with a metal rod plunger immersed concentrically in a vertical cylindrical glass tube filled with the liquid. The tube is closed at the bottom and thermostatted. The diameter of the metal plunger is ≈68% of the inside diameter of the glass tube. The weight of the plunger forces the liquid upward through the narrow annular space between plunger and tube. The terminal or steady-state velocity of descent of the plunger is proportional to the viscosity of the liquid.

All of these instruments have guides to ensure that the probes descend along the vertical axis of the cylindrical containers.

Tensile And Torsion Testers / Penetrometers—In the case of semisolids or very viscous liquids, a cone or needle attached to a holding rod is released and plunges vertically into the sample

Table 23-6. Non-Newtonian Correction Factors

VISCOMETER	CORRECTION FACTOR, f(n)
Capillary Viscometer	$f(n) = \frac{3n + 1}{4n}$
Cup-and-Bob Viscometer	$f(n) = 1 + K_1\left(\frac{1 - n}{n}\right) + K_2\left(\frac{1 - n}{n}\right)^2$
	Where: $K_1 = \frac{S^2 - 1}{2S^2}\left(1 + \frac{2}{3}\ln S\right)$
	$K_2 = \frac{S^2 - 1}{6S^2}\ln S$
	And $S = \frac{R_c}{R_b}$
Cup-and-Bob Viscometer – Infinite Gap	$f(n) = \frac{1}{n}$
Cone-and-Plate Viscometer	$f(n) = 1$
Parallel Plate Viscometer	$f(n) = \frac{3 + n}{4}$

under the influence of its own or added weight. The depth of penetration within a given time interval, eg, 10 sec, is used to rate the consistency of the material. The results cannot be translated into viscosity and yield values.

A modern variation of this principle is illustrated by the "Texture Analyzer" (www.texturetechnologies.com), which can provide a wide range of static and dynamic measurements of penetration and stress.

Comparison Between Instruments

When a material is to be studied over a wide range of shear rates, more than one viscometer may be used because each individual instrument may have too limited a range. When the flow curves are plotted as shear stress versus rate of shear, instruments of different dimensions and even based on different principles produce a single curve for a given material at a given temperature if the material is Newtonian. The shear rate and shear stress are measured at the surface of the bob in coaxial-cylinder viscometers, at the wall of the capillary in capillary viscometers and at the ball surface in a falling ball viscometer. When studying a material with two viscometers, it is advisable to use both instruments in the range of overlapping shear rates to ensure that the corresponding flow curves do indeed coincide. When flow curves are plotted in units other than shear stress and shear rate, such as torque units versus rpm, they depend on the geometry of the viscometer and are not directly comparable between viscometers.

In addition, all of the preceding discussion provides Newtonian parameters, even if the material being evaluated is non-Newtonian. In this case non-Newtonian corrections must be applied in order for flow curves from different viscometers to be comparable.

Non-Newtonian Corrections[83,84]

All of the preceding equations have been derived based on Newtonian behavior, which means that the shear rate is constant everywhere in the viscometer, ie, at the bob surface or at the cup surface in a cup-and-bob viscometer. This is not true for non-Newtonian fluids. Comparison of non-Newtonian fluids requires that viscosity data be corrected to a common reference point. The result is a correction to the shear rate term in reference to a fixed point in the viscometer, ie, the bob surface in a cup-and-bob viscometer and the wall in a capillary viscometer, and depends on both the viscometer and the fluid being tested.

In general, the correction takes for form:

$$\dot{\gamma}_{\text{corrected}} = \dot{\gamma} f(n) \qquad (52)$$

where f(n) is the correction factor and n is the slope of a log – log plot of shear stress vs. shear rate. For many non-Newtonian fluids of pharmaceutical interest, n is a constant. If the log – log plot is not linear, n must be determined numerically at each data point. Flow curves plotted as shear stress vs. corrected shear rates are then comparable between viscometers.

Correction factors for the most common viscometers are given as follows in Table 23-6.

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PART **3**

Pharmaceutical Chemistry

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CHAPTER 24

Inorganic Pharmaceutical Chemistry

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Inorganic chemicals have been used in pharmacy and medicine for many reasons, ranging from therapeutic agents to nutritional supplements to pharmaceutical necessities. In this chapter a review of some chemical principles and properties of elements is followed by a discussion of the wide variety of useful inorganic chemicals.

BASIS OF CHEMICAL REACTIONS

Although many subatomic particles have been identified, only the protons and neutrons of the nucleus of an atom and the extranuclear electrons will be considered here.

Each atom of an element is described uniquely by two pure numbers: its atomic number and its atomic weight. The atomic number gives the number of protons present in the nucleus and, therefore, its positive charge. Because the ground state atom must be neutral, this in turn defines the number of extranuclear electrons. The difference between the atomic number and the atomic weight of a given *isotope* of an element defines the number of neutrons in the nucleus. (Atomic weights in the tables are not whole numbers because they represent the weighted average of the atomic weights of all isotopes present.)

The electrons are arranged in major quantum groups (energy levels or orbitals) occupying the space about the nucleus. Each electron is assigned four quantum numbers:

The principle quantum number, n, describes the relative position of an energy level with respect to the other energy levels present.

The subquantum number, l, describes the different electron distributions possible for a given value of n.

The magnetic quantum number, m_l, is best described as the magnetic contribution to the angular momentum due to the movement of the electrons in space.

The magnetic spin quantum number, m_s, is the magnetic component contributed by the spin of the electron.

The permitted values for n are 1, 2, 3, . . . , for l are 0, 1, 2, . . . $(n-1)$, for m_l are $-$l, . . . 0, . . . +l, and for m_s $\pm$ 1/2. Returning to the subquantum number l, when l is 0 the electrons occupying the suborbital are known as s electrons; when l is 1, they're known as p electrons; when l is 2, they're known as d electrons; and when l is 3, they're known as f electrons. Thus if 2 electrons occupy suborbital 0 of major quantum group 3, they are represented as $3s^2$.

In assigning electrons to the atom the Aufbau Principle is used. It is an application of quantum theory, Hund's rules, and the Pauli exclusion principle. Simply stated, a given entering electron must occupy the lowest unoccupied energy level of the atom. In other words, each electron must have a unique set of quantum numbers.

As a result of the above process, all atoms, except hydrogen and the inert gases, have one or more completely occupied lower major quantum groups and have the suborbitals of their highest major quantum group only partially filled. The electrons of this outer, partially filled, energy level give each element its distinct chemical properties. These are the *valence electrons*.

Chemical reactions entail the removal of valence electrons, adding electrons to a partly filled valence shell, or sharing a pair of valence electrons between two atoms. Most atoms attempt to achieve a rare gas outer shell (ns^2 or ns^2np^6) by these processes. The energy required for the removal of the electron of least energy is known as the *first ionization potential*. It is unique for each element. The metals have low ionization potentials and, therefore, readily form cations. Nonmetals have high ionization potentials.

The attraction of a nucleus for electrons is termed its *electronegativity*. Metals have low electronegativities (they are electropositive), whereas nonmetals (especially the halogens) have high electronegativities. This allows the latter to attract additional electrons to form anions.

When atoms with widely differing electronegativities react, such as sodium, 0.93, and chlorine, 3.98, an electron transfer takes place. The one valence electron of sodium ($3s^1$) enters the incompletely filled ($3s^23p^5$) valence shell of the chlorine. Sodium now has an inert gas (Ne) electron structure with a +1 charge. The chlorine achieves the argon structure with a -1 charge. There is no formal electron-pair bond between the two entities. A crystal of sodium chloride consists of equal numbers of sodium and chloride ions held in place by the interaction of the spherically symmetrical positive cation field and the spherically symmetrical negative anion field. These ionic (electrostatic) compounds are characterized by high boiling and melting points and most are water soluble.

If two reacting atoms have similar electronegativities, such as two hydrogen atoms, a sharing of electrons takes place. One electron is donated to the bond from an incompletely filled suborbital of each atom. A covalent bond is formed by the overlap of the two atomic orbitals involved. With the formation of the bond a molecule results. The bonding electrons are no longer restricted to their atomic orbitals. They now are free to move in a molecular orbital between the two atoms in what is known as a σ molecular orbital.

When the electronegativities of the two atoms involved in the formation of a covalent bond are not identical the atom with the higher electronegativity tends to attract the electrons of the molecule more strongly than its partner. This leads to polariza-

†Deceased

tion of the molecule and a *dipole* results. The extent of polarization is directly proportional to the difference in electronegativities. Such bonds are said to have partial ionic character.

In practice, only the most electropositive atoms reacting with the most electronegative atoms result in purely electrostatic compounds, and only atoms with equal electronegativities form purely covalent bonds. Those bonds formed from elements between these extremes have partial covalent or partial electrostatic character.

Atoms with orbitals occupied by an unshared pair of electrons can share this electron pair with an atom lacking two or more electrons in its valence shell. The bond formed is said to be a *coordinate covalent bond.* Once this bond has been formed it cannot be distinguished from an ordinary covalent bond; the difference lies only in the manner of formation.

The formation of the ammonium ion from an ammonia molecule, which has an unshared electron pair, and a hydrogen ion, which has an empty *s* orbital, illustrates this type of reaction.

Covalent compounds have low melting and boiling points, and usually are insoluble in water. Solubility in water can be induced by introducing an acid or base group into the molecule. Reaction with base or acid will now give a soluble salt.

Other types of bonding exist. Those of interest are weakly bonded; the compounds formed decompose more readily than the electrostatic and covalent types. Hydrogen bonding (bridging) is quite common. Dipole–dipole bonding also is possible; very weak associations result.

Complexes are compounds or ions formed when an atom or cation *central unit* acts as a center about which anions or molecules, ligands, arrange themselves. The central unit is said to have a coordination number equal to the number of complexing ligands. The maximum number of ligands that can arrange themselves about the central unit is known as its *maximum coordination number* and is a function of the size of the central unit. Usual maximum coordination numbers are 2, 4, 6, or 8. The number of ligands that can coordinate with the central unit also is a function of ligand size. Thus, even though the maximum coordination number of aluminum is 6, only four of the relatively large chloride ions can be accommodated as ligands, for example, $[AlF_6]^{3-}$ versus $[AlCl_4]^{1-}$.

The bonding involved in the formation of complexes can be coordinate covalent or electrostatic. Bonds depending on permanent dipoles are also common, such as with hydrates.

NOMENCLATURE

The great advances in chemistry during the past several decades have made necessary constant revision of systems of nomenclature, designed to give precise information with respect to the composition of chemical compounds. Whereas oil of vitriol and lunar caustic at one time were useful names, today they must be looked upon as trivial.

CLASSICAL NOMENCLATURE—Prior to elucidation of the structure of coordination complexes, the naming of compounds was handled reasonably well by using nonnumerical prefixes and suffixes and Latin or Greek numerical prefixes. In general the main function of these prefixes and suffixes was to indicate the oxidation state of elements of variable valence, although some were intended to connote structural characteristics.

Systematic nomenclature must consider two problems; order of citation and stoichiometry. Order of citation is usually well defined; for salts and salt-like compounds the most electropositive element is named first, for example, sodium chloride. For nonmetals the International Union of Pure and Applied Chemistry (IUPAC) recommends the following order of citation: B, Si, C, Sb, As, P, N, H, Se, S, I, Br, Cl, O, F.

Cations with a single oxidation state simply are named as the element. If a cation has two oxidation states the suffix *-ous* is used to indicate the lower oxidation state; for example, mercur*ous*; the suffix *-ic* indicates a higher oxidation state: mercur*ic*. (Obviously this system breaks down when an element exists in more than two oxidation states.) The simple anions are named using the suffix *-ide.* Although the newer Stock system of nomenclature uses only the English names of the elements, classical nomenclature uses the stems of the Latin names in identifying the cations of copper, gold, tin, lead, and iron.

Table 24-1. Nomenclature for Oxygenated Acids and Salts

CL OXID STATE	ACID FORMULA	ACID NAME	ANION NAME
−1	HCl	*Hydro*chloric acid	Chlor*ide*
+1	HClO	*Hypo*chlor*ous* acid	*Hypo*chlor*ite*
+3	$HClO_2$	Chlor*ous* acid	Chlor*ite*
+5	$HClO_3$	Chlor*ic* acid	Chlor*ate*
+7	$HClO_4$	*Per*chlor*ic* acid	*Per*chlor*ate*

For the oxygenated anions a system of prefixes and suffixes was developed to indicate the oxidation state of the central atom. These are illustrated in Table 24-1 using the chlorine anions.

Sometimes one or more oxygen atoms of the anion are replaced by another element. The stem of the name of the substituting element is used as a prefix to the name for the fully oxygenated anion, for example, $Na_2S_2O_3$ is sodium thiosulfate, or Na_3AsS_4 is sodium thioarsenate (sodium tetrathioarsenate).

In addition to variable oxidation numbers, oxygenated acids (and their salts) present two other nomenclature problems: (1) a variation in the degree of hydration of the parent acid anhydride and (2) the naming of the different salts arising from partial neutralization of polyprotic acids. Table 24-2 shows the prefixes used for naming the different phosphoric acids (P^{5+}).

For salts of diprotic acids, the salt resulting from neutralization of only one proton per acid molecule is named by using the prefix *bi-* or the words *hydrogen* or *acid* with the anion; for example, $NaHCO_3$ is sodium bicarbonate, acid carbonate, or hydrogen carbonate. The latter form is preferred. Several methods have been devised for the triprotic acids. These are shown in Table 24-3. Due to very strongly basic reaction of the solutions of Na_3PO_4 and other tertiary phosphates, the pharmacist must be alert, especially when using containers labeled sodium phosphate.

It is evident from Table 24-3 that the numerical Greek prefixes hemi-, mono-, sesqui-, di, tri-, tetra-, penta-, hexa-, hepta-, octa-, ennea- (nona-), and deca- also are used in naming compounds. In fact there are compounds such as N_2O_4, dinitrogen tetraoxide, that must be named using numerical prefixes because modern systems of nomenclature are unable to identify them precisely.

STOCK NOMENCLATURE—Classical nomenclature is satisfactory for simpler compounds involving atoms with one or two oxidation states. It cannot indicate proper stoichiometry when atoms having three or more oxidation states are involved. The Stock system of nomenclature attempts to overcome the problem.

In the Stock system simple cations are named as the element followed by its oxidation state, expressed in Roman numerals enclosed in parentheses—for example, Fe^{2+} is iron(II), Fe^{3+} is iron(III), and Fe^{6+} is iron(VI). Simple anions use the suffix *-ide* as before. However, complex anions are named using the stem of the name of the central unit and the suffix *-ate* fol-

Table 24-2. Nomenclature for the Phosphoric Acids

WATER MOLECULES	RESULTANT ACID	NAME
$H_2O + 1/2P_2O_5$	HPO_3	*Meta*phosphoric acid
		*Pyro*phosphoric acid
$2H_2O + P_2O_5$	$H_4P_2O_7$	*Di*phosphoric acid
$3H_2O + P_2O_5$	H_3PO_4	*Ortho*phosphoric acid
		Phosphoric acid[a]
$5H_2O + 3P_2O_5$	$H_5P_3O_{10}$	*Tri*phosphoric acid

[a] The phosphoric acid of commerce and science is orthophosphoric acid.

Table 24-3. Nomenclature of the Phosphate Salts

FORMULA	NaH_2PO_4	Na_2HPO_4	Na_3PO_4
Preferred name	Sodium dihydrogen phosphate	Sodium monohydrogen phosphate	Sodium phosphate
Other names	Monobasic sodium phosphate	Dibasic sodium phosphate	Tribasic sodium phosphate
	Primary sodium phosphate	Secondary sodium phosphate	Tertiary sodium phosphate
USP 23	Monobasic sodium phosphate	Dibasic sodium phosphate	—

lowed by its oxidation state, in Roman numerals enclosed in parentheses. The ligand(s) involved are cited before the central unit of the complex. If two or more different ligands are present they are cited in alphabetical order, ignoring Greek prefixes. The number of each of the individual ligands involved is indicated by the use of Greek numerical prefixes. These latter rules also govern the citing of ligands associated with complex cations. The preferred nomenclature for common ligands is given in Table 24-4.

Stock names are not used for complex anions with well-established classical names. These include sulfate, sulfite, nitrate, nitrite, carbonate, phosphate, thiosulfate, cyanate, and thiocyanate.

EWENS-BASSETT SYSTEM—Sometimes it is advantageous to cite the charge on a complex ion rather than the oxidation state of the central unit. The Ewens-Bassett system gives the charge of the complex ion in Arabic numerals enclosed in parentheses, after the name. Other than this, the rules for naming a compound are similar to the Stock system. Thus, the common ferrocyanide ion, $[Fe(CN)_6]^{4-}$ becomes hexacyanoferrate(II) using Stock nomenclature, and hexacyanoferrate(−4) using the Ewens-Bassett system. Table 24-5 gives some examples of modern nomenclature.

A more thorough review of inorganic nomenclature may be found in Discher *et al*[1] or Huheey, Keiter, and Keiter.[2] A comprehensive report on the subject will be found in Report of the Commission on Nomenclature of Inorganic Chemistry, issued by IUPAC.[3]

THE PERIODIC TABLE AND FAMILIES OF ELEMENTS

The periodic table constitutes a valuable tool that systematizes the physical and chemical properties of the elements.

The utility of the periodic table lies in its ability to provide clues to the physical and chemical behavior of the elements and their compounds. Mendeleyev, the chemist who first arranged atoms systematically, could predict the existence and behavior of elements unknown during his time, such as eka-silicon, now known as germanium. A knowledge of periodic relationships enabled atomic scientists to postulate the properties of unknown post-uranic elements successfully so that procedures could be designed for their recovery from atomic reaction products.

Table 24-4. Nomenclature for Common Ligands

LIGAND	PREFERRED PREFIX	LIGAND	PREFERRED PREFIX
H_2O	Aqua	HS^-	Mercapto
NH_3	Ammine	S^{2-}	Thio (sulfo)[a] (sulfido)
CO	Carbonyl	S_2^{2-}	Disulfido
F^-	Fluoro	SO_3^{2-}	Sulfito
Cl^-	Chloro	SO_4^{2-}	Sulfato
Br^-	Bromo	$S_2O_3^{2-}$	Thiosulfato
I^-	Iodo	NO	Nitrosyl
O^{2-}	Oxo (oxy)	ONO^-	Nitrito
O_2^{2-}	Peroxo (peroxy)	NO_2^-	Nitro
OH^-	Hydroxo (hydroxy)	CN^-	Cyano
$C_2O_4^{2-}$	Oxalato	SCN^-	Thiocyanato
$NH_2CH_2CH_2NH_2$	Ethylenediamine, or *en*	NCS^-	Isothiocyanato

[a] Forms in parentheses are also used.

Based on periodic law, the periodic table arranges the elements into horizontal rows, with the same outermost, partly filled, major quantum groups, and into vertical columns that have elements with the same valence electron structures. As a result, in any given vertical group (*family*) the members exhibit similar behavior patterns. Differences are a matter of degree, depending upon atomic radius and the type of closed shell underlying the valence electron(s).

The preferred way of designating columns in the periodic table is controversial. In this chapter the vertical groups of the periodic table are identified by the Roman numerals I to VIII, except for the inert gases which are assigned as Group 0. Each group divides into two subfamilies, A and B. In this chapter the *typical elements* will be designated the A subgroup—thus, I-A is the alkali metals; the transition element members of the family will be designated the B subgroup. Group VIII is not divided into A and B subgroups. It consists of three triads of elements. The members of a given triad are remarkably similar in both physical and chemical properties, such as the first triad of cobalt, nickel, and iron.

Hydrogen ($1s^1$) and helium ($1s^2$) constitute the first row of the periodic table. Although helium clearly is the first member of Group 0, hydrogen customarily is placed at the head of both Group I-A, the alkalies, and Group VII-A, the halogens. Like the alkali metals, it exists as the monovalent cation H^+, but like the halogens, it also can exist as the monovalent anion H^-, the hydride ion.

Many of the vertical groups of the periodic table have common names. Those already identified are Group 0, the inert gases; Group I-A, the alkali metals; Group II-A, the alkaline earths; and Group VII-A, the halogens. Additional named groups are Group VI-A, the chalcogens; Group I-B, the coinage elements; and Group II-B, the volatile elements.

Those elements in which a *d* orbital is filled partially, starting at Group III-B and ending at Group II-B, are known as the *transition elements.* Horizontal similarities exist to a varying degree in the transition elements, especially in the lower oxidation states. As an example, the element palladium, to the left of silver, forms an insoluble chloride, $PdCl_2$, which is soluble in ammonia.

The lanthanides and actinides (inner transition elements) are fourteen member families in which *f* orbitals have 1 to 14 electrons. Each family has very strong horizontal similarities because the electrons in the partly filled external *s*, *p*, and *d* orbitals are identical for most.

Because the energy levels of the electrons in the *d* and *f* orbitals of the transition elements and the inner transition elements, respectively, differ only slightly, these elements give rise to colored compounds. The energy emitted when an excited electron falls to a vacant lower level within the *d* or *f* orbitals is that of radiation in the visible range of light.

Starting at the upper-right corner of the periodic table, as one proceeds down and to the left, the elements assume increasing metallic character; they become more basic, and less electronegative (more electropositive). The simple anions become less stable and the simple cations more stable. Thus, it may be said the nonmetals occupy the upper-right area of the periodic table and the metallic elements are found to the left and toward the bottom. The so-called *heavy metals* are found in the two bottom rows. Metallic elements, for the most part, are *protein precipitants,* the major exception being the alkali metals. Being pro-

Table 24-5. Examples of Modern Nomenclature

FORMULA	CLASSIC NAME	STOCK NAME	EWENS-BASSETT[a]
$K_2[HgI_4]$	Potassium mercuric iodide	Potassium tetraiodomercurate (II)	(−2)
$[Ag(NH_3)_2]^+$	Silver ammonia ion	Diamminesilver (I) ion	(+1)
$Na_3[Au(S_2O_3)_2]$	Sodium gold thiosulfate	Sodium dithiosulfatoaurate (I)	(−3)
$[Fe(H_2O)_6]Cl_3$	Hydrated ferric chloride	Hexaaquairon (III) chloride	(+3)
BiOCl	Bismuthyl chloride	Bismuth (III) chloride oxide	[c]
$[Ni(CO)_4]$	Nickel carbonyl	Tetracarbonyl nickel (O)	[c]
$[(NH_3)_5CoO_2Co(NH_3)_5]^{4+}$	—	Decammine-μ-peroxodicobalt (III) ion[b]	(+4)
$Na_2[Fe(CN)_5(NO)] \cdot 2H_2O$	Sodium nitroprusside	Sodium pentacyanonitrosylferrate (III) dihydrate	(−2)

[a] This number, as shown, substitutes for the Roman numeral of the Stock name.
[b] This ion illustrates the use of μ to indicate a bridging structure, in this case the peroxo group.
[c] Not applicable.

tein precipitants, metals, especially heavy metals, are toxic. For example Ba, Tl, Pb, and Hg are violent poisons.

From the above it is obvious there must be an area in the periodic table where the elements are equally acidic and basic, that is, *amphoteric.* If a line is drawn diagonally through hydrogen and beryllium and through aluminum, germanium, antimony, and polonium, the elements on the line and some adjacent to it, are amphoteric. Thus, as a base, aluminum forms compounds such as aluminum chloride; as an acid, it forms sodium aluminate equally well.

In every *typical* element family the first member of the family can be quite unlike the other members. It more closely resembles the second member of the adjacent group to the right. These diagonally related elements are known as *diagonals* or *bridge* elements. They are

IA	IIA	IIIA	IVA	VA	VIA	VIIA
Li	Be	B	C	N	O	F
Na	Mg	Al	Si	P	S	Cl

Beryllium and aluminum constitute a bridge pair. Beryllium fluoride is water soluble (but poorly ionized), whereas the fluorides of magnesium and the other alkaline earths are sparingly soluble. Unlike magnesium and the alkaline earths, beryllium readily acts as the central ion of complexes, both in the solid state and in solution. Like aluminum, beryllium is amphoteric, gives rise to alums, catalyses the Friedel-Craft reaction, and so on.

Tables 24-6 to 24-17 will summarize some useful properties and facts concerning the groups of the periodic table. The second and third row *triads* of Group VIII and the lanthanides and actinides are not included in these tables because they present no important applications in pharmacy and medicine.

The *orbital electrons* are important because they predict the possible oxidation states, the shielding of the nuclear charge, and the polarizability for each element. Those oxidation states that have been identified for each element also are listed.

The *atomic radius* and the *ionic radii* give an indication of the relative size of the members of a family. The negative ions of an element are always larger than the neutral atom; the positive ions are always smaller. Because of the increasing effective nuclear charge for a given element, cations of higher charge always are smaller than those with a lower charge. This is important because it gives an indication of the effective coordination number of cations and atoms as central units of complexes.

The *ionization potential* is a measure of the energy required to remove an electron by overcoming the attractive force of the nucleus. *Note:* This use of the word *potential* is improper; ionization potential is a measure of energy. It is related to atomic size; removal of the first electron from beryllium and barium requires 9.3 ev and 5.2 ev, respectively. Because the removal of one electron effectively increases the nuclear charge by one unit, the second ionization potential is about double that of the first, 18.2 ev and 9.95 ev for beryllium and barium, respectively.

Electronegativity, discussed previously, gives an indication of the type of bonding resulting when two atoms react. It gives an indication of the extent of polarization in covalent compounds. It also is used to determine the order of citation in the naming of binary compounds.

ELEMENTS OF GROUP 0

Because the inert gases were unknown at the time, Mendeleyev made no provision for them in his proposed atomic table. With their subsequent discovery Group 0 seemed the most appropriate designation. The group fits very nicely into Mendeleyev's arrangement. Its presence explains the extreme transition of properties in going from the very electronegative halogen family to the very electropositive alkali metal family. This shift in properties in going from halogen to inert gas to alkali metal is shown clearly by the change in the valence electron structures:

$$(n-1)s^2(n-1)p^5 \rightarrow (n-1)s^2(n-1)p^6 \rightarrow (n-1)s^2(n-1)p^6ns^1$$

All Group 0 elements except radon occur in the atmosphere. Helium also occurs in commercial quantities in certain natural gases in the southwestern US. Argon, neon, krypton, and xenon are produced from liquid air by fractional distillation. Helium is produced similarly from the natural gases named above. Radon is recovered from the natural decay products of radium.

The inert gases are monoatomic and are colorless, odorless gases under ordinary conditions of temperature and pressure. They vary widely in atomic mass and atomic volume. These differences are reflected in the values of their physical constants (Table 24-6).

Each inert gas, except helium, is characterized by an outermost electron shell of the *inert gas* structure, ns^2np^6 (see Table 24-6). Helium has the $1s^2$ structure; the ns^2 structure is achieved in many stable cations, for example, Pb^{2+}. Because all electrons are paired, the chemical inertness of the group is predictable and is reflected in terms of peak ionization potentials and various other characteristics. However, under unusual reaction conditions, there is evidence of hydrate formation. Some relatively stable fluorides, such as XeF_2, XeF_4, and XeF_6, a crystalline sodium perxenate, and possibly a perkryptate, are known.

However, in comparison with other elements, those of Group 0 still are classed logically as chemically inert.

Helium, because of its low density and low solubility in blood is used to prepare synthetic airs.

Argon is relatively plentiful as it is a byproduct of the fractionation of liquid air for the production of oxygen and nitrogen. It is used as an inert atmosphere for industrial processes in

Table 24-6. The Elements of Group 0[a]

ELEMENT	HELIUM	NEON	ARGON	KRYPTON	XENON	RADON
Symbol	He	Ne	Ar	Kr	Xe	Rn
Atomic number	2	10	18	36	54	86
Atomic weight[b]	4.003	20.18	39.95	83.80	131.3	(222)[d]
Orbital electrons	$1s^2$	$[He]2s^2p^6$	$[Ne]3s^23p^6$	$[Ar]3d^{10}4s^24p^6$	$[Kr]4d^{10}5s^25p^6$	$[Xe]4f^{14}5d^{10}6s^26p^6$
Atomic radius (A)	1.80	1.60	1.92	2.00	2.20	2.29
Ionization potential,[c] ev	24.6	21.6	15.8	14.0	12.1	10.7
% by volume in air	5×10^{-4}	15×10^{-4}	0.94	11×10^{-5}	9×10^{-6}	—

[a] Physical data are from reference 4. Atomic and ionic radii are from Pauling[5] and modified by the work of Shannon and Prewitt.[6] See also reference 7.
[b] Given to four significant figures.
[c] First ionization potential, unless otherwise noted.
[d] Atomic weights in parenthesis are now known exactly.
Note: The above apply to Tables 24-6 to 24-17.

which nitrogen, the usual inert atmosphere, reacts with the materials present.

Krypton and xenon have been investigated for possible use as anesthetics. However, the sparsity of these elements in nature imposes severe limitations on such use. ^{133}Xe is used for diagnostic studies both by inhalation and intravenous injection.

Radon is used instead of radium in the treatment of certain types of cancer. Sealed tubes containing the gas are embedded in the tissues to be treated. Both radium and radon emit alpha particles in the first stage of their radioactive decay. Radon is a public health concern because it has been found in the basements of some private homes.

ELEMENTS OF GROUP I

The elements of Group I (Tables 24-7 and 24-8) are characterized by having only one valence electron, ns^1. The subgroups differ in that Group I-A has an underlying, stable, inert gas shell, $(n-1)s^2(n-1)p^6ns^1$, whereas in Group I-B this has been replaced by a completed d shell, $(n-1)d^{10}ns^1$.

These elements are strongly metallic, giving rise to cations, M^+. Because electrons can be removed from the underlying d shell, Group I-B elements can exhibit higher positive oxidation states, M^{2+} and M^{3+}.

Elements of Group I-A

Group I-A comprises the most reactive of all the metallic elements, and the activity increases with atomic number. The cations of these elements are stable chemically; the free elements are not found in nature. The single positive charge of the nucleus is screened effectively by the inert gas shell, thus these cations have little or no polarizing effect on anions and molecules and therefore do not form complexes.

The hydroxides give alkaline solutions, alkalinity increasing with atomic number. Alkali metal salts of common inorganic and organic acids are ionic, are usually colorless and, with few exceptions, are readily soluble in water. Aqueous solutions of the salts are neutral to strongly basic, depending on the strength of the anion as a Brønsted base. Most distinguishing properties of the salts and their solutions are due to the anion present, rather than the cation; if they are colored, the anion is responsible.

The cations hydrate in aqueous media; the degree of solvation decreases with increasing atomic number. In the crystalline state only lithium and sodium regularly form hydrates. Potassium and ammonium salts (below) rarely are hydrated; if hydrated, the water usually is associated with the anion.

SODIUM AND POTASSIUM

Except for those properties due to mass and degree of hydration, sodium and potassium compounds are remarkably similar. Sodium salts are selected more frequently for use on a strictly economic basis. In addition, because of the lower atomic weight of sodium, there usually are more reactive units per gram when using sodium salts. (However, the greater hydration of the sodium versus the potassium salts may partially or entirely erase this latter advantage.)

Despite the foregoing factors, subtle differences often favor use of the potassium salt. Generally, a given potassium salt is more soluble in nonpolar solvents. Potassium salts generally are

Table 24-7. Elements of Group I-A

ELEMENT	HYDROGEN	LITHIUM	SODIUM	POTASSIUM	RUBIDIUM	CESIUM	FRANCIUM
Symbol	H	Li	Na	K	Rb	Cs	Fr
Atomic number	1	3	11	19	37	55	87
Atomic weight	1.008	6.94_1	22.99	39.10	85.47	132.91	(223)
Orbital electrons	$1s^1$	$[He]2s^1$	$[Ne]3s^1$	$[Ar]4s^1$	$[Kr]5s^1$	$[Xe]6s^1$	$[Rn]7s^1$
Oxidation states	−1, +1	+1	+1	+1	+1	+1	+1
Atomic radius (Å)	0.37	1.50	1.86	2.31	2.44	2.62	—
Ionic radius (Å)	1.36 (−1)[a]	0.60 (+1)	0.95 (+1)	1.33 (+1)	1.48 (+1)	1.69 (+1)	1.76 (+1)
Ionic (hydrated) radius (Å)	—	3.40	2.76	3.32	2.28	2.28	—
Ionization potential	13.527	5.39	5.14	4.34	4.18	3.89	—
Electronegativity,[b] ev	2.1	0.98	0.93	0.82	0.82	0.79	0.7
% of earth's crust	0.127	6.5×10^{-3}	2.8	2.6	3.1×10^{-2}	7×10^{-4}	—

[a] Hydride ion; figure in parenthesis is the oxidation state.
[b] Pauling scale.[5]

Table 24-8. The Elements of Groups I-B and II-B

ELEMENT	COPPER	SILVER	GOLD	ZINC	CADMIUM	MERCURY
Symbol	Cu	Ag	Au	Zn	Cd	Hg
Atomic number	29	47	79	30	48	80
Atomic weight	63.54	107.87	196.97	65.38	112.4	200.5_9
Orbital electrons	$[Ar]3d^{10}4s^1$	$[Kr]4d^{10}5s^1$	$[Xe]4f^{14}5d^{10}6s^1$	$[Ar]3d^{10}4s^2$	$[Kr]4d^{10}5s^2$	$[Xe]4f^{14}5d^{10}6s^2$
Oxidation states	+1, +2	+1, +2	+1, (+2), +3	+2	+2	+1, +2
Atomic radius (Å)	1.40	1.70	1.70	1.40	1.60	1.50
Ionic (crystal) radii (Å)	0.96 (+1)	1.26 (+1)	1.37 (+1)	—	—	1.27 (+1)
	0.72 (+2)	0.89 (+2)	0.99 (+3)	0.88 (+2)	1.09 (+2)	1.16 (+2)
Ionization potential, ev	7.724	7.574	9.223	6.92	8.99	10.42
Electronegativity	1.90	1.93	2.54	1.65	1.69	2.00
% of earth's crust	10^{-4}	10^{-8}	10^{-9}	1.3×10^{-2}	1.5×10^{-5}	ca 10^{-6}

less deliquescent than the corresponding sodium salt; for example, potassium permanganate is used rather than the deliquescent sodium permanganate. Finally, the living cell differentiates between the two cations; sodium is the cation of the extracellular fluids, whereas potassium is the cation of the intracellular fluids.

Sodium compounds are used widely in pharmacy and medicine. With a few exceptions, such as sodium chloride in electrolyte replenishers, the therapeutic activity is referable to the anionic component of the salt. Sodium is commonly the cation of choice to optimize the pharmaceutical utility of organic medicaments, as in methiodal sodium, phenobarbital sodium, or sodium citrate.

Because of the propensity of sodium ion to promote retention of water in the tissues, sodium salts are used with caution in the treatment of cardiac and renal conditions in which edema is a problem. Some drugs, such as hydrochlorothiazide, promote excretion of potassium ion to an extent requiring auxiliary dietary intake of potassium, usually as the chloride or gluconate. Potassium ion has a diuretic effect. The thiazides also cause the excretion of magnesium ion.

RUBIDIUM AND CESIUM

Rubidium and its cation are very similar in behavior to potassium. Neither rubidium nor cesium find application in pharmacy and medicine at this time.

LITHIUM

Being a bridge element, the behavior of the element lithium and its compounds often is decidedly different from that of the other members of the alkali family. At room temperature the free metal is much less reactive with water; on burning it forms the normal oxide rather than the peroxide. Lithium carbonates and phosphates are only slightly water-soluble. Its chloride is soluble in organic solvents. Lithium salts are highly hydrated. In all of these properties lithium resembles magnesium, and to some extent calcium, more closely than sodium.

Lithium has no normal physiological role. In its former therapeutic applications (eg, lithium bromide) the activity was inherent in the anion. However, because of the toxic character of the lithium ion, as revealed by use of lithium chloride in salt substitutes, continued use of these lithium compounds is not justified. Lithium Carbonate USP and Lithium Citrate USP have been found valuable in the treatment of hypomanic and manic states. However, these patients must be monitored carefully for blood lithium levels because of the toxicity of the cation.

AMMONIA AND AMMONIUM COMPOUNDS

Ammonia [NH_3] coordinates readily with a proton to form the ammonium ion [NH_4]$^+$. This ion displays many of the properties of the alkali metal ions. Its salts show a striking resemblance to potassium and rubidium salts, with which they are commonly isomorphous. The relationship extends to solubilities, as evidenced by the general water solubility of ammonium salts of inorganic and organic acids, but the low water solubility of such salts as the bitartrate, chloroplatinate, and perchlorate.

However, there are important differences. *Ammonium hydroxide* (mainly a solution of ammonia molecules in water) is feebly basic. The equilibrium

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

lies strongly to the left unless the hydroxyl ion is removed by neutralization. Solutions of ammonium salts are acidic rather than basic.

Ammonium salts commonly used therapeutically include the carbonate, chloride, and bromide. The bromide is used as a central depressant. Both the chloride and carbonate are common ingredients in expectorant preparations.

In aqueous solution form, ammonia is used in pharmacy as a mild alkalizer. It often is preferred to the alkali bases because of its volatility, any excess being detected by its odor, and it is removed readily by heat. The ammonia in household use contains 10% NH_3 and is known as 16° ammonia (degrees Baumé, a concentration term).

Elements of Group I-B

The Group I-B elements have been known since antiquity. Because they occur in the free metallic state, are relatively easy to recover from their ores, and they are very malleable, they have been used throughout history to make decorative vessels and jewelry. They have been employed for centuries as a measure of monetary wealth and for the fabrication of coins, hence the family name *coinage metals*.

These elements and their compounds are strikingly different from those of Group I-A. Colored compounds are numerous. The hydroxides and many of the simple salts are insoluble in water. All readily act as the central unit of complexes. The soluble compounds of these elements are toxic. A summary of their important characteristics is given in Table 24-8.

COPPER

Of the monovalent compounds, copper(I) oxide, Cu_2O, and copper(I) chloride, Cu_2Cl_2, are used most frequently. Important copper(II) (cupric) salts are the oxide, CuO, and sulfate, $CuSO_4 \cdot 5H_2O$. Copper compounds are toxic.

Copper is an essential trace element. Small quantities enhance the physiological utilization of iron. It occurs in the respiratory pigment hemocyanin, in many enzymes, and is distributed widely in foods.

Copper compounds have been used in a variety of medicinal applications. Copper gluconate, cupric chloride dihydrate, and cupric sulfate pentahydrate are the officially cited copper com-

pounds at this time. The radioactive ^{64}Cu isotope has been employed in mineral metabolism studies. Copper(II) sulfate is the basis for Fehling's and Benedict's Solutions, the classic test solutions for reducing sugars. Various copper compounds find commercial application as fungicides and insecticides, and they are particularly effective algaecides.

SILVER

With the exception of the nitrate and fluoride, the common salts of silver in the +1 oxidation state are insoluble or only slightly soluble in water. Many, including the oxide, react with and dissolve in ammonia water; the iodide and sulfide are important exceptions. Silver also forms a +2 series of salts. Silver has an oligodynamic action. Water distilled in contact with silver metal remains sterile over long periods of time.

Because of the ability of silver ion to precipitate protein and chloride in the affected tissue, silver compounds such as silver nitrate are employed to provide local germicidal action. Silver sulfadiazine is used topically as a germicide. Silver is released slowly from these *in situ* precipitates to give lasting germicidal action. Cosmetic problems can result because of discoloration due to the photosensitivity of silver ion.

Preparations containing silver or silver compounds in colloidal solution once were used widely as topical antiseptics; eg Mild Silver Protein, for which there is a renewed interest in ophthalmology. By increasing their concentration, silver ions may be used to bring about protein precipitation. To reduce brittleness, some silver chloride (5%) is formed in silver nitrate by adding hydrochloric acid or potassium chloride; the product, Toughened Silver Nitrate, is cast into sticks and used as a styptic.

The ready reducibility of silver ion to elemental silver gives rise to various instability problems and incompatibilities. Because silver compounds are light sensitive, they must be protected by the use of light-resistant containers. The soluble silver salts are toxic. However, the toxicity usually is limited, owing to local precipitation of adherent layers of silver protein and silver chloride.

GOLD

Two series of gold compounds exist: for example, AuCl, gold(I) chloride (aurous chloride); and $AuCl_3$, gold(III) chloride (auric chloride). Gold readily acts as the center for the formation of complexes, for example, $Na_3[Au(S_2O_3)_2]$, sodium dithiosulfatoaurate(I), sodium dithiosulfatoaurate(−3), gold sodium thiosulfate.

Chemically gold salts are characterized by instability to heat, light, and even very mild reducing agents. Simple gold(I) salts can undergo *autoxidation,* giving rise to finely divided metal and the corresponding gold(III) compound. The stability of the gold ions is improved by complexation. This particularly is true if a sulfur linkage is available. Because of the ease of reduction, gold compounds must be handled with exceptional care and, if possible, dispensed separately.

At the present time, gold compounds are employed in the treatment of lupus erythematosus and rheumatoid arthritis. Aurothioglucose and gold sodium thiomalate are listed in the USP. Because these gold compounds are absorbed poorly when given orally, parenteral administration is required.

Dimercaprol (BAL) is used as an antidote if the patient shows signs of gold toxicity. Auranofin, [(2,3,4,6-tetra-*O*-acetyl-1-thio- β-d-glucopyranosato)(triethylphosphine)gold], is available in a tablet dosage form and is showing some success in the oral treatment of rheumatoid arthritis.

The radioactive isotope ^{198}Au is employed therapeutically in the treatment of certain malignancies.

Each element in Group II is characterized by the presence of two *s* electrons in the outermost orbital. Subgroup II-A elements have a $(n-1)s^2(n-1)p^6ns^2$ outer electron structure, except for the small beryllium atom whose structure is $1s^22s^2$. Subgroup II-B differs in that its underlying electron structure is the filled *d* orbital, $(n-1)d^{10}ns^2$.

Elements of Group II-A

Although Group II-A is called the *alkaline earth group,* there is some question whether magnesium, and especially beryllium, should be included under that title. Except for amphoteric beryllium, these elements are strictly metallic. Like the alkali metals, because of chemical reactivity, they do not occur free in nature. They function uniformly in the +2 oxidation state (Table 24-9).

The similarity existing between calcium, strontium, and barium is especially striking. Calcium, strontium, and barium react readily with water to form hydroxides with the simultaneous evolution of hydrogen. Magnesium reacts similarly but only at elevated temperatures. The hydroxides of beryllium and magnesium are insoluble in water; that of beryllium is amphoteric. Although less soluble than the alkali hydroxides, the hydroxides of calcium, strontium, and barium give strongly basic solutions. The carbonates, phosphates, sulfates, and fluorides are insoluble; they are important in analytical work.

Except for hydrate formation, the three heavier members of the family do not form complex ions. Magnesium forms a few crystalline complexes of the type K_2MgF_4.

BERYLLIUM

Being amphoteric, the element beryllium appears both as simple salts and berylates. The cation complexes readily, as in $[Be(H_2O)_4]^{2+}$ or $[Be(NH_3)_4]^{2+}$. As a *bridge element,* beryllium

Table 24-9. The Elements of Group II-A

ELEMENT	BERYLLIUM	MAGNESIUM	CALCIUM	STRONTIUM	BARIUM	RADIUM
Symbol	Be	Mg	Ca	Sr	Ba	Ra
Atomic number	4	12	20	38	56	88
Atomic weight	9.012	24.31	40.08	87.62	137.3	226.03
Orbital electrons	$[He]2s^2$	$[Ne]3s^2$	$[Ar]4s^2$	$[Kr]5s^2$	$[Xe]6s^2$	$[Rn]7s^2$
Oxidation states	+2	+2	+2	+2	+2	+2
Atomic radius (Å)	0.90	1.70	1.74	1.92	1.98	—
Ionic (crystal) radius (Å) (coordination number 6)	0.31 (+2)[a]	0.65 (+2)	0.99 (+2)	1.13 (+2)	1.35 (+2)	1.43 (+2)
Ionization potential, ev (II)[b]	9.3	7.6	6.1	5.7	5.2	5.252
	18.2	15.0	11.9	11.0	9.95	10.099
Electronegativity	1.57	1.31	1.00	0.95	0.89	0.9
% of earth's crust	6×10^{-4}	2.1	3.6	0.03	0.025	1.3×10^{-10}

[a] Coordination number 4.
[b] Second ionization potential.

resembles aluminum in its behavior. This similarity is so striking that many early workers considered beryllium a lighter member of the aluminum family before Mendeleyev correctly placed it in Group II. Although its ionic diameter is considerably greater than that of beryllium, the higher +3 charge on the aluminum ion results in a polarizing ability similar to that of beryllium. Both elements dissolve in caustic alkalis and both form a protective coating on their surface when placed in nitric acid. The halides of both elements have similar solubilities in organic solvents. Both elements act as Lewis acids and give rise to alums.

Beryllium metal and its compounds are extremely toxic when ingested, inhaled, or absorbed through the skin. None of its compounds are employed as therapeutic agents.

MAGNESIUM

Magnesium is a relatively abundant element that is chemically active. The cation, Mg^{2+}, is stable under all conditions ordinarily met in pharmaceutical practice. Magnesium compounds are employed for a variety of purposes in therapeutics. Many of its insoluble compounds are used as gastric antacids. The hydroxide and sulfate are used as cathartics, and the sulfate as an anticonvulsant. A concentrated solution of the sulfate often is used topically as a bath so that, by osmotic action of the concentrated sulfate solution, a local infection may be drawn to the surface of the skin and be expelled.

Toxic manifestations following magnesium administration are relatively rare; calcium gluconate given intravenously is an effective antidote. The stearate is employed as a lubricant in the preparation of compressed tablets. The artificial radioactive isotope ^{27}Mg, has been employed in research involving photosynthesis.

There is an increasing awareness of the critical importance of magnesium ions in human biochemistry. Because ion- specific electrode potentiometry now allows measurement of free, unbound magnesium ions, plasma concentrations may be measured and the concentration in the cytosol may be inferred. As the second most plentiful cation inside the cell and a natural calcium channel blocker, magnesium ions are important in many cardiovascular diseases. Successful absorption from the gastrointestinal tract appears to depend on the nature of the magnesium salt that is used.

CALCIUM

Calcium is a relatively reactive metal whose cation is stable. However, soluble calcium salts undergo metathesis with soluble borates, carbonates, citrates, oxalates, phosphates, sulfates, and tartrates to yield insoluble calcium compounds. These reactions often lead to pharmaceutical incompatibilities.

Calcium is indispensable to life. Calcium, and to a much lesser degree, magnesium, is the cation of hydroxyapatite, the major constituent (98%) of the bones and teeth. Calcium is essential to many physiological processes. Therapeutic categories represented by official calcium compounds include: antacids and calcium replenishers.

Calcium is frequently the cation of choice to carry therapeutically active anions, such as calcium aminosalicylate and calcium cyclobarbital. In some instances, this is referable to better physical characteristics of the calcium compound; in others, it is a deliberate attempt to avoid an unnecessary intake of sodium. The artificial radioactive ^{45}Ca isotope has been employed in studies involving mineral metabolism.

STRONTIUM

The behavior of the element strontium is very similar to calcium. Ingested, its distribution is similar to that of calcium. At this time it has no application in pharmacy or medicine. In the past it has been used as the carrier cation for therapeutically active anions, as in strontium bromide.

BARIUM

Chemically, barium is the most active of Group II-A. Its cation is stable under all ordinary conditions. Barium hydroxide is soluble and is a strong base. Because of this, it often finds application in analytical and synthetic operations.

In sharp contrast to the lighter members of Group II-A all barium compounds that are soluble either in water or in dilute acid are poisonous. The most readily available antidote for barium ingestion is magnesium sulfate (Epsom Salt).

With the exception of barium sulfate, which finds use as a radiopaque, barium compounds are not employed as medicinal agents. Barium hydroxide lime is employed as a carbon dioxide absorber. Artificial radioactive isotopes of barium have been employed in pharmacokinetic investigations.

Elements of Group II-B

Because zinc, cadmium, and mercury (see Table 24-8) have comparatively low boiling points, 907°, 768°, and 357°, respectively; they are referred to frequently as the *volatile metals.* The common oxidation state is +2, but mercury also exists in the +1 state. This latter state is achieved by the formation of a covalent, two electron bond between two mercury atoms. Thus the mercury(I) ion (mercurous) is always written Hg_2^{2+}. The filled $(n-1)d^{10}$ orbital is stable in this family. Unlike Group I-B there are no oxidation states involving loss of a *d* electron. There is increasing covalent character in the salts of these elements; for example, fused zinc chloride conducts electric current whereas the mercury chlorides do not. These elements readily complex with most common ligands and concentrated solutions exhibit autocomplexation. Only zinc is sufficiently amphoteric to form a stable oxygen complex, ZnO_2^{2-}, the zincate ion.

ZINC

All soluble zinc salts show some degree of hydrolysis,

$$Zn^{2+} + 2H_2O \rightleftharpoons [Zn(OH)]^+ + H_3O^+$$

Thus, all zinc salts of weak Brønsted bases show an acid reaction.

Zinc has many therapeutic applications in the treatment of various external surfaces of the body and in wound healing, taste acuity, and various ophthalmic problems (eg, macular degeneration). Strong zinc sulfate solution is used as an emetic; its emetic action is so rapid that little or no zinc salt is absorbed. Zinc is present in all living organisms; it is distributed widely in foods. It is an essential trace element and an essential component of carbonic anhydrase and many other enzymes.

Zinc compounds soluble in water or in the gastric fluid, eg, ZnO, may be poisonous. There is a relatively wide margin of safety between the required intake and toxic intake. The most readily available antidote is sodium bicarbonate (baking soda).

Artificial radioactive isotopes of zinc have been employed in studies of mineral metabolism.

CADMIUM

Cadmium is truly intermediate in properties to zinc and mercury. Soluble cadmium compounds are astringent; $CdSO_4$ has been used both as a topical astringent and for eye infections. Cadmium sulfide has been introduced for the treatment of seborrheic dermatitis. In Japan, Itai-Itai disease is believed to be caused by drinking water contaminated with cadmium.

Table 24-10. The Elements of Group III-A

ELEMENT	BORON	ALUMINUM	GALLIUM	INDIUM	THALLIUM
Symbol	B	Al	Ga	In	Tl
Atomic number	5	13	31	49	81
Atomic weight	10.81	26.98	69.72	114.8	204.3_7
Orbital electrons	$[He]2s^2 2p^1$	$[Ne]3s^2 3p^1$	$[Ar]3d^{10}4s^2 4p^1$	$[Kr]4d^{10}5s^2 5p^1$	$[Xe]4f^{14}5d^{10}6s^2 6p^1$
Oxidation states	+3	(+1), +3	+1, +2, +3	+1, +3	+1, +3
Atomic radius (Å)	0.82	1.25	1.26	1.44	2.0
Ionic (crystal) radius (Å)	—	—	1.90 (+1)	1.90 (+1)	1.64 (+1)
(coordination number 6)	0.20 (+3)[a]	0.675 (+3)	0.76 (+3)	0.94 (+3)	1.03 (+3)
Ionization potential, ev	8.30	5.95	6.0	5.8	6.1
(II)[b]	25.15	18.82	20.4	18.8	20.3
(III)[b]	37.92	28.44	30.6	27.9	29.7
Electronegativity	2.04	1.61	1.81	1.78	1.62
% of earth's crust	3×10^{-4}	8.13	1.5×10^{-3}	10^{-5}	ca 10^{-4}

[a] Coordination number 4.
[b] Second and third ionization potential.

MERCURY

Mercury is a true metal. As indicated previously, it alone of the family has two series of salts. Mercury and its compounds are extremely toxic. Mercury metal, because of its low boiling point, has an appreciable vapor pressure even at room temperature.

All common mercury salts are poisonous. The best antidote for mercury poisoning, particularly the bichloride, is Sodium Formaldehyde Sulfoxylate NF. Egg albumen may be used in an emergency if the poisoning is discovered shortly after ingestion. The white of one egg should be administered for each 250 mg of mercuric chloride ingested. Emesis should be induced promptly thereafter. If mercury is spilled it should be recovered immediately. Mercury that falls into cracks and other difficult to clean places is removed best by covering with powdered sulfur, allowing several days for conversion to sulfide, then vacuuming.

In former years, metallic mercury was important therapeutically as a cathartic and parasiticide, but it has been replaced largely by more efficacious and less toxic medicaments. The FDA has now issued guidelines for the over-the-counter use of mercury compounds. The April 22, 1998 *Federal Register* contained an FDA announcement about OTC mercury compounds, a summary of which is given here.

"Since 1980, the FDA has instituted progressively restrictive rules on mercury-containing OTC drug products. Now in the absence of any components or data from manufacturers supporting the use of these products, FDA has declared all mercury-containing drugs for OTC products as 'not generally recognized as safe and effective' or 'misbranded.' Effective October 19, 1998, the new rule outlaws well-known products such as Mercurochrome (merbromin), calomel (mercurous chloride), and thimerosal for all OTC first-aid antiseptics, diaper rash products, and vaginal contraceptives."

Monographs for Ammoniated Mercury (ointment and ophthalmic ointment) and Nitromersol (and topical solution) are found in the USP.

The radioactive nuclides ^{197}Hg and ^{203}Hg are used in a diagnostic capacity.

ELEMENTS OF GROUP III

Group III of the periodic table includes some 36 elements which, on the basis of external electron structure, divide into the usual Group III-A (Table 24-10) with 5 elements, and Group III-B with 31 elements. Subgroup III-B further divides into the usual transition elements (Table 24-11), the *lanthanides* (14 elements) and *actinides* (14 elements). (See the Periodic Chart of the Elements in the back of this textbook.) The lanthanide cerium, as cerium(IV), is a widely used analytical reagent. Because the lanthanides and actinides have no applications in pharmacy, further discussion is unnecessary.

The members of this family are very reactive and do not appear in nature in the free state. They have no known biological role.

Table 24-11. Transition Elements

	GROUP III-B			GROUP IV-B		
ELEMENT	SCANDIUM	YTTRIUM	LANTHANUM	TITANIUM	ZIRCONIUM	HAFNIUM
Symbol	Sc	Y	La	Ti	Zr	Hf
Atomic number	21	39	57	22	40	72
Atomic weight	44.96	88.91	138.9	47.90	91.22	178.5
Orbital electrons	$[Ar]3d^1 4s^2$	$[Kr]4d^1 5s^2$	$[Xe]5d^1 6s^2$	$[Ar]3d^2 4s^2$	$[Kr]4d^2 5s^2$	$[Xe]4f^{14}5d^2 6s^2$
Oxidation states	3+	3+	3+	2+, 3+, 4+	2+, 4+	(2+), 4+
Atomic radius (Å)	1.51	1.8	1.87	1.36	1.45	1.44
Ionic radii (Å)	0.81 (3+)	0.93 (3+)	1.15 (3+)	1.00 (2+)	—	—
(coordination number 6)				0.75 (4+)	0.86 (4+)	0.85 (4+)
Ionization potential, ev	6.7	6.5	5.6	6.82	6.84	ca 5.5
Electronegativity	1.54	1.53	1.3	—	—	—
% of earth's crust	0.44	0.022	4.5×10^{-4}	0.629	0.028	—

Elements of Group III-A

In this family of elements an electron appears in the *p* orbital of the valence shell for the first time; each element has the structure ns^2np^1. Theoretically two oxidation states are possible. The first, +1, arises by the loss of the single *p* electron. The resulting helide structure, ns^2, has sufficient stability to give rise to stable ions such as Ga^+, In^+, and Tl^+. Aluminum has this oxidation state only at elevated temperatures and it is not evident with B, Sc, Y, La.

With the loss of all three valence electrons the +3 oxidation state appears in all the elements of the family. With increasing atomic number the +3 state becomes more electrovalent in character. Boron trichloride is a covalent compound, aluminum chloride is for practical purposes covalent, and gallium(III) chloride has some covalent character. Because a normal octet is not achieved in these compounds, an electron deficient structure results. As there are only three electron pairs in the valence shell the electron-pair repulsive forces are weaker, and the molecules become electron-pair acceptors.

Due to the weaker repulsive forces, these MX_3 molecules give rise to triangular structures with hybrid sp^2 orbitals. The metal occupies the center of the triangle. By accepting a fourth electron-pair the octet is completed and sp^3 hybrids form. The addends rearrange to give tetrahedral structures with the metal ion in the center of the tetrahedron.

Because the initial compounds, such as $AlCl_3$, are electron-pair deficient, they are Lewis acids. As such, they act as catalysts for the Friedel-Crafts synthesis.

Members of this family give rise to an interesting series of double salts, the *alums*. The common formula is $M^+_2M^{3+}_2(SO_4)_4{\cdot}24H_2O$, where M^+ is a monovalent ion (eg, Na^+, K^+, Rb^+, NH_4^+, Tl^+) and M^{3+} is a trivalent ion (eg, Al^{3+}, Tl^{3+}, Cr^{3+}, or Fe^{3+}). The prototype of these double salts is alum, $K_2Al_2(SO_4)_4{\cdot}24H_2O$.

BORON

Boron appears only in the +3 oxidation state and is a nonmetal. Several oxyacids are known. Metaboric acid, $(HBO_2)_n$, and the metaborate ion do not exist as monomers. Orthoboric acid, $(H_3BO_3)_n$, exists as a hydrogen-bonded layered structure, which explains the flaky form in which it is available. Discrete H_3BO_3 molecules exist in the gaseous state and in solution. It is a weak acid, ionizing in solution.

$$H_3BO_3 + 2H_2O \rightleftharpoons H_3O^+ + [B(OH)_4]^-$$

The pH of a 0.1*M* solution is 5.3. In addition there is a tetraborate, available as borax, usually formulated as $Na_2B_4O_7{\cdot}10H_2O$. In water the tetraborate ion reacts as

$$[B_4O_5(OH)_4]^{2-} + 5H_2O \rightleftharpoons 2[B(OH)_3] + 2[B(OH)_4]^-$$

The strong alkalinity of solutions of all borates is due to the reaction

$$[B(OH)_4]^- \rightleftharpoons [B(OH)_3] + [OH]^-$$

Boric acid is soluble in polyhydroxy compounds such as glycerol. In anhydrous media esterification takes place to form *glyceroborate*. In aqueous media glyceroboric acid forms an acid that is valuable in the analytical determination of boric acid.

Since it is a bridge element, certain properties of boron resemble those of silicon, its diagonal neighbor in Group IV-A. The boron hydrides and boranes resemble the silanes. The borohydride ion, $[BH_4]^-$, is available commercially as the sodium salt, which is a valuable reducing agent.

Boron and its compounds are toxic, both by ingestion and by absorption through broken or inflamed skin. Numerous fatalities have occurred; especially depressing are infants deaths as a result of the use of dusting powders containing boric acid. However, some dietary mineral formulas include boron in some form, such as amino acid chelate, because boron appears to be involved in bone metabolism.

Boric acid and the borates have no germicidal activity and, at best, are feebly bacteriostatic. On the basis of their toxicity and negligible antiseptic value the use of these compounds is unwarranted.

Boric acid in various dosage forms is employed as a topical anti-infective; in solution it is used as an eye wash. Sodium borate is bacteriostatic and is a frequent ingredient of cold creams, eye washes, and mouthwashes. Sodium perborate is an oxidizing type of local anti-infective. Various borate buffers are used in collyria. A common incompatibility in the use of these buffers is the precipitation of insoluble borates from neutral or alkaline buffers. All common metals, except the alkalies, precipitate as insoluble borates.

Boric Acid and Sodium Borate (borax) are cited in the NF.

ALUMINUM

Aluminum is the most abundant of the metals and the third most abundant element, being exceeded in natural occurrence only by oxygen and silicon. The metal and its hydroxide are amphoteric, but only those compounds in which it acts as a base are pharmaceutically important. As a result of its high charge, small diameter, and electron-pair deficiency, the aluminum (III) ion is incapable of independent existence in polar solvents. Due to the very high field strength surrounding this ion, complexation always takes place.

Many insoluble aluminum compounds find use as gastric antacids. Due to their astringency, soluble aluminum salts are used for various skin conditions and in antiperspirants and deodorants. Kaolin is used as an adsorbent and demulcent, and bentonite is useful as a suspending agent. In paste form, elemental aluminum is employed topically as a protective.

There is some concern about chronic aluminum toxicity and its effect on the brain, possibly manifesting itself in the elderly. The use of aluminum sulfate at very low levels in water purification and the presence of aluminum in baking powder is being questioned.

GALLIUM, INDIUM, AND THALLIUM

The remaining elements of Group III-A, gallium, indium, and thallium, are not of interest in pharmacy except for the use of their radioactive isotopes as diagnostic aids, ^{67}Ga, ^{111}In, ^{113}In, and ^{201}Tl.

Thallium compounds are among the most toxic and are absorbed from the intestine and through the skin from ointments and creams. Its action is somewhat similar to that of arsenic. Deaths have been recorded from a thallium cosmetic use. Thallium compounds have been used in insecticides, especially ant poisons. Thallium(I) is similar to potassium ion in that TlOH is a strong base and their salts are isomorphous. Thallium(III) is similar in behavior to aluminum(III) and gold(III).

Gallium is interesting because, except for mercury, it has the lowest melting point of the metals (29.75°). It also is unusual for its +2 oxidation state. Because this requires an odd electron it is difficult to explain because gallium(II) compounds are not paramagnetic. It has been postulated that equal numbers of gallium(I) and gallium(III) ions may exist in these compounds to give a formula $M^+[MX_4]^-$. Gallium(III) has properties very similar to iron(III). In fact, gallium (III) binds to transferrin, an iron transport protein, and appears to be useful in treating cancer-related hypercalcemia.

Indium is quite similar to both aluminum and gallium. It too, under very special conditions, exists as a divalent chloride.

Elements of Group III-B

Some properties of the Group III-B elements are given in Table 24-11. These three elements exhibit only the +3 oxidation state and are quite similar. The differences are mostly of degree, dependent on the increasing atomic radius. As scandium is the smallest, it has the greatest polarizing power and most readily forms complexes of the type K_3ScF_6. Yttrium has properties approximately midway between scandium and lanthanum. This gradation of properties is shown nicely with the three hydroxides: $Sc(OH)_3$ is a weak base, $Y(OH)_3$ is stronger, and $La(OH)_3$ is a very strong base.

ELEMENTS OF GROUP IV

The elements of this group are similar in that each has four valence electrons, two of which are *s* electrons. However, the remaining two valence electrons enter different orbitals to give the structure ns^2np^2 for Group IV-A and $(n-1)d^2ns^2$ for Group IV-B. Because of this there is a strong tendency for all members of the family except carbon and silicon to form *inert pair* ions. Except for the larger atoms, many of the compounds are covalent or predominantly covalent. All elements of the family show the +4 oxidation state. Important characteristics of these elements are found in Tables 24-11 and 24-12.

Elements of Group IV-A

Of the Group IV-A elements (Table 24-12), carbon and silicon usually are considered apart from germanium, tin, and lead because of their nonmetallic character and property of catenation. Boron, with which silicon forms a bridge element pair, is quite similar to silicon. The +2 oxidation state rarely is encountered in carbon and silicon. The bonding in carbon is covalent; corresponding silicon bonds have a somewhat greater electrovalent character. Simple carbon compounds are either linear (CO_2), planar triangular (CO_3^{2-}), or tetrahedral (CCl_4). Because the radius of the carbon atom is small, and it lacks *d* orbitals to expand its valence shell, carbon never increases its coordination number beyond four. Unlike carbon, because of its available *d* orbitals, silicon can achieve sp^3d^2 hybridization and appears in the octahedral configuration, SiF_6^{2-}, with a maximum coordination number of six. Similarly, germanium, tin, and lead have a maximum coordination number of six.

Carbon is exclusively nonmetallic. Metallic properties appear with silicon and germanium and become predominant in tin and lead. The oxides of carbon and silicon are acidic, whereas those of the other elements of the group are amphoteric. The characteristics such as electron configuration, atomic size, and electronegativity of the carbon atom combine to give the chemistry of carbon a uniqueness that is the basis for the classical division of the field of chemistry into inorganic and organic disciplines.

Silicon also is unique for the extensive range of complex, insoluble alumino-silicates it forms.

CARBON

Carbon appears widely distributed in nature, both in the free and combined states. The free element is produced in various forms, such as coke, lampblack, or charcoal. Activated charcoals are prepared from ligneous materials (sometimes pretreated with a dehydrating agent) by carbonization in the absence of air. This is followed by heat and/or chemical treatment to increase surface area and porosity. Activated charcoal is available in two forms: finely powdered (300 to 350 mesh) for use in liquid media; and coarse, hard, porous particles for gas absorption. The fine form is official in the USP, and is used as an adsorbent in the treatment of diarrhea.

Carbon dioxide usually is obtained as a byproduct from either the production of alcohol by fermentation or by recovery from the stack gases of power plants. Unlike carbon monoxide, its toxicity is not due to interaction with hemoglobin, but through suffocation. Carbon dioxide is an effective respiratory stimulant, cited in the USP.

Under appropriate conditions, carbon forms many binary compounds, such as cyanogen, carbon disulfide, carbon tetrachloride, and numerous carbides. Its important inorganic acids are carbonic, percarbonic (peroxocarbonic) and the pseudobinary hydrocyanic acid (HCN). All are weak acids and are available primarily in the form of salts.

Sodium bicarbonate and the slightly soluble carbonates or basic carbonates of calcium, magnesium, and aluminum find extensive use as gastric antacids. Potassium bicarbonate is used as a source of potassium ion in electrolyte replenishers. Bismuth subcarbonate is an astringent and protective. Ammonium carbonate is an effective reflex stimulant and expectorant.

Table 24-12. The Elements of Group IV-A

ELEMENT	CARBON	SILICON	GERMANIUM	TIN	LEAD
Symbol	C	Si	Ge	Sn	Pb
Atomic number	6	14	32	50	82
Atomic weight	12.01	28.08	72.5_9	118.6_9	207.2
Orbital electrons	$[He]2s^22p^2$	$[Ne]3s^23p^2$	$[Ar]3d^{10}4s^24p^2$	$[Kr]4d^{10}5s^25p^2$	$[Xe]4f^{14}5d^{10}6s^26p^2$
Oxidation states	4− to 4+	4− to 4+	2+, 4+	2+, 4+	2+, 4+
Atomic radius (Å)	0.77	1.17	1.22	1.41	1.54
Ionic (crystal) radii	2.60 (4−)	2.71 (4−)	0.87 (2+)	0.93 (2+)	1.20 (2+)
(coordination number 6)	0.30 (4+)[a]	0.54 (4+)	0.67 (4+)	0.83 (4+)	0.91 (4+)
Ionization potential, ev	11.264	8.149	8.09	7.30	7.38
Electronegativity	2.55	1.90	2.01	1.58	1.87
% of earth's crust	2.7×10^{-2}	27.7	7×10^{4}	6×10^{-4}	1×10^{-3}

[a] Coordination number 4.

SILICON

Next to oxygen, silicon is the most abundant element on earth. It does not appear free in nature. Silicon forms an inert oxide, silicon dioxide (silica), which occurs abundantly in nature in both amorphous and crystalline states such as sand, quartz, opal, or siliceous earths.

Siliceous earth (diatomaceous earth, Fuller's earth, Kieselguhr, Celite) and *infusorial earth* are the siliceous skeletal remains of diatoms and infusoria. The deposits are in the form of spicules, rods, and stars of silica. Because of their shapes, these materials act as excellent, inert, nonadsorbent filter aids. Because of their moderate hardness they are used as mild abrasives. Purified Siliceous Earth is official in the NF.

Synthetic amorphous silicas are manufactured by two methods. *Silica fume* is prepared by condensation of silica from its vapor phase. *Silica gel* is prepared by hydrolysis of inorganic or organic orthosilicates. Structurally, both forms may be considered condensation polymers of the silicic acids. They are available in various commercial grades, differing in such variables as particle size, degree of hydration, surface type (silanol and/or siloxane), porosity, and hardness. By selection of the product having the desired properties, amorphous silicas find employment as gas adsorbents, desiccants, carriers, fillers, thickeners, and abrasives. Colloidal Silicon Dioxide (fumed form) is official in the NF; Silicon Dioxide, a more general monograph title, replaces the title Silica Gel and now provides for both forms of SiO_2, silica gel and precipitated silica.

Silicosis, a lung condition resembling chronic tuberculosis, develops after long exposure (7 years or more) to *respirable dust* (silica particles 5 μm or less in mean diameter).

Silicon forms numerous silicic acids, such as metasilicic acid [H_2SiO_3], orthosilicic acid [H_4SiO_4], or disilicic acid [$H_6Si_2O_7$]. These and others occur in nature as silicates. Except for the alkali salts, silicates are insoluble in water or acids, but they are attacked readily by hydrofluoric acid, forming gaseous silicon tetrafluoride. The alkali silicates do not occur in nature, but rather are prepared by fusion of finely divided silica with the desired alkali base or carbonate.

The *insoluble* silicates have structural arrangements dominated by the large diffuse oxide ion. Because cations of high charge, such as Si^{4+} or Al^{3+}, are small and compact, they have only a secondary role in determining the structures. Physical properties such as density, hardness, and refractive index are determined almost completely by the *oxygen-packing* arrangement.

There are two *close-packed* oxide ion arrangements, cubic and hexagonal. In each, the oxygen arranges in identical layers; the difference arises from the placement of the layers with respect to one another. Two types of openings are possible between neighboring spheres. The smaller openings are occupied by small cations, such as Si^{4+}, resulting in a tetrahedral arrangement of four oxide ions around each cation. The larger openings between adjacent oxide ions are occupied by somewhat larger cations, such as Li^+, Mg^{2+}, or Fe^{3+}. Six oxide ions surround each cation in an octahedral arrangement. The aluminum ion, which is intermediate in size, can occupy either tetrahedral or octahedral spaces.

When cations too large to occupy either of the inter-oxide ion spaces, such as NH_4^+, Na^+, K^+, Ca^{2+}, are present, the oxide structure opens in one of two ways. Groups of the oxide ion layers separate to give an overall layered structure with the large cations forming a new layer between. The clays have this structure. Or the oxide ions may spread in a three-dimensional manner to give room-like cavities within the structure. The cavities are occupied by the large cations. Feldspars and zeolites have this latter structure.

A persistent problem preventing early workers from successfully elucidating silicate structures was their failure to recognize that ions of the ideal structure may be substituted to some extent by other ions of the same radius, irrespective of charge. This phenomenon, *isomorphous replacement,* is widespread among the silicates. Because of this, empirical formulas based on analytical data are meaningless. The illustrative formulas used in the following discussions are *ideal* formulas. Because of isomorphous replacement, the actual formula of a given silicate may differ somewhat from the ideal.

Before discussing specific insoluble silicates it must be said that all are chemically inert. The properties that distinguish them and determine their use are structural or related to surface phenomena.

Chain silicates are unidimensional arrangements of silicate tetrahedra sharing two oxygens per tetrahedron; in effect each chain is a macroanion. Because these chains consist of Si—O bonds having 50% covalent character, they are difficult to break. Electrical neutrality is maintained by placing a sufficient number of cations, usually K^+ and/or Ca^{2+}, between the chains. Electrostatic forces being weaker than covalent forces, these crystals cleave readily to give rise to the typical fibrous structure of asbestos, such as serpentine asbestos, $(HO)_6Mg_6(Si_4O_{11})\cdot H_2O$. These asbestos chains are useful as filter aids and as insulation. *Note:* Asbestosis is a pulmonary condition similar to silicosis.

Attapulgite, $Mg_5(Si_8O_{20})(OH)_2\cdot 8H_2O$, is a double-chain structure with rather large open spaces between the chains. These spaces are occupied by water molecules, which provide hydrogen bonding to hold the chains together. It has adsorptive properties similar to kaolin.

The layer silicates include talc (talcum, soapstone), the micas, the chlorites (no relationship to ClO_2^-) and the three clay minerals, the montmorillonites (bentonites), kaolins, (kaolinite) and the illites.

Talc, $Mg_3(OH)_2Si_4O_{10}$, is the softest mineral known. There are no cementing cations or molecules between silicate layers; they are held together by van der Waals forces. Consequently, the talc layers cleave easily to give the characteristic smooth, unctuous feel. Talc adheres readily to the skin, is chemically inert, and has very low adsorptive powers. It is used in dusting powders as a protective and lubricant, to prevent irritation due to friction. It also is used in medicated dusts and used widely in cosmetic applications. There are no problems in its use on intact skin, but talc must not be used on broken skin, wounds, or surgical incisions. This precludes its former use as a dusting powder and lubricant for surgical gloves.

Because of its inertness and nonadsorptive character, talc is a useful filter aid. Only particles which are passed by a No 80 sieve, but retained by a No 100 sieve, should be used. Finer particles suspend and are not removed easily by subsequent filtration. Talc is official in the USP.

In mica, $Al_2[(OH)_2(Si_3O_{10})]K$, and chlorite, $Mg_3[(OH)_2(Si_4O_{10})]$, negatively charged silicate layers are bound together by cations. Thus, these silicates cleave readily along the cation layer because the electrostatic forces are weaker than the covalent bonds within the silicate layer. Neither has pharmaceutical applications.

The clays—montmorillonite (Smectite), $Al_4[(OH)_4(Si_8O_{20})]\cdot 3_nH_2O$ and kaolinite, $[(OH)_6Al_4][(OH)_2(Si_4O_{10})]$—are layer structures built of alternating layers of aluminum oxide (hydrargillite) and silicate. The montmorillonites have higher SiO_2:Al_2O_3 ratios with much isomorphous replacement of aluminum. Magnesium never is present in the kaolins.

The distinguishing feature of the bentonite (montmorillonite) clays is the insertion of up to three distinct layers of hydrogen-bridged water molecules between the aluminosilicate layers. Not all water hydrogens are needed to bond the water molecules within their layer; the unused hydrogens bind the layers to each other and to the aluminosilicate layers. These water layers may be removed, one at a time, by heat. The thickness of the individual crystals decreases in steps as each water layer is removed. By treating with water, the water layers are restored, one at a time, with a return to the original thickness. This may be repeated indefinitely. Because of this phenomenon, bentonite clays are known as *swelling clays.*

The bentonites have gelling properties that make them useful suspending agents, as well as ion-exchange properties and detergent properties. Bentonite and Bentonite Magma are official in the NF, as is Purified Bentonite, a colloidal montmorillonite.

Kaolins are found always in the form of microcrystals of colloidal dimensions. The properties are somewhat similar to bentonite. They are used as clarifying agents and are good excipients for inorganic salts. They find employment as intestinal adsorbents and protectives. Externally they are used as dusting powders. Kaolin is official in the USP.

The *three-dimensional* or *lattice silicates* have been described previously. In the feldspars, $KAlSi_3O_8$, the most common rock, the large cations (eg, K^+) are trapped in enlarged cavities within the aluminosilicate network. On the other hand, in the zeolites, $CaAl_2Si_4O_{12}{\cdot}6H_2O$, and in the synthetic *molecular sieves,* these cavities have connecting openings, or hallways, between one another and to the exterior of the crystal. Thus the cations (and water molecules) in these cavities are free to move about within the crystal and may be exchanged with external cations. These latter silicates are valuable as ion exchangers, desiccants, carriers for catalysts and for the separation of organic gases, as with ethylene from ethane. Certain forms of molecular sieves have been tried as antacids.

Pumice is a porous rock of volcanic origin, usually found in the vitreous state. Being a three dimensionally linked sodium aluminosilicate it is a hard, chemically inert, nonadsorptive material. In the powdered form it is used as a filter medium and dispersing agent. It is found in dental preparations as an abrasive.

Magnesium trisilicate is prepared by precipitation, using a soluble silicate and a soluble magnesium salt. Although it has an analytical composition approaching disilicate, it is actually a mixture of magnesium hydroxide, hydrated magnesium oxide, and silica gel. The insoluble magnesium compounds are responsible for the antacid action; the silica gel acts as a protective. Magnesium trisilicate also is employed as a suspending agent.

GLASS—*Glass* is a generic term used to identify vitreous silicate materials prepared by fusing a base, such as Na_2CO_3 and $CaCO_3$, with pure silica. On cooling, a clear vitreous mass results. There is no clearly defined melting point; a gradual softening takes place on heating as a result of the somewhat haphazard arrangement of the silicon–oxygen bonds.

Certain other cations may be included, such as manganese dioxide, to hide the blue-green color of the iron usually present in silica; borates, to reduce the coefficient of expansion; and potassium ion to give a brown and light-resistant glass.

Since the surface of the glass is an exposed oxide network, it can be reactive. On standing in contact with aqueous solutions, alkali will leach from it. This leaching is accelerated by heat, as occurs with sterilization. The surface of glass also has adsorbing powers, but this can be a problem only in extremely dilute solutions. The compendia usually specify the type of glass container to be used for certain materials and include tests for four types of glass.

SILANES AND SILOXANES—The close relationship between carbon and silicon has prompted much interest in the *organic chemistry of silicon*. The compounds involved are analogs of carbon compounds or compounds in which silicon functions in place of one or more of the carbon atoms. Simple silanes and their derivatives, such as silane [SiH_4], silanol [SiH_3OH], and disiloxane [$H_3SiOSiH_3$], have been known for a long time. The present interest is in complex compounds that contain both carbon and silicon. The silicones (alkylsiloxanes), condensation polymers of various types of alkylsilanols, represent a field finding extensive commercial application. Simethicone USP, a polymeric dimethylsiloxane, is employed as an antifoaming agent. It has found use as an antiflatulent in gastric bloating and in postoperative gaseous distention in the gastrointestinal tract.

GERMANIUM

The properties of the element germanium are intermediate to those of silicon and tin. Germanium, found in bis-β-carboxyethyl germanium sesquioxide, is purported to have immune system enhancing and antitumor effects. Germanium also has remarkable electrical properties, which make it valuable in the manufacture of semiconductors and other microelectronic parts.

TIN

Tin forms compounds in both +2 and +4 oxidation states. The lower oxidation state is somewhat electrostatic but the higher state is largely covalent in character. Both oxides are amphoteric, giving rise to stannate(II) (stannite) $[SnO_2]^{2-}$, and stannate(IV) (stannate) $[SnO_3]^{2-}$ions.

The only official compound is stannous fluoride tin(II) fluoride, applied topically as a dental prophylactic. Experimental evidence demonstrates the superiority of this fluoride over other soluble fluorides for this application. The ready susceptibility of tin(II) fluoride to oxidative and hydrolytic decomposition causes problems in the preparation and storage of suitable dosage forms. Various tin dioxide [tin(IV) oxide] preparations have been used externally for their germicidal effect, particularly against staphylococcal organisms that are often resistant to other germicides.

LEAD

Lead is the most metallic element of the group. However, some residual amphoteric character is present, particularly in the +4 oxidation state. At one time, lead compounds found employment in pharmacy and medicine, usually as astringents. However, because of its highly toxic nature as a *cumulative poison*, it is no longer used. It is absorbed readily in the intestinal tract and broken skin, and is deposited in the bone.

Elements of Group IV-B

Because of their minor importance, a detailed treatment of Group IV-B elements is unnecessary. Some important characteristics are given in Table 24-11. All members of the group occur in nature only in the combined state. The +2 and +4 oxidation states are common to all. All members of the group possess amphoteric properties and their cations readily form complexes.

TITANIUM

Titanium forms three oxides (TiO, Ti_2O_3, and TiO_2) and corresponding binary salts. The soluble salts of divalent and trivalent titanium are violet or red and are powerful reducing agents.

The most important compound is the dioxide, TiO_2, which is official in the USP. It is used as a solar-ray protective. As such, it is a popular ingredient in various lotions and creams for the prevention of sunburn. This action is the result of its high covering power as a white pigment, a consequence of its high refractive index.

ZIRCONIUM AND HAFNIUM

Hafnium occurs in small quantities in zirconium ores. As a consequence, unless highly purified, zirconium compounds include varying percentages of hafnium. Zirconium as the hydrous oxide or carbonate has been used as a lotion or cream for contact dermatitis. There are a number of basic aluminum–zirconium compounds used as antiperspirants. However, the prohibition against the use of zirconium in aerosols where inhalation is possible is still in effect.

Table 24-13. The Elements of Group V-A

ELEMENT	NITROGEN	PHOSPHOROUS	ARSENIC	ANTIMONY	BISMUTH
Symbol	N	P	As	Sb	Bi
Atomic number	7	15	33	51	83
Atomic weight	14.01	30.97	74.92	121.7_5	208.98
Orbital electrons	$[He]2s^2 2p^3$	$[Ne]3s^2 3p^3$	$[Ar]3d^{10} 4s^2 4p^3$	$[Kr]4d^{10} 5s^2 5p^3$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^3$
Oxidation states	3−, 1+, 3+, 5+	3−, 3+, 5+	3−, 3+, 5+	3−, 3+, 5+	3−, 3+, 5+
Atomic radius (Å)	0.70	1.06	1.21	1.41	1.5
Ionic (crystal) radii (Å)	1.32 (3+)	0.58 (3+)	0.72 (3+)	0.90 (3+)	1.17 (3+)
(coordination number 6)	0.27 (5+)	0.52 (5+)	0.60 (5+)	0.74 (5+)	0.90 (5+)
Ionization potential, ev	14.48	11.10	10.5	8.5	8.0
Electronegativity	3.04	2.19	2.18	2.05	2.02
% of earth's crust	4.6×10^{-8}	0.12	5×10^{-4}	10^{-4}	2×10^{-5}

ELEMENTS OF GROUP V

The elements of this group have five valence electrons. Two of the electrons occupy *s* orbitals. The three remaining electrons are in different orbitals in the A and B subgroups, giving the structures ns^2np^3 and $(n-1)d^3ns^2$, respectively.

Elements of Group V-A

This group displays strikingly regular gradations in properties, ranging from exclusively nonmetallic nitrogen to almost exclusively metallic bismuth (Table 24-13). Oxidation states of +3 and +5 are common to all. Bismuth functions primarily in the +3 state. All members except bismuth also exist in a −3 oxidation state. Hydrides are of the covalent MH_3 type, characterized by an unshared electron pair. This allows these hydrides to form coordinate covalent bonds. The oxides of nitrogen and phosphorus are acidic. Those of arsenic and antimony are amphoteric, but are sufficiently acidic for the elements to be classified as nonmetals. The common oxide of bismuth, Bi_2O_3, is basic; the less-important pentoxide is acidic.

NITROGEN

Nitrogen occurs free in the atmosphere (78%) and combined in nitrates and organic compounds. It is a colorless, tasteless, and odorless inert gas. It is nonflammable and does not support combustion. Due to its stable triple-bond structure, the N_2 molecule shows little reactivity with other elements. The free nitrogen atom is very reactive.

The inertness of nitrogen is the result of the bonding existing in the molecule. There is a σ bond between the atoms and two π bonds, which fuse to form an electron cloud (doughnut) encasing the entire molecule. This electron cloud effectively prevents breaking of the σ bond for reaction with other elements. The cyanide ion and carbon monoxide have electron structures similar to that of the nitrogen molecule and also show an extraordinary stability.

Nitrogen is prepared primarily by the fractional distillation of liquid air. At the temperature of the electric arc it combines with oxygen forming nitrogen(V) oxide, which is converted into nitric acid. In the presence of catalysts and at great pressure and elevated temperature, it combines with hydrogen to form ammonia.

Unlike phosphorus and the other members of the family, nitrogen does not expand its coordination sphere beyond three. The nitric acid of chemistry is the meta acid. There is no ortho acid (hypothetically H_3NO_4). Nitrogen in the +5 state is too small to accommodate four oxygen atoms.

Therapeutically inactive, elemental Nitrogen NF is employed pharmaceutically as an inert atmosphere in ampules and other containers of substances that would be affected adversely by air. Nitrogen(I) Oxide (nitrous oxide) USP, is an inhalatory general anesthetic. Sodium Nitrite USP is used as an antidote to cyanide poisoning; it also is a vasodilator but is slower acting than the organic nitrite and nitrate esters commonly used for this purpose. The nitrate ion frequently is used as an anion for medicinally active cations, such as silver nitrate and thiamine mononitrate.

Very significant work has shown that the simple, paramagnetic molecule, nitric oxide, NO, is an important neurotransmitter produced by neurons and other cells, causing responses such as vasodilation by acting as a ligand for iron in a heme group with a resulting lowering of blood pressure. This knowledge rationalizes the action of drugs such as the organic nitrites and sodium nitroprusside.

Nitrite ion is toxic; it reacts with hemoglobin to form methemoglobin. Nitrites are also potentially dangerous because they can form *N*-nitroso derivatives of amines and amides, which may be carcinogenic. Nitrate ion is reducible to nitrite in the intestine and may cause methemoglobinemia. For the above reasons the use of nitrates and nitrites as food preservatives has been questioned.

PHOSPHORUS

Phosphorus exists in two common allotropic forms, yellow and red. Yellow phosphorus (white phosphorus) has a distinctive, disagreeable, ozone-like odor. On exposure to air, or when heated at about 50°, it ignites spontaneously. It is almost insoluble in water, but is soluble in chloroform, benzene, or carbon disulfide. It is poisonous, and on the skin it causes severe, slow to heal burns. Copper(II) sulfate is used as an antidote.

Red phosphorus is a brown to red amorphous powder. It is nonpoisonous and nonflammable in air, except at high temperatures. It is insoluble in any common solvent.

The use of inorganic phosphorus compounds in modern medicine is restricted primarily to the orthophosphates. Tribasic calcium, magnesium, and aluminum phosphates are used as gastric antacids, and the monobasic alkali phosphates are effective urinary acidifiers. Dibasic sodium phosphate is the active ingredient in various saline cathartics and enemas.

Phosphoric Acid NF, is used to form soluble salts of insoluble medicinal bases. The dihydrogen phosphate–monohydrogen phosphate system is a valuable buffer in physiological ranges. Hypophosphorous Acid NF is an antioxidant, used primarily with iodide and iron(II) salts. The radioactive isotope, ^{32}P, is employed therapeutically.

Table 24-14. Transition Elements

	GROUP V-B			GROUP VI-B		
ELEMENT	VANADIUM	NIOBIUM	TANTALUM	CHROMIUM	MOLYBDENUM	TUNGSTEN
Symbol	V	Nb	Ta	Cr	Mo	W
Atomic number	23	41	73	24	42	74
Atomic weight	50.94	92.91	180.95	52.00	95.94	183.8_5
Orbital electrons	$[Ar]3d^34s^2$	$[Kr]4d^45s^1$	$[Xe]4f^{14}5d^36s^2$	$[Ar]3d^54s^1$	$[Kr]4d^55s^1$	$[Xe]4f^{14}5d^46s^2$
Oxidation states	2+, 3+, 4+, 5+	2+, 3+, 4+, 5+	2+, 3+, 4+, 5+	2+, 3+, 4+, 6+	2+ . . . 6+	2+ . . . 6+
Atomic radius (Å)	1.22	1.34	1.34	1.18	1.30	1.30
Ionic (crystal) radii (Å) (coordination number 6)	0.40 (5+)	0.70 (5+)	0.73 (5+)	0.76 (3+) 0.58 (6+)	0.79 (4+) 0.73 (6+)	0.80 (4+) 0.74 (6+)
Ionization potential, ev	6.71	6.79	ca 6	6.77	7.38	7.98
Electronegativity	—	—	1.33	1.66	2.2	2.36
% of earth's crust	0.021	—	—	2×10^{-2}	ca 5×10^{-4}	ca 1.5×10^{-4}

Phosphorus is essential to plant and animal life. A complex basic calcium phosphate, called hydroxyapatite, constitutes the main inorganic component of bones and teeth. Dihydrogen phosphate and monohydrogen phosphate ions constitute the ion pair of one of the buffer systems of the blood and body fluids. The phosphate moiety has important roles in the metabolism of various organic materials, such as carbohydrates.

ARSENIC

Inorganic arsenic compounds rarely are employed in modern medicine. There no longer are official compounds; arsenic trioxide and potassium arsenite were the last; they were used as alteratives, tonics, and antileukemics. In the past, Potassium Arsenite Solution (Fowler's Solution) was used as an antileukemic agent. There is available an arsensic trioxide injection (1 mg/mL) that has been used to treat promyelocytic leukemia. The treatment must be carefully supervised owing to possible serious side effects that include ECG abnormalities. Sodium arsenate, (^{74}As), has been used as a diagnostic aid.

Arsenic compounds are poisonous. If they are still in the gastrointestinal tract, a freshly prepared mixture of iron(III) and magnesium hydroxides is administered orally as an antidote. If the arsenic has already been absorbed, dimercaprol by intramuscular injection is effective.

ANTIMONY

Antimony compounds have physiological reactions resembling those of arsenic. The compounds are potentially toxic. Except for Antimony Potassium Tartrate (antimonyl potassium tartrate, tartar emetic) USP, and for Antimony Sodium Tartrate USP, antimony compounds are no longer in common medical usage. Both antimony potassium and antimony sodium tartrates are used in the treatment of schistosomiasis, a parasitic disease involving flukes.

BISMUTH

With the exception of sodium bismuthate, [$NaBiO_3$] in which the bismuth functions anionically in the +5 oxidation state, the important bismuth compounds of commerce are the Bi^{3+} variety. The basic salts—bismuth subcarbonate, bismuth subgallate, and bismuth subnitrate—are employed for their astringent, mildly germicidal, and antacid properties.

Bismuth Subnitrate, Bismuth Subgallate, and Milk of Bismuth are official in the USP. Milk of Bismuth owes its antacid properties to the hydroxyl and carbonate ions present. Because of the adherent properties, it provides protective action. The small amount of dissolved bismuthyl ion present exerts a mild antiseptic effect. Colloidal bismuth subcitrate is used clinically in the treatment of peptic ulcer disease.

Hydrogen sulfide, from the breakdown of proteins in the gut, reacts with bismuthyl ion to form the insoluble, dark brown, bismuth(III) sulfide. As a result stools appear black. Soluble bismuth compounds are poisonous; intramuscular dimercaprol is an effective antidote.

Elements of Group V-B

Unlike previous transition elements, the valence electron structure of the Group V-B elements is not identical. Vanadium and tantalum have a $(n-1)d^3ns^2$ structure, whereas niobium has the structure $(n-1)d^4ns^1$ (Table 24-14). The difference has no apparent effect on their chemistry. In addition to the Group V oxidation states, +3 and +5, these elements also appear in a +2 and +4 oxidation state. The −3 oxidation state does not occur. There is a close similarity between niobium and tantalum. Tantalum, because of its size, has a maximum coordination number of eight and the compounds of these elements are colored.

The Group V-B elements are of little pharmaceutical importance; only tantalum metal is employed therapeutically. Because tantalum is unaffected by the body fluids, it is used in sheet form for the surgical repair of bones. Muscle tissue will attach itself to tantalum as though it were bone.

ELEMENTS OF GROUP VI

The members of Group VI have six valence electrons. Although theoretically a −2 oxidation state is possible for all, −2 and −1 appear only in the subgroup A elements. The common positive oxidation states are +4 and +6; +1 and +2 also exist.

Elements of Group VI-A

There is a very clear gradation of properties in the Group VI-A family (the chalcogens). Oxygen is nonmetallic in character

Table 24-15. The Elements of Group VI-A

ELEMENT	OXYGEN	SULFUR	SELENIUM	TELLURIUM	POLONIUM
Symbol	O	S	Se	Te	Po
Atomic number	8	16	34	52	84
Atomic weight	16.00	32.06	78.9_6	127.6	(209)
Orbital electrons	$[He]2s^2 2p^4$	$[Ne]3s^2 3p^4$	$[Ar]3d^{10}4s^2 4p^4$	$[Kr]4d^{10}5s^2 5p^4$	$[Xe]4f^{14}5d^{10}6s^2 6p^4$
Oxidation states	2−, 1−	2−, 2+, 6+	2−, 4+, 6+	2−, 4+, 6+	4+, 6+
Atomic radius (Å)	0.66	1.04	1.16	1.37	1.53
Ionic (crystal) radii (Å)					
(simple anion)	1.26 (2−)	1.70 (2−)	1.84 (2−)	2.07 (2−)	1.08 (4+)
(coordination number 6)	—	0.43 (6+)	0.56 (6+)	0.57 (6+)	0.81 (6+)
Ionization potential, ev	13.61	10.36	9.75	9.0	—
Electronegativity	3.44	2.58	2.55	2.1	2.0
% of earth's crust	46.6	0.052	10^{-7}	10^{-7}	10^{-14}

whereas polonium is metallic; the other members show both characteristics. Polonium is further distinguished by its natural radioactivity.

The sulfur–selenium–tellurium triad displays especially strong family relationships. Allotropic varieties of each element in the triad are numerous. Although there are quantitative differences, each functions generally in the −2, +4, and +6 oxidation states, forming many analogous compounds. Some of the more important characteristic properties of Group VI-A elements are presented in Table 24-15.

OXYGEN

In free form, oxygen constitutes about one-fifth of air, by weight. The primeval atmosphere of the earth probably had no oxygen. In combined form, it constitutes about seven-eighths, by weight, of water and important fractional parts of minerals such as $CaCO_3$ or Fe_2O_3. The industrial process for preparing oxygen is the fractional distillation of liquid air. When liquid air is allowed to evaporate under controlled conditions, the nitrogen and inert gases escape initially, followed by nearly pure oxygen.

The weighted atomic mass of the mixture of naturally occurring oxygen isotopes formerly was the standard for all chemical atomic weights. This standard has been replaced by the most abundant carbon isotope, ^{12}C. The isotopes of oxygen have been separated and introduced into specific molecules as tracer elements.

Oxygen USP is employed as a therapeutic gas in the treatment of conditions involving hypoxia. Ozone, O_3, an allotropic form of oxygen, is a powerful oxidizing agent. Ozonized air (air treated to convert some of its oxygen into ozone) is used in various disinfecting and bleaching operations.

Chemically, oxygen is very reactive, combining directly, under appropriate conditions, with all elements except mercury, silver, gold, and members of the platinum family. It is electronegative with respect to all elements except fluorine. The oxides of nonmetallic elements are acidic, while those of metals are basic. The oxides of many elements, such as antimony and tellurium, are amphoteric. In all, oxygen has the −2 oxidation number.

Hydrogen peroxide and the peroxides are a series of oxygen compounds in which oxygen has an oxidation number of −1. They are valuable oxidizing and reducing agents.

Hydrogen peroxide is prepared by the electrolysis of a concentrated solution of either sulfuric acid or ammonium sulfate. Persulfate, $[S_2O_8^{2-}]$, forms in the anode compartment. After electrolysis the analyte is reacted with water and the hydrogen peroxide formed is separated by distillation under reduced pressure.

Pure concentrated hydrogen peroxide is stable. However, commercial preparations must be stabilized; usually, a preservative is added such as acetanilid. Traces of mineral acid (eg, phosphoric acid) often are added, as the stability increases in acid medium.

Hydrogen peroxide is available as the 3, 6, 30, 70, and 90% solutions. Concentration also is expressed as volume strength, the volume of oxygen gas released from one volume of solution; ten volume is 3%. Hydrogen Peroxide Concentrate USP is the 30% solution. It is a powerful oxidant and must not be used on the skin. Hydrogen Peroxide Topical Solution USP is the 3% solution. It is a mild, fast acting, oxidizing germicide that will destroy most pathogenic bacteria. Hydrogen peroxide, 6%, is the only common bleach mild enough for use on hair.

Hydrogen peroxide is available as a solution in anhydrous glycerine (1.5%) and as urea peroxide, a stable crystalline 1:1 compound, usually in 4 to 10% solution in anhydrous glycerine. A monograph for Carbamide Peroxide is found in the USP, and the monograph for Carbamide Peroxide Topical Solution USP has a generic purity rubric statement. These preparations are preferable to hydrogen peroxide in treatment of oral and ear infections. Zinc peroxide and sodium perborate, a compound that has a hydrogen peroxide molecule in its hydration complement, have been listed in past compendia.

SULFUR

Sulfur is an element that exists in several allotropic forms. At room temperature α-sulfur (rhombic sulfur) is the stable form. At the equilibrium point, 96°, β-sulfur (monoclinic sulfur) becomes the stable form. Other allotropes exist. Commercial, Sublimed Sulfur USP and Precipitated Sulfur USP are α-sulfur. Precipitated sulfur has a smaller particle size than sublimed; therefore, it is more reactive.

As an ointment, precipitated sulfur is used as the scabicide. Sulfur ointments and lotions are used in dermatological applications as keratolytics. Elemental sulfur also has fungicidal action. Sublimed sulfur is used as a cathartic.

Sulfur appears in three series of compounds. The first, based on the −2 oxidation state, gives rise to hydrogen sulfide and the sulfides. The second and third series, based on +4 and +6 oxidation states, give rise to the two sulfur oxides and their acids and salts.

Hydrogen sulfide and soluble sulfides in solution react readily with suspended, finely divided sulfur to give rise to mixtures of polysulfides, S_2^{2-}, S_3^{2-}, S_4^{2-}, S_5^{2-}, usually written S_n^{2-}.

Sulfurated Potash consists largely of potassium polysulfides, sulfate, and thiosulfate. It is prepared by careful heating of a mixture of potassium carbonate and sublimed sulfur. The compound is very soluble in water, giving an alkaline reaction. The polysulfide component is soluble in ethanol. Sulfurated potash is used in the form of lotions, ointments, and aqueous solutions for the treatment of psoriasis and other chronic skin conditions and has parasiticidal activity.

Sulfurated potash must be stored in tightly sealed containers to prevent reaction with carbon dioxide and oxygen. It is incompatible with acid.

White Lotion USP is prepared by adding freshly prepared, filtered, sulfurated potash solution to zinc sulfate solution.

Table 24-16. The Elements of Group VII-A

ELEMENT	FLUORINE	CHLORINE	BROMINE	IODINE	ASTATINE
Symbol	F	Cl	Br	I	At
Atomic number	9	17	35	53	85
Atomic weight	19	35.45	79.90	126.90	(210)
Orbital electrons	$[He]2s^2 2p^5$	$[Ne]3s^2 3p^5$	$[Ar]3d^{10} 4s^2 4p^5$	$[Kr]4d^{10} 5s^2 5p^5$	$[Xe]4f^{14} 5d^{10} 6s^2 6p^5$
Oxidation states	1−	1−, 1+, 3+, 5+, 7+	1−, 1+, (3+), 5+	1−, 1+, (3+), 5+, 7+	—
Atomic radius (Å)	0.64	0.99	1.14	1.33	—
Ionic (crystal) radii (Å)					
(halide anion)	1.19	1.67	1.82	2.06	—
(coordination number 6)	0.022 (7+)	0.41 (7+)	0.53 (7+)	0.67 (7+)	0.76 (7+)
Ionization potential, ev	17.42	13.01	11.84	10.44	—
Electronegativity	3.98	3.16	2.96	2.66	2.2
% of earth's crust	8×10^{-2}	3×10^{-2}	1.6×10^{-4}	3×10^{-5}	—

The order of mixing is important. It is an astringent and protective.

Selenium Sulfide (and Lotion) USP is employed as a 2.5% suspension in the topical treatment of seborrheic dermatitis (dandruff). Care is essential to prevent introduction into the eyes or mouth. In addition, the hands must be cleansed thoroughly after using because selenium is toxic. Cadmium sulfide also is used in the treatment of seborrheic dermatitis. Although it is less irritating, it requires the same precautions as selenium sulfide.

Sulfur Dioxide NF usually is prepared industrially by burning sulfur. It is the acid anhydride of sulfurous acid and its salts, the sulfites. All are used in pharmaceutical practice as antioxidants and preservatives.

Attempts to crystallize sodium bisulfite yield, instead, normal sodium sulfite crystals. If the crystallization is carried out under a sulfur dioxide atmosphere crystals of the metabisulfite, $Na_2S_2O_5$, form. On dissolving metabisulfite in water, a solution of bisulfite results

$$S_2O_5^{2-} + H_2O \rightarrow 2HSO_3^-$$

Sodium Metabisulfite NF should be used when sodium bisulfite is specified. It is used as an antioxidant. A monograph for Potassium Metabisulfite is included in the NF.

Sodium Thiosulfate USP is prepared from the sulfite by reaction with sulfur. Because the sulfite ion has an unshared electron pair, and elemental sulfur lacks one electron pair for completion of a stable octet, a coordinate covalent bond forms easily, giving the thiosulfate ion. It is used as an antidote for cyanide poisoning. It is a valuable analytical reagent for the determination of iodine.

In the +6 oxidation state sulfur gives rise to sulfuric acid and the sulfates. Sulfuric acid is an important acid and is listed in the NF. Several sulfates are cited officially but with the exception of sodium sulfate (saline cathartic), all applications are ascribed more appropriately to the cation present, such as barium sulfate or bleomycin sulfate.

SELENIUM AND TELLURIUM

In general, selenium and tellurium compounds are analogous to those of sulfur. Observed differences are largely those to be expected in terms of relative atomic size and electronegativity.

Although selenium is toxic in large doses, it is an important trace element. It is absorbed very slowly through the skin. Toxicity usually is not a problem if it is applied to small areas of unbroken, unirritated skin. Prolonged contact with the skin results in contact dermatitis. The use of selenium sulfide, the only official compound, is described in the section on sulfides. Selenomethionine Se 75 Injection USP is used in the diagnosis of pancreatic tumors and growths.

Tellurium has no medicinal applications at this time.

Elements of Group VI-B

The Group VI-B elements are metallic in behavior. The lower oxidation state oxides are basic, whereas those of the higher oxidation states are acidic, giving rise to the chromates, molybdates, and tungstates. The cations of high oxidation numbers have a tendency to unite with oxygen to give stable *-yl* cations, such as CrO^{2+} chromyl. These elements show great similarity in behavior to their horizontal neighbors in Groups V-B and VII-B. Some properties are given in Table 24-14.

Chromium and molybdenum are essential trace elements. Monographs for Chromic Chloride (and Injection) and Ammonium Molybdate (and Injection) are found in the USP and Chromium Picolinate is listed in the NF. Chromium has a wide margin of safety between amounts usually ingested and those showing adverse effects. The radioactive isotope, ^{51}Cr, is employed as a biological tracer in certain hematological procedures. Their compounds are important in analytical pharmaceutical operations.

ELEMENTS OF GROUP VII

The elements of Group VII subdivide into Group VII-A (Table 24-16), members of which have an outer electron configuration ns^2np^5, and Group VII-B (Table 24-17) with the $(n-1)d^5ns^2$ valence electron configuration.

The halogens are nonmetallic in character; the transition elements of the family are metallic. Except for the higher oxidation states of +5 and especially +7, the elements of the subgroups and their compounds are quite dissimilar. The free halogens are colored, but almost all of their compounds are not.

Elements of Group VII-A

Examination of the valence electron structure of Group VII-A elements suggests −1, +1, +3, +5, and +7 as possible oxidation states. Fluorine, the most electronegative element, appears only as the simple fluoride ion (which readily acts as a ligand). Only chlorine forms compounds in all five oxidation states.

The halogen binary compounds may be ionic and/or covalent, depending on electronegativity differences. All halogens unite

Table 24-17. Transition Elements

	GROUP VII-B			GROUP VIII—FIRST TRIAD		
ELEMENT	MANGANESE	TECHNETIUM	RHENIUM	IRON	COBALT	NICKEL
Symbol	Mn	Tc	Re	Fe	Co	Ni
Atomic number	25	43	75	26	27	28
Atomic weight	54.94	(98)	186.2	55.85	58.93	58.71
Orbital electrons	$[Ar]3d^5 4s^2$	$[Kr]4d^5 5s^2$	$[Xe]4f^{14} 5d^5 6s^2$	$[Ar]3d^6 4s^2$	$[Ar]3d^7 4s^2$	$[Ar]3d^8 4s^2$
Oxidation states	2+, 3+, 4+, 6+, 7+	2+, 3+, 4+, 6+, 7+	3+, 4+, 5+, 6+, 7+	2+, 3+	2+, 3+	2+, 3+
Atomic radius (Å)	1.17	1.27	1.25	1.17	1.16	1.15
Ionic (crystal) radii (Å)	0.81 (2+)	—	0.81 (3+)	0.75 (2+)	0.79 (2+)	0.83 (2+)
(coordination number 6)	0.40 (6+)	0.56 (7+)	0.69 (5+)	0.69 (3+)	0.69 (3+)	0.70 (3+)
Ionization potential, ev	7.43	7.23	7.87	7.83	ca 8.5	7.6
Electronegativity	1.55	1.9	1.9	1.85	1.88	1.91
% of earth's crust	0.085	zero (?)	10^{-7}	5	2.3×10^{-3}	8×10^{-3}

with hydrogen to form covalent gaseous hydrogen halides. These gases are extremely soluble in water, giving rise to very strong acids such as hydrochloric acid. The ionic binary compounds show a displacement series: a halogen of lower atomic weight will displace a halide ion of higher atomic weight,

$$2I^- + Cl_2 \rightarrow 2Cl^- + I_2$$

Thus, of the halogens, fluorine is the strongest oxidizing agent and iodine the weakest. Conversely, iodide is the strongest reducing agent, and fluoride the weakest. In fact, the fluoride ion is the most stable of all simple anions.

Chlorine, bromine, and iodine form well-defined oxides, oxyacids, and their salts in most of the positive oxidation states. The stability of the higher oxidation states increases with increasing atomic weight. (For the nomenclature of these acids and salts, see Table 24-1.)

FLUORINE

Fluorine is the most reactive of the electronegative elements. With the exception of gold and platinum it attacks all metals at ordinary temperatures. It combines directly with all nonmetals, including the other halogens. Beryllium fluoride is one of the very few fluorides not ionized completely. Fluorine is an essential element and is present in the teeth and bone.

Sodium Fluoride, Sodium Fluoride Tablets, Sodium Fluoride Oral Solution, Stannous Fluoride (Tin(II) Fluoride), Stannous Fluoride Gel, Sodium Fluoride and Phosphoric Acid Gel, Sodium Fluoride and Phosphoric Acid Topical Solution and Sodium Monofluorophosphate are listed in the USP.

Stannous fluoride is oxidized easily by oxygen of the air to give the tin(IV) ion, which is ineffective as a dental prophylactic. For this reason solutions of this salt must be prepared freshly at the time of use. A developing cloudiness of the solution indicates that the oxidation is proceeding, as the tin(IV) ion formed is precipitated as the insoluble hydroxide.

In addition to its use over several decades as a dental prophylactic, fluoride also has found use, in larger doses, in the treatment of osteoporosis. However, in spite of its officially sanctioned addition to some drinking water, controversy over the advisability and safety of ingesting fluoride at the 1 ppm level for long periods persists.

The use of fluoride to prevent, halt, or reverse osteoporosis is questionable because studies have been reported in which a positive correlation exists between the use of fluoridated water and an elevated risk of hip fracture.

CHLORINE

Elemental chlorine is a very reactive nonmetallic element. Most common chlorides are water soluble, the main exceptions being AgCl, Hg_2Cl_2, and Cu_2Cl_2. A few, eg, $PbCl_2$, are slightly soluble. The oxygenated chlorine compounds are mostly water soluble.

Hydrochloric acid NF is a pharmaceutical necessity for purposes such as neutralizing, stabilizing, or solubilizing other substances. In diluted form, it is a gastric acidifier but other compounds, more readily amenable to administration, usually are preferred. Sodium, potassium, and calcium chlorides are employed in electrolyte replenishers; the first named is the sole ingredient of physiological salt solution. Ammonium chloride is an expectorant and a systemic acidifying agent. The chloride ion is frequently the carrier of choice for other metal cations such as those of zinc, aluminum, and mercury, but with these the medicinal value is referable to the metal rather than the chloride.

Sodium Hypochlorite Solution USP (Dakin's Solution) is an effective germicide, viricide, and deodorant because of the oxidizing power of hypochlorous acid, but is too alkaline and concentrated to be used on wounds. The hypochlorite ion is reduced rapidly by organic matter.

Sodium Hypochlorite Topical Solution contains 0.025% sodium hypochlorite, has a pH of 8 (close to plasma pH of 7.4), and, with the use of a phosphate buffer system, has an osmolality that is very close to that of human plasma. This solution allows tissue to regenerate, as noted by tissue culture studies, as when burns are healing but it is also antiviral and antimicrobial.

Sodium hypochlorite is prepared by electrolysis of sodium chloride solutions under conditions such that the chlorine formed at the anode reacts with the hydroxyl ion resulting from removal of hydrogen ion as hydrogen gas at the cathode

$$Cl_2 + 2OH^- \rightarrow ClO^- + H_2O + Cl^-$$

Sodium chloride is always an impurity in the resulting solution. To improve its stability the pH is adjusted to 10 or greater.

Bleaching powder, calcium hypochlorite, is one of the most effective and least expensive disinfectants. The product is formed by passing chlorine gas over moist, slaked lime. Its composition is variable, but hydroxide, hypochlorite, and chloride ions are present in the mixture.

Potassium chlorate occasionally is present in mouth washes, vaginal douches, and other local cleansing preparations; however, its antiseptic value is too weak to be of any value.

BROMINE

Bromine is a dark reddish brown, fuming liquid with a suffocating odor. The fumes are highly irritating to the mucous membranes and they burn and blister the skin. It attacks most metals and organic tissue. Chemically, bromine resembles chlorine with slight differences referable to the comparative size of the two atoms and their electronegativities.

Bromine is a powerful caustic and germicide but is not employed as such. It is a common chemical reagent.

Utmost care should be exercised in handling bromine. All work with bromine should be done under ideal conditions of

ventilation. If the skin is exposed to bromine, the area should be washed immediately with a solution of sodium bicarbonate and treated with glycerine. *Caution:* Bromine containers should be opened only after they have been cooled thoroughly.

Bromine has no known biological role. In proper dosage the bromide ion provides central depressant action. Sodium, potassium, and ammonium bromides are employed commonly. Excessive continued dosage may elicit a toxic condition, brominism.

IODINE

Except for astatine, iodine is the most metallic of the halogens. Its oxo-salts are very stable while the simple anion is oxidized slowly by the oxygen of the air. When reacting with the other halogens it assumes the cationic role, such as ICl_3. Many workers consider IOH the hydroxide of iodine. Iodine is an effective antimicrobial.

Iodine solutions include potassium or sodium iodide to enhance the solubility of the iodine by the formation of polyiodide ions. Loss of the element to air is reduced greatly because polyiodide solutions have a lower iodine vapor pressure. Iodine, Potassium Iodide, Sodium Iodide, and various iodine solutions are cited in the USP, as is Povidone-Iodine and its dosage forms. Povidone is a synthetic polymer that has a special affinity for iodine molecules. The advantages of povidone-iodine are reduced volatility of the iodine and a decreased irritation on application. Iodine also is available in the form of cationic and nonionic surface active salts, used as sanitizing agents.

Iodine is essential for proper thyroid functioning and is utilized physiologically either in the elemental form or as potassium or sodium iodide. In proper dosage, iodide ion exerts expectorant action; examples are hydrogen iodide (as hydriodic acid syrup) and potassium iodide. Potassium iodide (in solution) is used to protect the thyroid when the possibility of accidental exposure to ^{131}I is anticipated as, for example, in a nuclear power plant failure. The radioactive isotopes, ^{125}I and ^{131}I, have diagnostic and therapeutic applications.

Elemental iodine is toxic; corn starch and sodium thiosulfate are effective chemical antidotes.

ASTATINE

Astatine is a synthetic radioactive element. It resembles iodine but is more metallic. It has no pharmaceutical applications.

PSEUDOHALOGENS (HALOGENOIDS)

Inorganic anions such as CN^-, CNO^-, CNS^-, N_3^-, and $[Fe(CN)_6]^{3-}$ resemble the halide anions and are known as *pseudohalogens.* The similarity of the cyanide ion especially is marked; it has properties intermediate to those of the chloride and bromide ions. Similarities include insoluble silver salts soluble in ammonia, preparation of HX by adding concentrated sulfuric acid to the sodium salt, preparation of X_2 by adding MnO_2 and concentrated sulfuric acid to the sodium salt, the formation of polyions, etc.

The most striking difference is the very weak acidic character of the pseudohalogen hydrides; for example, the pK_a of HCN is 8.9, whereas that of HCl is about -10.

The pseudohalogens have no pharmaceutical applications.

Elements of Group VII-B

The elements of Group VII-B are metallic in character. The higher oxides give rise to very stable oxo-salts with the +6 and +7 oxidation states, such as manganate (MnO_4^{2-}) and pertechnetate (TeO_4^-). A summary of important properties appears in Table 24-17. Compounds of these elements are colored.

MANGANESE

Pharmaceutically, manganese is the most important element in this group. Potassium Permanganate USP is categorized as a local anti-infective of the oxidizing type and is also an astringent and a powerful deodorant and cleanser. It is used in the form of dilute (0.01 to 1.00%) solutions. As the compound reacts, manganese(IV) oxide precipitates on the skin causing a temporary darkening of the surface. Gastric lavage using dilute permanganate solutions is antidotal for various alkaloids and other toxic substances that have been ingested in small amounts and are readily susceptible to oxidation.

Caution must be exercised to keep permanganate from contact with organic and other easily oxidized compounds either in the dry state or in solution. Dangerous explosions may occur.

Manganese is an essential trace element, being necessary for the activation of a variety of enzymes such as pyruvate carboxylase. Manganese Chloride, Manganese Gluconate, and Manganese Sulfate are listed in the USP. It is included in mineral supplements, but there are no well-defined deficiency states in humans.

TECHNETIUM

Technetium (from Greek *technetos,* meaning "artificial") was so named because it was the first element produced artificially. Radioactive technetium, ^{99}Tc, is used diagnostically in various forms.

RHENIUM

Rhenium is a very rare element and finds few technical applications. Alone and in combination with other metals, it has been employed as a catalyst for dehydrogenation.

ELEMENTS OF GROUP VIII

Group VIII of elements represents those in which the single electron already present in each of the five *d* orbitals is being paired with a second electron of opposite spin. The group consists of three elements (triads) in each of the long rows and fills the space between the elements of Groups VII-B and I-B.

The first triad follows manganese and includes iron, cobalt, and nickel (see Table 24-17), known as the *ferrous metals.* They are characterized by their strong ferromagnetism. The second triad follows technetium and includes ruthenium, rhodium, and palladium. The third triad follows rhenium and includes osmium, iridium, and platinum. The elements of these latter two triads are known as the *platinum metals;* the term *noble metals* also is used. The platinum metals are characterized by their extreme inertness to chemical reaction.

These elements are definitely metallic and all participate readily in the formation of coordination complexes. The compounds of the first row triad are stable under most conditions whereas those of the second triad are moderately stable. However, osmium, iridium, and platinum compounds are unstable and easily revert to the free element. All form colored compounds.

None of the elements of the second triad have compounds of medicinal value, but platinum, a member of the third triad, is used in cancer chemotherapy as cisplatin, *cis*-diaminedichloroplatinum(II); monographs for Cisplatin and Cisplatin for Injection are found in the USP. Carboplatin, *cis*-diamine (1,1-cyclobutanedicarboxylato)platinum, is another compound used in cancer therapy.

Elements of the First Triad

The important oxidation states are +2, achieved by the loss of the two *s* electrons, and +3 in which an additional *d* electron is lost (see Table 24-17). The stability of the +2 oxidation state increases from iron to nickel. The free metals and the +2 cations are important reducing agents. The cations have a tendency to form both cationic and anionic complex ions of high stability.

IRON

Iron is distributed widely in nature. It functions in divalent and trivalent states to form iron(II) ferrous and iron(III) ferric compounds, respectively. Iron(II) compounds are usually green in the hydrated state and white in the anhydrous state. Iron(III) salts are usually yellow to brown in the hydrated state but vary in color when anhydrous. Aqueous solutions of iron(III) salts hydrolyze strongly to give acid solutions. Iron(II) salts undergo slight hydrolysis and are oxidized easily in solution. The behavior of the iron(III) ion is similar to that of aluminum(III).

Iron, in either oxidation state, readily forms soluble coordination complexes with ligands such as phosphate, citrate, tartrate, and amines. Iron does not precipitate from many of these complexes with the usual iron precipitants.

Iron is an essential trace element. It is the important element in the transportation of oxygen by hemoglobin. It functions in various cytochromes, which are essential oxidative enzymes of the body cells.

A study carried out in Finland has cast doubt on the advisability of the routine use of hematinics because men with higher levels of ferritin (an iron storage protein) were found to be more prone to heart attacks. Interpretation of the results included speculation about iron's ability to give rise to free radicals after reaction with oxygen. The caveat that persists is that ferritin levels must be measured and found to be low before an iron deficiency is pronounced requiring use of a hematinic. The use of hematinics without substantiated need is not advised.

Numerous iron(II) and iron(III) compounds, complexes, and solutions have been used as hematinics in the past. However, because of their greater gastrointestinal irritation and poor absorption, iron(III) compounds and their preparations are used rarely today. Ferrous Fumarate (Tablets and, together with Docusate Sodium, Extended Release Tablets), Ferrous Gluconate (Tablets, Capsules, and Elixir), Ferrous Sulfate (Oral Solution, Syrup, and Tablets) and Dried Ferrous Sulfate are official in the USP. Iron Dextran Injection, a colloidal iron(III) hydroxide with partially hydrolyzed dextran, and Iron Sorbitex Injection, a complex of iron with sorbitol and citric acid, are cited in the USP as injectable forms for patients with poor gastrointestinal tolerance or poor absorption of iron. Reduced iron formerly was used as a hematinic; it survives today in the fortification of foods such as flour.

Iron(III) compounds are astringent. Sodium nitroprusside USP, $Na_2[Fe(CN)_5(NO)]\cdot 2H_2O$, is a vasodilator. A monograph for Sterile Sodium Nitroprusside is provided in the USP.

COBALT

The important cobalt salts of commerce are those of cobalt(II). Most contain water of hydration and are red in color, but when rendered anhydrous they are blue. Because of this color change anhydrous cobalt(II) chloride is included in dehydrating agents for gases to indicate when they are spent.

There is evidence that the presence of traces of cobalt may catalyze the physiological utilization of iron. This has led to the introduction of medicinal specialty products containing iron in association with cobalt designed for use in the treatment of iron deficiency anemias. Cyanocobalamin (vitamin B_{12}) is the only cobalt compound officially cited. The radioactive isotopes, ^{57}Co and ^{60}Co, are used diagnostically and therapeutically.

NICKEL

The important nickel compounds are in the +2 oxidation state. There are no nickel compounds of medical importance.

WATER

Water is omnipresent. About 75% of the earth's surface is covered with liquid water. Land masses in polar regions are covered with thick sheets of ice. In vapor form, water is an important constituent of the earth's atmosphere. In combined form, water occurs abundantly in many minerals, such as gypsum ($CaSO_4\cdot 2H_2O$). In addition, water occurs in all animal and vegetable tissues; it constitutes some 70% of the human body and over 90% of vegetables such as cucumbers and watermelons.

Together with ammonia and hydrogen fluoride, water is distinguished from other covalent hydrides by the strong hydrogen bonds existing between adjacent molecules. Despite the ability of fluoride ion to form stronger hydrogen bonds than oxide, hydrogen bonding reaches its peak in water because two protons are available per molecule. Hydrogen fluoride has only one available proton per molecule and ammonia has only one open site per molecule for hydrogen bonding.

Because of the extensive hydrogen bonding, the physical properties of water are unique among the other hydrides. Most obvious is the existence of water as a liquid under normal conditions. All other covalent hydrides are gases. The heat of fusion and melting point, heat of vaporization and boiling point, specific heat, surface tension, viscosity, and dielectric constant of water are all much higher in absolute value than those of other covalent hydrides. The world as we know it would be impossible without these unusual properties of water.

Water is a chemically stable compound. Even at 2000 K, less than 1% is dissociated into its elements. The K_w for water is only 10^{-14}. Despite this relative nonreactivity it acts as a solvent, especially for ionic compounds, as a ligand, as an acid or base, and as an oxidizing or reducing agent. In traces, water is frequently a catalyst. The acid–base properties are discussed later.

Because of its strong permanent dipole, water often acts as a ligand in complex substances. Almost all cations form one or more hydrates, divalent cations being more highly hydrated than the monovalent because of their stronger electrostatic fields. Having reduced field strengths because of their greater size, large cations (eg, cesium) do not hydrate. Many anions hydrate; for example, $CuSO_4\cdot 5H_2O$ is actually $[Cu(H_2O)_4][SO_4\cdot H_2O]$.

Water acts as a solvent for an unusual range of substances. This solvent action results from one or more of its properties: small size, strong permanent dipole, high dielectric constant, and availability of protons for hydrogen bonding.

NATURAL WATERS

Naturally occurring waters contain dissolved minerals indigenous to the region. Such waters are described variously as mineral waters, lithia waters, sulfur waters, and so on. Owners of springs or other sources of such waters often claim fanciful

therapeutic effects but, in general, these claims have not been substantiated.

Natural waters contain varying amounts of suspended matter, such as clay, sand, microorganisms, and fragments of plants and animals. Commonly, they are a very dilute solution (parts per million or ppm) of calcium, magnesium, iron(III), sodium, and potassium ions, having bicarbonate, sulfate, and chloride as counterions.

The dissolved bicarbonate constitutes *temporary* hardness whereas sulfate and chloride constitute *permanent* hardness. In addition, natural water contains traces of dissolved atmospheric gases, ammonia, and metabolic decomposition products. Waters in inhabited areas often include dissolved minerals such as nitrate, phosphate, and organic compounds from homes, industry, and farms. Detergents and dissolved traces of insecticides and herbicides are proving especially troublesome. The Environmental Protection Agency (EPA) has water-quality criteria for a number of priority pollutants.

POTABLE WATER

Potable water is water that is *fit to drink*. Providing potable water is one of the most important functions of modern communities. The overall process involves the removal of insoluble matter through appropriate coagulating, settling, and filtering processes; destruction of pathogenic microorganisms by aeration, chlorination, or other methods; and improvement of palatability through aeration and filtration through charcoal.

Activated charcoal also removes some harmful trace impurities (eg, trihalomethanes) not removed or destroyed by previous operations. In regions where water is excessively hard, *softening* is effected by adding lime or ammonia to partially remove dissolved salts by precipitation as carbonates (Ca^{2+} and Mg^{2+}) and hydroxide [iron(III)]. To assure an adequate provision of the essential element fluorine, fluoridation is accomplished by adding sodium fluosilicate. Standards for potable water are issued by the EPA.

In emergencies water may be purified (rendered free of viable microorganisms) by boiling for 15 to 20 minutes, or by treatment with halazone or iodine.

PURIFIED WATER AND OTHER WATERS USED IN PHARMACY

Purified water is prepared by distillation, ion-exchange (deionized, demineralized), reverse osmosis, or other methods. Potable water, meeting EPA standards, is used in its preparation. The object is the removal of dissolved solids. Ion-exchange and reverse osmosis are particularly effective in removing electrolytes. Distillation is not effective in the removal of weak electrolytes and nonelectrolytes if they are volatile.

Purified water may be rendered sterile and pyrogen-free by repeated distillation.

Primarily because of its solvent powers and physiological inertness, water is an extremely important pharmaceutical agent. It is official in six different monographs: Purified Water, Sterile Purified Water, Water for Injection, Bacteriostatic Water for Injection, Sterile Water for Inhalation, Sterile Water for Injection, and Sterile Water for Irrigation. General Chapter <1231> in the USP is an excellent summary of the various waters and a guide to their use.

HEAVY WATER

The isotopes of hydrogen have been named deuterium (two neutrons) and tritium (three neutrons). The presence of three neutrons in tritium results in an unstable nucleus. However, like hydrogen, deuterium is stable and gives rise to deuterium oxide, D_2O. This compound occurs in ordinary water in a few parts per million. Because of its greater molecular weight, the physical properties of deuterium oxide differ from those of water (eg, bp 101.4°, sp gr 1.10).

Deuterium oxide has no known therapeutic role. It has been used as a research tool in biological and pharmacological investigations. Use of deuterium oxide for drinking purposes has caused retardation or stunted growth in experimental mammals. It is available commercially and finds use as a moderator in nuclear reactors and as a solvent in nuclear magnetic resonance studies.

ACIDS, BASES, AND BUFFERS

ACIDS AND BASES

Acid–base theories range from the limited, classic Arrhenius theory to the comprehensive theory of Lewis. In between are the Franklin solvent system of acids and bases and the Brønsted proton donor theory.

As the body functions with aqueous media and pharmaceuticals frequently are dispensed in aqueous solution, the Brønsted theory is convenient for use in pharmacy. A molecule or ion that can provide a proton (proton donor) is an *acid;* one that can accept a proton (proton acceptor) is a *base.* On accepting a proton, a base becomes an acid; on losing its proton, the acid becomes a base. An acid and its base are related by the presence or absence of a proton, and are known as a *conjugate pair.* The transfer of a proton from the acid of one conjugate pair to the base of another conjugate pair is *neutralization*. Some conjugate pairs of pharmaceutical interest are given in Table 24-18. It is evident that acids and bases may be cations, neutral molecules, or anions. Some structures may be members of two different conjugate pairs, as an acid in one and as a base in the other.

Table 24-18. Conjugate Acid–Base Pairs

ACID	BASE	ACID	BASE
H_2O	OH^-	H_2SO_4	HSO_4^-
H_3O^+	H_2O	HSO_4^-	SO_4^{2-}
NH_4^+	NH_3	H_3PO_4	$H_2PO_4^-$
RNH_3^+	RNH_2	$H_2PO_4^-$	HPO_4^{2-}
HCl	Cl^-	$[A](H_2O)_6]^{3+}$	$[A](H_2O)_5(OH)]^{2+}$
H_2CO_3	HCO_3^-	$[A](H_2O)_5(OH)]^{2+}$	$[A](H_2O)_4(OH)_2]^+$
HCO_3^-	CO_3^{2-}	$H_3BO_3 \cdot H_2O$	$[B(OH)_4]^-$

A strong acid is an acid that loses its proton easily; a *weak acid* holds its proton tenaciously. The conjugate base of a strong acid is a *weak base,* whereas that of a weak acid is a *strong base.* In neutralization, the proton goes to the strongest of the bases present. The percent ionization and the ionization constant are measures of the strength of a given acid.

Acids and bases are used in pharmacy for analytical procedures, as buffer systems, and to dissolve insoluble medicinals. To accomplish the latter the insoluble compound must have a functional group capable of acting as a strong base or as an acid. Lidocaine Hydrochloride Injection USP and Niacin Injection USP are examples. The former is prepared by reacting lidocaine with hydrochloric acid; the diethylamino group is a stronger base than either the water molecule or the chloride ion. Lidocaine goes into solution as a cation. Niacin Injection is prepared by reacting niacin with either sodium carbonate or sodium hydroxide; the carboxyl group loses its proton to the carbonate or hydroxyl ion and the niacin goes into solution as an anion.

In neutralization, as above, the pharmacist must be cognizant of two requirements that are not important in ordinary chemical neutralizations. The counterion being introduced—chloride ion and sodium ion, respectively, in the above examples—must be compatible physiologically with the body fluids. Also, because strong acids or bases are being used, there can be no excess acid or base because of the corrosive nature of these reagents.

Acids and bases are also necessary for the preparation of effervescent mixtures, a medicinal dosage form sometimes used to render a medicinal more palatable for oral administration. Sodium bicarbonate is used as the carbon dioxide source. Solid acids such as citric acid, tartaric acid, or sodium dihydrogen phosphate are used, frequently in combination. Reaction rate is very important in these formulations. Sodium bicarbonate must have the correct particle size; if too fine, the reaction is too violent, and if too coarse, the reaction is too slow. To lower the activity of the acid, a normal salt of the acid is included in the mixture as a diluent.

Some acids and bases listed in the compendia at present are Calcium Hydroxide, Potassium Bicarbonate, Potassium Hydroxide, Sodium Bicarbonate, Sodium Carbonate, Sodium Hydroxide, Strong Ammonia Solution, Acetic Acid, Hydrochloric Acid and Diluted Hydrochloric Acid, Nitric Acid, Sulfuric Acid, Phosphoric Acid and Diluted Phosphoric Acid.

Stability and storage problems of these compounds must be considered. All strong bases are subject to reaction with carbon dioxide if proper closures are not maintained. Volatile compounds, such as ammonia and hydrogen chloride, must be sealed tightly at all times, as must hygroscopic compounds such as sodium hydroxide.

BUFFERS

Buffers are used to maintain the pH of a medicinal at an optimal value. A *buffer* is a solution of a weak acid and its conjugate base, the base being provided by one of its soluble salts.

PHYSIOLOGICAL CONTROL OF pH

Brønsted acids and bases have been used to maintain and adjust the pH of body fluids for many years. By far the greatest interest has been in development of gastric antacids. However, an adequate number of suitable reagents are available for systemic pH adjustments.

GASTRIC ANTACIDS

The present official magnesium antacids include Magnesium Hydroxide, Milk of Magnesia, Magnesia Tablets, Alumina and Magnesia Oral Suspension (and Tablets), Magnesium Carbonate, Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension, Magnesium Oxide, Magnesium Phosphate, and Magnesium Trisilicate (and Tablets). The official aluminum antacids include Aluminum Hydroxide Gel, Dried Aluminum Hydroxide Gel (and Capsules and Tablets), Aluminum Phosphate Gel, Dihydroxyaluminum Aminoacetate (and Magma, and Capsules and Tablets), Dihydroxyaluminum Sodium Carbonate (and Tablets), Alumina, Magnesia, and Calcium Carbonate Oral Suspension (and Tablets), Alumina and Magnesium Trisilicate Oral Suspension (and Tablets), and the Alumina and Magnesia preparations already listed. The calcium antacids include Precipitated Calcium Carbonate (and Tablets), Calcium Carbonate and Magnesia Tablets, and Calcium and Magnesium Carbonates Tablets. Magaldrate, an aluminum magnesium hydroxide sulfate, is official, as is its Oral Suspension and Tablets. Miscellaneous official antacids include Milk of Bismuth, Sodium Bicarbonate, and Potassium Bicarbonate.

There are other gastric antacid dosage form monographs, some including simethicone, an antiflatulent, and they are Magnesium Oxide Capsules (and Tablets); Basic Aluminum Carbonate Gel; Dried Basic Aluminum Carbonate Gel Capsules (and Tablets); Alumina and Magnesium Carbonate Oral Suspension (and Tablets); Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets; Alumina, Magnesia, and Simethicone Oral Suspension (and Tablets); Calcium Carbonate Oral Suspension; and Magaldrate and Simethicone Oral Suspension (and Tablets). A monograph for Magnesium Hydroxide Paste, which contains about 31 g of magnesium hydroxide per 100 g, describes a suspension that is an intermediate in the manufacture of Milk of Magnesia and other suspensions of magnesium hydroxide.

SYSTEMIC ALKALIZERS AND ACIDIFIERS

Sodium Bicarbonate USP and Potassium Bicarbonate USP are used as systemic alkalizers. Because the bicarbonates are unstable to heat, chemical problems arise in the sterilization of bicarbonate solutions,

$$2HCO_3^- \rightleftharpoons CO_3^{2-} + CO_2 + H_2O$$

To depress the forward reaction the solution can be saturated with carbon dioxide. To prevent the loss of the gas, which would result in the permanent formation of the strong carbonate base, the ampules used must be sealed tightly before sterilization, and must be made of glass sufficiently strong to withstand the gas pressure developed during sterilization. On cooling the reverse reaction becomes dominant.

Ammonium Chloride USP, Monobasic Sodium Phosphate USP, and Calcium Chloride USP are employed as systemic acidifiers.

ELECTROLYTES AND ESSENTIAL TRACE ELEMENTS

The roles and behavior of inorganic elements in the electrolyte and essential trace elements categories are discussed elsewhere in this book, but it is instructive to review the physical and chemical properties that make possible their respective roles. Examination of orbital electron structures, ionic radii, oxidation states, etc, as given in Tables 24-7 through 24-17, can yield valuable clues to their behavior.

The transition elements have incompletely filled 18-electron outer shells and each can exist in several different oxidation states. In most cases the shift between two electron states is relatively easy; for example,

$$Fe^{2+} \rightleftharpoons Fe^{3+} + e^-$$

As a result, the transition elements can act as electron sinks and are active in those systems involved in oxidation or reduction reactions.

On the other hand, an element such as zinc achieves a completely filled outer 18-electron shell on becoming zinc ion. In

the 2+ oxidation state this shell becomes stable. Unlike the tightly held spherical 8-electron shell the 18-electron shell is *mushy* and deformed or polarized easily by external fields. In turn, it can cause polarization of other moieties. This ion is not found in redox systems, but rather in systems such as carbonic anhydrase, which aid in the splitting or forming of molecules.

Unlike the incompletely filled shells of the transition elements or the 18-electron shell of the zinc ion, 8-electron shell ions ordinarily are stable and are not deformed easily by external fields. Those 8-electron outer shell ions with a high charge (eg, calcium) have intense charge densities in the volume surrounding the ion. This results in strong interactions with the fields of other moieties to form strong permanent associations. However, an 8-electron shell effectively screens the single charge of ions such as sodium. They are, therefore, chemically inert with very weak interactions with other ions. This explains their simple roles in the body fluids as osmotic regulators, etc.

There are a number of monographs for parenteral infusions intended to supply electrolytes, water, and carbohydrates as nutrients. In addition to monographs in the USP for Ringer's and Dextrose Injection and Lactated Ringer's and Dextrose Injection (with Half-Strength and Modified variations), a series of monographs are found with the designation Multiple Electrolytes in each title; these monographs offer choices of cations from Na^+, K^+, Ca^{2+}, Mg^{2+}, and NH_4^+; of anions from chloride, acetate, citrate, lactate, gluconate, phosphate, and sulfate; plus a choice of carbohydrate nutrient from invert sugar and dextrose. These monographs indicate an awareness of the importance of inorganic cations (including magnesium) and anions and provide a variety of choices to allow treatment of patients on an individualized basis.

In addition to providing official standards for various infusions used as parenteral rehydration solutions or electrolyte replenishers, USP has a generic monograph for Oral Rehydration Salts, a dry mixture of sodium chloride, sodium bicarbonate (or sodium citrate), potassium chloride, and dextrose to be dissolved and used to treat chronic diarrhea.

In recent years there has been an increased awareness of the importance of minerals in the diet and of the value of mineral supplements. Generally, gluconates, like other organic salts, are less irritating to the gastrointestinal tract; thus, the following metal gluconates are found in the USP: Zinc, Sodium, Copper, Magnesium, and Manganese. The USP includes a monograph USP for Selenious Acid Injection, which can provide a source of selenium as a mineral supplement.

In a new USP section entitled Nutritional Supplements are monographs for Mineral Capsules and Mineral Tablets. The minerals present in these dosage forms are potassium, calcium, magnesium, phosphorous, zinc, iron, manganese, copper, molybdenum, fluorine, chromium, iodine, and selenium.

When it is necessary to administer trace elements parenterally, the monograph entitled *Trace Elements USP* describes a sterile solution that may be used to administer zinc, copper, chromium, manganese, selenium, iodine, and molybdenum.

TOPICAL AGENTS

OXIDIZING GERMICIDES

Hydrogen Peroxide, Sodium Hypochlorite, Iodine, and/or their various solutions are cited in the USP. Hypochlorous acid, the active moiety in sodium hypochlorite solution, owes its germicidal activity to both oxidizing and chlorinating activity.

PRECIPITATING GERMICIDES

Silver Nitrate, Silver Nitrate Ophthalmic Solution, and Toughened Silver Nitrate are listed in USP, as is Ammoniated Mercury. Zinc Acetate, Zinc Chloride, Zinc Sulfate, and Zinc Undecylenate also are official. Only two boron compounds are cited in NF: Boric Acid and Sodium Borate. The antimony compounds listed are Antimony Potassium Tartrate USP and Antimony Sodium Tartrate USP.

ASTRINGENTS

Aluminum ion in solution is an excellent local astringent over wide concentration ranges. It also is mildly antiseptic. Aluminum Chloride USP once was used in this application, but the high acidity of its solutions caused problems. The acidity results from ionization of the hexaaquo ion

$$[Al(H_2O)_6]^{3+} + H_2O \rightleftharpoons [Al(OH)(H_2O)_5]^{2+} + H_3O^+$$

and is about that of acetic acid. Today, the mixture of two compounds (aluminum hydroxychloride, aluminum chlorhydrate, aluminum chlorhydrol) obtained by partial neutralization of aluminum chloride is used.

$$[Al(H_2O)_6]^{3+} + OH^- \rightarrow [Al(OH)(H_2O)_5]^{2+} + H_2O$$

$$[Al(OH)(H_2O)_5]^{2+} + OH^- \rightarrow [Al(OH)_2(H_2O)_4]^{+} + H_2O$$

The reaction is stopped before complete conversion to the dihydroxy hydrate. The resulting solution (or dried product) retains the excellent astringent (and deodorant) properties of the aluminum ion, but the pH of the solutions approximates neutrality (5 to 6).

Aluminum Subacetate Topical Solution USP is essentially a solution of the above ions prepared from aluminum sulfate using carbonate ion ($CaCO_3$) as the base. Aluminum Sulfate and Ammonium Alum and Potassium Alum are found in the USP and also are used as astringents. Alum may be either the potassium or ammonium form. It is shaped into a pencil form to be used as a styptic.

Iron(III) and aluminum ions are very similar. Iron(III) is astringent, and preparations of ferric salts for such use formerly were recognized. Although it is efficient in this capacity, its staining property is a major disadvantage. Lime water, a saturated solution of fresh calcium hydroxide, is used as a local astringent. Bismuth subnitrate and the other bismuth sub-salts are used as astringents and protectives.

PROTECTIVES

In order to possess good adhering properties, protectives must be in very finely powdered form. They also must be relatively inert, insoluble compounds. A wide range of compounds are suitable as protectives. They usually are used externally, but some applications involve the gastrointestinal tract. Some are slightly soluble (eg, ZnO) and give some astringent action; others (eg, kaolin) have adsorbent action.

Zinc Oxide, Calamine (and Calamine Lotion and Phenolated Calamine Lotion), and Zinc Stearate (all USP) are used for their protective and slightly astringent properties. Calamine is the calcined native zinc oxide ore. The iron oxide impurity gives calamine a flesh color that is cosmetically more appealing. Zinc stearate, a mixture of fatty acid zinc soaps, has an unctuous feel. White Lotion USP is used for its astringent and protective powers.

Magnesium trisilicate, basic aluminum carbonate, and chalk are used as protectives, as are the various insoluble bismuth sub-salts. Talc is used because of its smooth, unctuous feel. Kaolin and bentonite are used as they also have some absorptive properties; titanium dioxide is used as a solar screen.

INORGANIC PIGMENTS

The most important innocuous pigments are the iron oxides. They give colors throughout the visible spectrum. Three variables are involved: particle size, oxidation state, and degree of hydration.

MISCELLANEOUS INORGANIC APPLICATIONS

ARTIFICIAL ATMOSPHERES

Five gases are official: nitrogen, oxygen, helium, carbon dioxide, and nitrogen(I) oxide (nitrous oxide or laughing gas). Nitrogen is used as a diluent for oxygen and may be used as a protective atmosphere for easily oxidized medicinals.

Helium, because of its low density compared to nitrogen, is used to prepare a gaseous mixture composed of 20% oxygen and helium. This mixture is used to alleviate respiration difficulties. Because of the low solubility of helium in blood, the same mixture is used as an atmosphere for those performing under high atmospheric pressures (deep-sea divers, caisson workers). When ordinary air is used, rapid decompression causes bubbles of gaseous nitrogen to form in the blood; the resulting painful, and sometimes fatal, condition is known as the bends.

Oxygen is used when respiratory problems exist. Ordinarily, it is diluted with nitrogen or helium; 100% oxygen should not be used continuously. In hyperbaric oxygen therapy, oxygen is breathed inside a tank at up to 3 atm (atmospheres) of pressure. Although the amount of oxygen carried by the hemoglobin is little affected, the higher oxygen pressure increases the amount of dissolved oxygen in the plasma (Henry's law).

It is possible to produce oxygen that is medicinally useful on site, as in a hospital or nursing home, by the use of oxygen concentrators. There are two types of membranes that are used in the concentrators, permeable plastic membranes and molecular sieves. The monograph for Oxygen 93% USP sets standards for the oxygen produced by the molecular-sieve process.

Nitrogen(I) oxide usually requires 20 to 25% oxygen during administration. It is used for surgical operations of short duration. Xenon has a general anesthetic action but is too rare for use. Magnesium ion has anesthetic action; however, the anesthetic dose and the toxic dose of magnesium are too close for use as a general anesthetic. Magnesium Sulfate Injection USP is used as an anticonvulsant and central depressant.

CARBON DIOXIDE ABSORBERS

When, as in general anesthesia, a patient rebreathes air, dangerous levels of carbon dioxide build up. To prevent this *carbon dioxide absorbers* are used. Soda Lime NF is prepared by fusing calcium hydroxide with sodium hydroxide and/or potassium hydroxide with sufficient diatomaceous earth to yield a hard, nonfriable product. For Barium Hydroxide Lime USP, barium hydroxide is substituted for the alkali hydroxide. The particles formed must be large enough to allow free passage of air, but small enough to give a large surface area for absorption. The particles must be hard to prevent dust formation with handling. Entrainment of absorber dust in the breathed air could cause serious alkali burns in the respiratory tract. A colored indicator is included in the preparation to indicate when the carbon dioxide capacity is depleted.

RESPIRATORY STIMULANTS

Carbon dioxide is used as a respiratory stimulant, usually with 5 to 7% oxygen. Because it is the normal respiratory stimulant it is of no value where the respiratory center is already depressed. Carbon dioxide also is used as an inert gas in the headspace over medicinals in sealed containers.

Ammonium Carbonate NF is used as a respiratory stimulant. The name is a misnomer, as it is a mixture of ammonium bicarbonate and ammonium carbamate. At room temperature it decomposes to ammonia and carbon dioxide, two respiratory stimulants.

$$NH_4HCO_3 + NH_2CO_2NH_4 \rightarrow 3NH_3 + 2CO_2 + H_2O$$

The substance must be stored in tightly sealed containers.

Aromatic Ammonia Spirit USP is prepared from ammonium carbonate, strong ammonia solution, various aromatic oils, alcohol, and water. Light-resistant containers must be used.

EXPECTORANTS

Water vapor, an excellent expectorant, is currently considered the best. Ammonium chloride and carbonate, and ammonium and potassium iodides are used commonly as expectorants. Hydriodic acid syrup was official at one time. If the iodides are used in solution, they must be protected by an antioxidant such as sodium thiosulfate.

LAXATIVES, ENEMAS, AND IRRIGATION SOLUTIONS

Cathartics are divided into classes according to mode of action. With the exception of sulfur, the inorganic cathartics are saline (osmotic, bulk) laxatives. For laxative action one or both of the ions of the salt must not be absorbed, or be absorbed with difficulty. This sets up an osmotic imbalance in the intestinal tract that the body attempts to correct by secreting water into the intestine. The large volume of fluid in the intestine acts as a mechanical stimulus for peristalsis.

The commonly used salts of the monohydrogen phosphate, monohydrogen tartrate, tartrate, and citrate ions are absorbed slowly, but in laxative doses their osmotic action is rapid and effective. They are swept out of the intestinal tract before appreciable absorption can take place. Sulfate ion is relatively nonabsorbable and is used either as the magnesium or sodium salt (Epsom Salt and Glauber's Salt, respectively).

Insoluble laxatives, such as Milk of Magnesia, must be dissolved in the stomach before they can exert a laxative effect. The soluble magnesium sulfate and citrate of magnesia are used widely as laxatives. However, soluble magnesium salts frequently are not recommended as laxatives because of the danger of absorbing free magnesium ion. Dibasic Sodium Phosphate, Sodium Phosphates Oral Solution, Sodium Citrate and Citric Acid Oral Solution, Potassium Sodium Tartrate, Milk of Magnesia, and Sodium Sulfate are cited officially.

PEG 3350 and Electrolytes for Oral Solution USP (Polyethylene- glycol 3350, $NaHCO_3$, NaCl, Na_2SO_4 and KCl) is a dry mixture that is to be dissolved at the time of use and then consumed within a prescribed time in order to function as a cathartic and accomplish oral colonic lavage in preparation for a barium enema or a colonoscopic examination.

Sulfur, when ingested, has an irritant laxative effect. The element is thought to be reduced to hydrogen sulfide by reducing

agents present in the intestinal fluid. Hydrogen sulfide is a mild intestinal irritant.

Sodium Phosphates Enema USP is a mixture of dibasic and monobasic sodium phosphates or dibasic sodium phosphate and phosphoric acid in water to give a pH of 5 to 5.8.

Some solutions are used for irrigating various parts of the body. For example, Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation USP is defined as a sterile solution that, after the chemical reactions between citric acid and the other two compounds are completed and the resulting solution is sterilized, is suitable for use as a urinary bladder irrigant; its acidic pH is conducive to dissolving any bladder calculi in patients such as those using an indwelling catheter.

RADIOPAQUES AND IMAGING AGENTS

Radiopaque compounds are capable of interfering with the passage of x-rays. This interference is directly proportional to atomic number. The soft tissues of the body are composed of atoms of very low atomic number (1, 6, 7, 8, 15, and 16) that do not interfere sufficiently to be discerned. To make the soft tissues, the lumen of organs, and body channels show, high atomic number atoms must be used.

Because of the toxicity of these elements, the choices are limited. Only two, barium and iodine, atomic numbers 56 and 53, have proved useful. Barium Sulfate USP and Barium Sulfate for Suspension USP are used for studies of the intestinal tract. Iodine is incorporated into organic molecules designed to concentrate in the organ or cavity to be studied, such as Iopanoic Acid USP designed for visualization of the gall bladder. Each molecule of the acid has three iodine atoms.

The introduction and development of magnetic resonance imaging (MRI) as a means of getting images of parts of the body by noninvasive methods has made medical diagnoses simpler and more scientific. The use of gadolinium (element 64) in various complexes such as a cationic diethylenetriamine pentaacetic acid complex with a meglumine anion has dramatically facilitated the visualization of intracranial lesions by paramagnetic enhancement.

STRUCTURAL REPAIRS

Occasionally, temporary or permanent replacement of support structures is necessary. The materials used should be chemically inert and insoluble in the body fluids, they must be nontoxic, and they must have the strength to withstand any physical stress to which they are subjected. Tantalum has been used as a bone replacement for temporary braces of long bones, and to close openings in the skull. Silver has found similar applications. It reacts slightly with body fluids, but as insoluble silver chloride is the principal product, this is not a serious threat. Mercury amalgams of gold and silver are used for dental fillings but this venerable use of mercury is being questioned because of possible chronic toxicity. Zinc-eugenol cement also is used for dental fillings.

Plaster of Paris is used for temporary support structures, especially for broken bones. The formula, $CaSO_4 \cdot 1/2H_2O$, suggests a hemihydrate, but there is experimental evidence indicating the existence of local gypsum ($CaSO_4 \cdot 2H_2O$) nuclei in anhydrous calcium sulfate.

Plaster of Paris also is used for taking dental impressions; because it expands slightly on setting, it fills all spaces completely to give a true surface replica.

EPILOGUE

Because of space considerations, many less important and older inorganic medicinals have been omitted. The chemistry given necessarily is abbreviated. For further details of basic chemistry and omitted uses and products see Discher et al.[1] For more thorough discussions of the etiology and treatment involving inorganic substances, see the appropriate chapters of this text or of Block *et al*.[8] For the chemistry and use of many products no longer in general use or entirely abandoned, refer to one of the older editions of Rogers, Soine, and Wilson.[9]

An excellent text by Rayner-Canham[10] considers the basic properties and descriptive aspects of many inorganic compounds and includes some biochemical and biological information. In addition, Emsley's excellent book[11] gives information about the presence of elements in humans and provides the background and history for the use of inorganic compounds for medicinal purposes.

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CHAPTER 25

Organic Pharmaceutical Chemistry

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It is not the purpose of this chapter to provide a fundamental treatment of organic chemistry. Readers are expected to have pursued the usual basic courses in organic chemistry and be cognizant of the various advanced texts and other readily available works of reference. (See Bibliography) Accordingly, this chapter is restricted primarily to a listing of the more prominent structural types of organic compounds, a brief presentation of the various nomenclature systems and of the major chemical classes of official (USP/NF) pharmaceuticals, followed by a discussion on the identification of organic functional groups and the possible assignment of an approximate acidic, basic, or neutral value to these groups. A detailed treatment of the individual pharmaceuticals is provided at other locations in this book (refer to the index).

TYPES OF ORGANIC COMPOUNDS

A comprehensive understanding of organic chemistry would be extremely difficult were it not for the fact that the hundreds of thousands of known compounds fall conveniently into a very much smaller number of general types based on molecular structure. Similarities and differences among the physical and chemical properties of the diverse compounds thus become more apparent and understandable, and this is useful both in providing explanations for observed phenomena and in making predictions for possible applications of known compounds and compounds projected for synthesis.

Organic compounds may be classified in many ways, the desired intricacy of any particular scheme depending on the purpose of performing the classification. Thus, for one purpose it may suffice to construct a single, broad class of hydroxy compounds, while for other purposes it is desirable to subdivide this broad class into alcohols and phenols and perhaps even subdivide these further into subclasses of alcohols and phenols. It is appropriate here, for purposes of convenient reference, to list those types of compounds most commonly encountered in the systematic study of organic chemistry and to display their general (type) formulas. The types of compounds that are pertinent, especially to pharmacy, are treated in greater detail later in the chapter where examples of official drugs belonging to each class also are provided.

To enhance the utility of this chapter as a reference tool, the listing in Appendix A is alphabetical rather than by any chemical classification scheme. Prefatorily, the following explanatory notes are provided.

Unless otherwise specified, the formulas shown are for compounds containing only one of the particular functional groups involved. Formulas for compounds containing more than one of the same functional group can be derived easily.

Naturally occurring classes of compounds such as carbohydrates, proteins, alkaloids, glycosides, or lipids are not treated as types of compounds in this classification. A separate, more detailed presentation of these is provided in Chapter 26.

Although a few heterocyclic types such as imines (azacyclic), anhydrides of dibasic acids (oxacyclic), lactides (dioxacyclic) automatically enter into the listing, it will be observed that parent heterocycles in general (eg, thiophene, pyridine, dioxane) are not included. Heterocycles represented in official drugs are listed later in the chapter.

In type formulas, such as in Appendix A, the symbol R is employed conventionally to denote a hydrocarbon radical. Unless otherwise specified, it may be aliphatic, alicyclic, or aromatic, and its valence varies to satisfy the requirements of its attachment to the rest of the molecule. The degree of saturation in R does not enter into the scheme. When a formula contains more than one R, the radicals may be either identical or different. In a few instances it is possible, that even if two monovalent Rs are replaceable by a single divalent R, the same type of compound is retained, as with aliphatic ketones ($R_2C{=}O$) and cyclic ketones ($R{=}C{=}O$).

The type formulas assume a useful broader meaning if R, instead of being restricted to designate only a *hydrocarbon* radical, is permitted to (1) be a residue from a heterocycle and (2) carry substituent groups. The latter definition automatically extends the listing to embrace polyfunctional compounds, but it also introduces the complicating feature of the *order of precedence* of functional groups. This matter is discussed later in the chapter.

Unless otherwise specified, the symbol X stands for a member of the halogen family. In addition to the type formulas, one or more specific examples of each type of compound also are provided, showing how the formulas usually appear in somewhat condensed form and illustrating the manner in which the type names become parts of individual compound names. However, it should be remembered that, although correct, such names are not always the preferred names in modern nomenclature practice.

A linear formula with a horizontal line above the symbols indicates a ring structure; the line is a bond joining the two atoms at each end. For example, $\overline{CH_2CH_2CH_2CH_2COO}$ is δ-valerolactone. The oxygen atom on the right end is bonded to the carbon atom on the left end, forming a 6-membered ring.

The only formulas and structures that will be depicted will be those of pharmaceutical interest.

NOMENCLATURE OF ORGANIC COMPOUNDS

In the early decades of organic chemistry, newly discovered compounds commonly were provided with names which indicated either the source or some outstanding property of the

compound. Thus, marsh gas, wood alcohol, salicylic acid, cadaverine, morphine, chlorophyll, and thousands of other similar names were invented. As more and more compounds were isolated or synthesized, it became apparent, however, that some systematic manner of naming organic compounds in terms of their structure would have to be devised. Early systems of nomenclature, while adequate for the period in which they were invented, soon required modification as the number of known compounds increased. The result has been that the system (or rather the combination of systems) now in use represents an evolution covering many decades.

That a truly effective system of nomenclature is bound to be very complex becomes obvious when one reflects that it must not only discriminate, unequivocally, among the many millions of compounds already known, but also must allow adequate provision for encompassing new compounds, which are being synthesized by the thousands each year. Fundamentally, therefore, such discrimination means that each specific name coined through the system must account for (1) the quantitative elementary composition (molecular formula) and (2) all of the structural features for one, and only one, specific compound.

The IUPAC and CAS Systems of Nomenclature

Of the various comprehensive systems which had been proposed, and used to a varying extent, the two most widely employed and most thoroughly updated through revision and enlargement are those devised by the International Union of Pure and Applied Chemistry (IUPAC) and the Chemical Abstracts Service (CAS). Each of these systems represents an implementation of the rules devised by the IUPAC Commission on the Reform of the Nomenclature of Organic Chemistry, which has been engaged actively and continuously in the subject for many decades.

The two systems are identical in many respects. The CAS system intentionally departs from that of IUPAC wherever such departure contributes to the main purpose of *Chemical Abstracts*—indexing the world's chemical literature. Recognizing the desirability to maintain compatibility between the two systems, however, CAS identifies each such departure and displays the alternative IUPAC treatment.

Because of the difficulty in converting many structural formulas into unique, descriptive names, CAS now assigns a *Registry Number* to every chemical compound (organic and inorganic). All editions of the USAN (see Chapter 27) and commencing with USP XIX and NF XIV, all monographs for pure chemical entities carry the CAS Registry Number, which uniquely identifies every compound. In the same editions of USP and NF, "New Chemical Abstracts Names" were assigned. Also, CAS has completely revised the older system (which parallels IUPAC rules) so that computer searches may be made using nomenclature fragments, rather than topological features, to locate molecular fragments as well as complete molecules.

It obviously is inappropriate and space-prohibitive to include in this text a discussion of the multiplicity of details in either of these two systems. Suffice it to state that, from a structural viewpoint, each system adequately must describe for each compound the following:

Composition and configuration of the carbon skeleton
Interruptions of the carbon skeleton by heteroatoms
State of hydrogenation of the skeleton
Presence and location of substituents, ie, atoms or groups of atoms (radicals) functioning in place of hydrogen
Features of stereoisomerism

The reader desirous of the details of the systems should consult the continuing series of reports issued by the IUPAC Commission on the Nomenclature of Organic Chemistry, and the CAS publication entitled *The Naming and Indexing of Chemical Compounds from Chemical Abstracts.* The latter, which first appeared as an introduction to the subject index of volume 56 of *Chemical Abstracts,* has undergone very extensive revision and enlargement. The introduction to the subject index of volume 66 provides a useful summary treatment. The publication of the American Chemical Society, *The Ring Index,* also offers a very detailed systematic presentation of closed-chain systems identified through the literature up to 1963.

Because of major changes in nomenclature and indexing procedures, mainly dictated by computerization of nomenclature and two-dimensional structures, each quinquennial index to *Chemical Abstracts* is accompanied by an index guide that allows the user to follow the transition between the old and new (or modified) nomenclature.

Three general features common to both systems deserve special comment, specifically the employment of trivial names, the order of precedence of functional groups, and permissive ambiguity.

TRIVIAL NAMES—A *trivial name* is one that does not describe a compound rigidly in terms of the absolute structure notations embodied in the system, but rather has earned worldwide recognition as being specific for that compound. Acetic acid (for ethanoic acid), purine (for 7*H*-imidazo[4,5-*d*]pyrimidine), and pregnane (for 10β,13β-dimethyl-17β-ethyl-9α,14α,5β,8β-perhydrocyclopenta[*a*]phenanthrene) are common examples. Without allowing for the judicious employment of such trivial names, any scheme of nomenclature would be hopelessly complex and of little, if any, practical use. On the other hand, the wholesale, indiscriminate admission of trivial names to a system equally is disastrous.

Arriving at a satisfactory compromise between these two extremes obviously requires detailed deliberation, and the compromise position taken by IUPAC also has been adopted by CAS: trivial names admitted by IUPAC are also those admitted by CAS. However, with the advent of computer techniques, long or unwieldy names are handled with relative ease. Thus, trivial and systematic names are assuming equal importance, because a trivial-name index cannot be computer-searched to locate fragments of two-dimensional structures as these fragments are not evident in the name. But with long, systematic names, every portion of a parent molecule, substituent, functional group, and so on is apparent in the name and will yield to the computer search.

PRECEDENCE ORDER OF FUNCTIONAL GROUPS—An *order of precedence* (priority) for functional groups is necessary to manage polyfunctional compounds systematically. As a simple example, in the absence of a systematic method, the compound $NH_2CH_2CH_2CH_2OH$ could be named either as an aminopropanol or as a hydroxypropylamine. But in the order of precedence, hydroxyl is higher than amino and, because the system requires that only the function of highest priority shall be represented by the suffix part of the name, the systematic name becomes 3-amino-1-propanol. The order of precedence of functional groups is described clearly (see Table 1 of the introduction to the subject index of *Chemical Abstracts,* volume 66, or the *11th Collective Index*, volumes 96 to 105, Appendix IV, *Chemical Substance Index Names*) and is identical in both the IUPAC and CAS systems.

PERMISSIVE AMBIGUITY—*Ambiguity* (lack of complete structural specificity) is permitted to the extent that it reflects structural features of a compound that either are unknown or have not yet been incorporated into the system. Prohibition of such ambiguity would disallow the cataloging of a very significant percentage of known compounds, especially among those that involve features of stereoisomerism.

Compendial Nomenclature

The lack of adherence to the principles of systematic nomenclature, in both the commercial and academic worlds, has led to a multiplicity in the types of chemical names in actual use. It is not at all unusual to find a specific compound referred to by several

different names, each of which is correct chemically. This, of course, creates a very confused state that, if it persists in the indexing literature, often renders searching via nomenclature extremely difficult, and frequently, impossible. It is for this reason that, wherever possible, *Chemical Abstracts* translates the nonsystematic nomenclature of the author into its CAS equivalent.

Recognizing the advantages of adhering to a standard system of nomenclature, the official compendia (USP/NF) elected to adopt names preferred by CAS. The principle of operation is simply that either the title or one of the subtitles of an official chemical must be the currently preferred CAS name. It is well to observe that the structural relationships established on the basis of the principal functional group automatically may hide relationships involving functional groups of lesser priority (eg, amphetamine is named as a derivative of phenethylamine, whereas hydroxyamphetamine becomes a derivative of phenol; similarly, sulfamerazine is named as a derivative of sulfanilamide, whereas phthalylsulfacetamide becomes a derivative of phthalanilic acid). Beginning with USP XIX and NF XIV each monograph carries the "new CAS name" along with the CAS preferred name currently in use. Also included is the Chemical Abstracts System *Registry Number,* which provides a unique identifier and simplifies locating a specific compound or drug in the literature, especially using a computer search.

Chemical Syllables

In addition to whatever numbers, numerical syllables, and individual Greek and English letters are required, systematic chemical names consist of a collection of syllables, each of which carry a chemical connotation of some sort. Many, such as chloro-, hydroxy-, and methyl-, clearly indicate specific elements or radicals.

Many others, such as andro- (from the Greek, "man"), tauro- (Latin, "bull"), neo- (Greek, "new"), or pseudo- or ψ (Greek, "false"), are of no chemical significance from a structural viewpoint, but often are very useful in forming the so-called trivial or common names for complex molecules such as androsterone, taurocholic acid, neoantergan, pseudoglobulin—the correct chemical names for these structures are often extremely cumbersome. Because of their lack of structural chemical significance, however, these will not be discussed further here.

The third group of these syllables consists of miscellaneous prefixes and suffixes and is of sufficient importance to warrant abbreviated treatment, because, like those of the first group, these have structural significance and often constitute a necessary part of systematic chemical names. A list of the more commonly encountered ones of this group is provided in Appendices B and C. Many of these have multiple meanings, and the definitions given herein represent the most common sense in which they are used in organic chemistry. Those shown in italics are used commonly in italicized form and/or enclosed in parentheses when used in organic nomenclature. It also must be remembered that the precise meanings shown here do not always apply to trivial names (eg, the meaning of -ene or of -ylene does not apply to acetylene; similarly, the meaning of -ol (alcohol) does not apply to benzol). Caution always must be exercised in attempting to attach significance to the various parts of such common names.

The systematic treatment of cyclic systems uses a generous miscellany of syllables with specific meanings; for listings and explanations, consult the *Ring Index* and Appendix E.

RADICALS AND GROUPS IN ORGANIC CHEMISTRY

Through the concept and use of radicals and groups, a logical and very helpful classification of the huge number of organic compounds is possible. Furthermore, knowledge of the chemical properties of commonly used individual radicals makes possible either a prediction or an explanation of the chemical properties of compounds because, in general, the chemical properties of a compound are completely or partially the combined properties of the radicals present in the molecule.

Several hundred different radicals have been recognized, named, and classified. A comprehensive list ordered by both names and formulas is published periodically as part of the *Collective Index* to *Chemical Abstracts,* as *Appendix IV*, in the *Chemical Substance Index Names* found in the index guide for volumes 96 to 105 of *Chemical Abstracts.*

For purposes of convenient reference, a list of radicals and groups frequently encountered in pharmaceutical chemistry is provided in Appendix D. Classification into chemical types has been sacrificed in favor of an alphabetical arrangement. Included in the list are many inorganic radicals that frequently are present in organic combination.

Chemical Notation Systems

The complexity and the cumbersome nature of modern organic chemical nomenclature have encouraged attempts to develop "shorthand expressions," variously referred to as notations, ciphers, codes, and alphamerics, which for certain purposes would be more convenient to use than the chemical names. Several systems have been proposed (eg, the NAS-NRC provided a comprehensive review of the history of the various systems), although none have fully survived. In general, they involved assigning chemical meanings to the characters usually available on, or readily adapted to, a standard typewriter or computer keyboard and devising rules for their use in constructing the notations. A recent addition to the nomenclature/notation foray is **SMILES**, an acronym for ***S***implified ***M***olecular ***L***ine ***E***ntry ***S***pecification. This is a valence model of a structure, not a computer data structure, and is relatively simple to master. (A tutorial is available at http://www.daylight.com/.)

Final assessment of the overall utility of notations has yet to be made; they particularly are appealing because their brevity (compared with descriptive chemical nomenclature as illustrated in Table 25-1) greatly increases storage efficiency in printed indexes and computer memories and facilitates computerized searching. In addition, they automatically avoid the troublesome "trivial name feature" encountered in practical nomenclature. However, they are not pronounceable words and do not eliminate the need for descriptive chemical nomenclature in the written and spoken word.

Several of these notations have been found useful for retrieving compounds on a structural basis from specialized files of compounds stored in computers using the same notations. The extent to which techniques for accomplishing such retrieval may be applied usefully to a file comprising the universe of chemical compounds is the subject of considerable interest and study.

Special typewriters have been devised whereby structural formulas may be coded directly on punched tape and also stored in the memory of a computer in the form of a matrix (a connection table of atoms) that can be searched at any future time on an atom-by-atom basis. This technique permits retrieval of compounds on a highly intimate structural basis that need not involve either nomenclature or the above-mentioned notations. Auxiliary devices exist for regenerating the actual structural formulas of retrieved compounds either by actual printout or by display on a computer monitor screen.

Table 25-1. Illustrations of Notation Brevity

DESCRIPTIVE CAS NAME	SMILES NOTATION
1-Chloro-3-methylbutane	ClCCC(C)C
4-Aminobenzoic acid	Nc1ccc(C(=O)O)CCl
1-Naphthalenemethanol	OCc1c2ccccc2cc1

Organic Chemical Literature

The constantly accelerating rate of research and development during the past five decades has created severe literature problems, not only in the areas of basic chemistry but also in the other fields of science and technology where chemical information is primarily applied, rather than generated. The history of *Chemical Abstracts* (*CA*) illustrates the magnitude of this so-called "information explosion." Commencing in 1906, the Chemical Abstracts Service (CAS) required 32 years for *CA* to produce its first million abstracts (1938), but only 17 years for the second million (1955), 8 years for the third million (1963), 6 years for the fourth million (1969), 5 years for the fifth million (1974), and somewhat less than 5 years for the sixth million (1979). By late 1983 the seventh million was surpassed, and the 8-million mark was reached in early 1987. Over 10 million abstracts were published by the end of 1992. One prediction suggests 20 million abstracts will be achieved by the year 2005.

Currently, the volume of chemical literature is so great that many libraries simply do not have enough shelf space to accommodate bound volumes and have resorted to microfilming, microfiche or, more drastically, cancellation of hardcopy in favor of electronic journals. More important is the fact that selective retrieval of information from the hardcopy literature has become an extremely arduous task. As a consequence, various industrial, academic, and governmental institutions (several pharmaceutical firms actually pioneered the effort) have developed computerized systems of storage and retrieval of those kinds of chemical information pertinent to their specific interests.

Currently, *Chemical Abstracts* may be searched via *SciFinder* or *SciFinder Scholar* and information may be found at the website *www.info.cas.org*. This facility allows a very rapid and thorough search of CAS to date; the current information is available on computer even before the printed copy reaches the subscriber. The *Institute for Scientific Information* (ISI) in Philadelphia also has computerized its abstract journal, *Index Chemicus,* a text and substructure searchable database which has several million compounds in its registry, and is adding new compounds at a rate of about 200,000 per year (See *www.isinet.com*.) Computer programs are available to customers that provide the capability to search and retrieve compound data either on the basis of structural features, or properties, applications, and bibliographic information.

The huge and continuing flood of published literature also has taxed severely the abilities of abstracting services to keep current. The magnitude of the task is illustrated by the experience of CA, which shows that the approximate number of papers and patents abstracted annually increased from 50,000 in 1950 to 120,000 in 1959; 230,000 in 1968; 400,000 in 1973; over half a million in 1978; approached 750,000 in 1983; and exceeded 1 million in 1988. The lag between publication of original articles and that of their abstracts has been sufficiently severe to foster the production of various so-called "current awareness tools" and specialty publications such as *Index Chemicus* and *Current Contents of ISI* and *Chemical Titles, Chemical-Biological Activities* (CBAC), *Polymer Science and Technology* (POST), *Basic Journal Abstracts* (BJA), and *CA Condensates* of CAS; which also are computer-based publications.

ORGANIC PHARMACEUTICALS

The contrast between the drugs of today and those of yesterday is a dramatic one in several respects. A century ago, humans relied almost exclusively on nature to produce the organic drugs they needed, and the contributions of pharmacy were confined largely to the preparation of extracts, tinctures, or other dosage forms of the crude drugs, and to the isolation of active principles, especially alkaloids and glycosides.

Synthetic drugs began to appear at a noticeably accelerated rate in the 1920s, and this generally is attributed to the very large expansion of the American chemical industry fostered by World War I. Many observers view the advent of the sulfa drugs in the early 1930s as the beginning of the modern era of synthetics.

The great majority of new basic drugs are distinct organic chemical compounds. Most of these are products of synthetic organic chemistry, although some, such as taxol, ACTH, and many of the antibiotics, hormones, and anticancer drugs are products of natural origin. Even with drugs of the latter group, however, the chemist has played a very important role in devising processes to produce them economically, not only in the large quantities required, but also in a sufficient state of purity. He also has succeeded in the deliberate chemical alteration of these naturally occurring compounds and produced derivatives that are either more potent or superior in some other respect (eg, dehydrocholic acid, dihydroergotamine, fluorocorticosteroids, semisynthetic penicillins, methyltestosterone).

Such molecular modification of known pharmacodynamic compounds, both natural and synthetic, constitutes one of the main kinds of research effort in the field of chemotherapy. Although it is true that such effort frequently results in cluttering the market with drugs that may not be superior to those being imitated, nevertheless, a critical review of the results achieved over the past half century provides abundant evidence that the effort yields a gratifying percentage of new, highly beneficial drugs (see Chapter 28). Many of the new admissions to the official compendia are of such genesis.

Chemical and Pharmacological Classifications

During the early years of the modern era of synthetic organic pharmaceuticals, it was common to classify these new drugs on a chemical basis. This was logical, not only because they were fundamentally the products of chemical research but also because the sciences of pharmacology and biochemistry were still in their early stages of development. Indeed, the ever-increasing need for more precise knowledge concerning the efficacy and safety of new drugs has fostered, to a significant degree, the rapid growth of these sciences to their present impressive status, and will undoubtedly continue to do so in the future. The most comforting result is that these complementary efforts continuously are providing medical science with better tools and knowledge to the end that effective prevention and treatment of human physiological and psychological ills constantly are becoming more and more of a science and less and less of an art.

The guiding hypothesis underlying all efforts to classify organic pharmaceuticals on a chemical basis is simply that some correlation will exist between the chemistry of the compounds and their actions and uses as medicinal agents. Early efforts to discover useful correlations were based largely on gross structural considerations with particular emphasis on the presence and location of chemically active (functional) groups. In a more sophisticated form, such efforts continue today, and the net result has been the accumulation of a very large body of knowledge on the broad subject of drug action. This knowledge materially strengthens the belief that the pharmacodynamics of drugs ultimately will be explicable in terms of their chemical characteristics. It also points indisputably to the fact that a complete understanding of the mechanisms of drug action is far in the future and that it will involve much more information than presently can be visualized from structural formulas and molecular models. (Refer to Chapter 28, *Structure-Activity Relationships and Drug Design*.)

It has become clear that the pharmacological actions of drugs must be viewed as functions of the *total* molecules. For example, all barbituric acids contain the malonylurea fragment, but the relative actions of the different barbiturates vary widely with respect to quantitativeness, onset time, and duration, depending upon substituents at the 1, 3, and 5 positions (Chapter 80, *Sedative and Hypnotic Drugs*). The official sulfa drugs provide another example. The antibacterial portion common to all sulfas is the parent compound sulfanilamide, but

chemical alterations at the N^1 and N^4 positions produce derivatives that differ importantly in their actions and chemotherapeutic applications.

Dependence of pharmacological activity on *total* molecular structure commonly is evident with drugs that are polyfunctional from a chemical viewpoint. The sulfa drugs provide a good example of this as elimination of either the amino or sulfonamido portions, or even a change in their relative positions, results in loss of bacteriostatic activity. Similarly, aspirin loses its analgetic action if either its carboxyl or acetoxy group is removed completely or if the relation of these groups is other than *ortho.*

Similar dependence is common in the area of stereochemistry. Thus, the *trans* form of diethylstilbestrol is estrogenically potent whereas the *cis* form is not. This is reminiscent of the α- and β-forms of estradiol, the latter being about ten times as potent as the former. As an example involving diastereoisomers, the widely different mydriatic and pressor potencies of ephedrine and pseudoephedrine might be cited. Similar differences in physiological activity also are commonly observed between enantiomorphs. Thus, the D- and L-ephedrines differ markedly in mydriatic and pressor potencies; the D- forms of the α-amino acids are vastly inferior to the L- forms as nutrients, and (−)-epinephrine is more than 20 times as potent a sympathomimetic agent as the (+)-form.

From the preceding discussion, it is clear that difficulties may be encountered whenever one attempts to classify organic drugs on a chemical basis and obtain a system that simultaneously separates these drugs on a pharmacological basis. As will be seen in subsequent parts of this text, drugs that fall into the same chemical category often display, collectively, quite a number of different actions. Conversely, drugs of widely different chemical characteristics frequently provide the same kind of action when used as medicinal agents. Since, from a practical viewpoint, these agents are important because of the actions they provide (irrespective of their chemical composition), in subsequent chapters of this text drug monographs are grouped and presented on a pharmacological basis.

HETEROCYCLES PRESENT IN OFFICIAL PHARMACEUTICALS

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. Numerous examples occur, among the carbohydrates, essential amino acids, vitamins, alkaloids, glycosides, and antibiotics. The presence of heterocyclic structures in such diverse types of compounds is indicative strongly of the profound effects such structures exert on physiological activity, and recognition of this is reflected abundantly in efforts to find useful synthetic drugs. Examples include researches leading to a wide variety of modern drugs such as chlordiazepoxide (tranquilizer), methazolamide (carbonic anhydrase inhibitor), guanethidine (antihypertensive), stanozolol (anabolic), dapsone (leprostatic), cyclophosphamide and thiotepa (antineoplastics), hydrochlorothiazide (diuretic and antihypertensive), imipramine (antidepressant), lucanthone (antischistosomal), and many others.

As is to be expected, this trend in research is reflected in the changing character of the contents of official drug compendia. Intensive research in diverse hetero areas continues to yield new medicinal agents, and Appendix E is designed to portray partially the spectrum of heterocycles presently represented in USP/NF drugs. The classification is patterned after that employed in the *Ring Index* and in *Chemical Abstracts.* The rings are presented in the order of increasing complexity. The boldface figures show the total number of atoms in the rings, and the number of boldface figures indicates the number of rings present in the systems. As an example, the notation 5, 6 indicates a system composed of two rings, one of which contains five atoms while the other one contains six atoms. The notations, such as C_3NS-C_6, portray the kind and number of atoms present in the ring or rings. Associated with each of these formulas are the graphic formulas and *Ring Index* names[1] of the individual heterocycles and, in italics, one or more examples of official drugs (or the portions of them) containing these heterocycles.

Structures and numbering schemes[2] are according to the *Ring Index* and thus do not portray any inherent features of stereospecificity.[3] It will be observed that some of the names for the heterocycles are trivial (eg, pyrimidine, nortropane) while others are rigidly systematic. Trivial names are employed in the table wherever advisable; ie, wherever, through continued use, they have become recognized by chemists (as reflected by IUPAC adoption and *Chemical Abstracts* indexing) as denoting the structures to which they refer. In all other instances, systematic names must be used to distinguish between the heterocycle of interest and its isomeric forms. Presentation is exclusively on the basis of the *most complex ring "system"* containing the hetero atom or atoms; the term "*system*" meaning either a single ring or a combination of rings of the fused, bridged, or spiro types. For example, quinine is presented *only* as a quinoline derivative and *not* also as a pyridine derivative, even though quinoline also is a benzopyridine. Similarly, caffeine is presented only as a purine derivative and not as either a pyrimidine or an imidazole derivative, even though purine also is an imidazopyrimidine.

In a complete presentation of this type, drugs containing two or more *separate* hetero ring systems would appear under each of the systems; eg, quinine would emerge both as a quinoline and quinuclidine derivative. Wherever possible, only that portion of the official title is used that embraces the heterocycle; eg, thiamine is used instead of thiamine hydrochloride.

The final volume (IV) of the *Ring Index* was published in 1964 and index numbers are no longer assigned to ring structures by CAS. Identifiers for all compound types (including ring systems) have been organized into a *Parent Compound Handbook,* published by CAS, which consists of the following index categories.

Parent Name—This includes the names of all parent compounds and undefined natural products arranged in alphabetical order. Complex parent names are permuted so that root terms, buried in the names, may be located.

Parent Formula—Compounds are arranged according to the Hill system (carbon first, hydrogen second, with other elements following in alphabetic order), but omitting hydrogen atoms in the molecular formula. Ring systems are grouped in the same fashion as the *Ring Index* (see Appendix E) under the appropriate molecular formula.

Registry Number—These are arranged in ascending CAS registry number order with associated *Parent Compound Identifiers.*[4]

Stereoparent—This consists of CAS *Index Parents* whose names imply stereochemistry and whose structures are known. The arrangement is alphabetical with *CA* references for undefined or partially defined natural products.

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[1]Heterocyclic structures often are synthesized actually or theoretically by relatively simple chemical operations such as condensation or dehydrogenation of aliphatic structures. Because of this, many authors prefer to name such compounds in a manner designed to disclose the relationship to the aliphatics, rather than employ *Ring Index* or *CAS* nomenclature, as is used in Appendix D

[2] Extreme caution must be exercised in interpreting position numbers (locants) as given the same compound by different texts, reference works or authors. The situation often exists in which two different numbering schemes, through long-continued usuage, have become established firmly for a particular ring system. This leads to the use of different numbers as locants in an otherwise identical pair of names for the same compound. Also, authors frequently indulge in the reprehensible practice of inventing their own numbering schemes.

[3]The *Ring Index,* 2nd ed, Washington DC: American Chemical Society, 1960 and supplements. Also, for each annual, quinquennial and decennial Index to *Chemical Abstracts*.

[4]An identifier consists of a 5-letter code through which an entry may be found in the Parent Compound File. Each section of this file is assigned a range of identifiers bt which the type of parent may be recognized. The ranges are:

BBBBB to BPZZY	Cage parents
BQBBR to BZZZP	Acyclic stereo parents
CBBBC to DZZZR	Cyclic stereo parents
FBBBF to ZZZZK	Ring parents

Ring Analysis—This includes ring systems only, arranged by the classical *Ring Index* system and states the *CA* name and *Parent Compound Identifier.*

Ring Substructure—Rings are listed by;

A *component ring formula* for each individual ring system listed in the *Ring Analysis Index,* arranged according to the Hill system, but not including hydrogen atoms. All entries are permuted to allow searching on any atom.

The *current CA index name* of a ring parent and cyclic stereoparent; a *Parent compound Identifier*.

ACIDS AND BASES

Organic pharmaceuticals are often complex molecules that have a variety of acidic and basic functional groups. The behavior of these groups in an aqueous environment will influence the activity of the drug, its transport through the body and its passage from one body compartment to another. There are two main theories of acids and bases, the *Brønsted* theory and the *Lewis* theory. According to the Brønsted theory an acid is a group that can donate a proton (a hydrogen ion), and a base is a group that can accept (bond to) a proton. Because a proton has no electrons, the base must be able to provide a pair of electrons to form a new bond. A Lewis acid is a group that can accept an electron pair and therefore must have an empty orbital. Groups that can donate an electron pair are termed *Lewis bases.* In this chapter the discussion will focus on Brønsted acids and bases. See also Chapter 17 *Ionic Solutions and Electrolytic Equilibria.*

Groups which function as acids must have a proton that can be removed in the presence of a base. In the laboratory extremely strong bases can be used in nonaqueous solvents to remove protons from alkyl groups and aromatic rings. Although such reactions are extremely important for drug synthesis, the concern of this chapter is with drugs in an aqueous environment. In water, the strongest base that can exist is hydroxide ion, OH^-, while the strongest acid is the hydrated proton or hydronium ion, H_3O^+. Although there are several exceptions, most hydrogen atoms bonded to carbon are not sufficiently acidic to be removed in aqueous solution. In general hydrogen atoms bonded to O, N, S, and sometimes P (in general, any electronegative atom) are potentially removable in aqueous solution. When an acid donates a proton, a new species called the *conjugate base* of the acid is formed.

$$\underset{\text{acid}}{CH_3COOH} \overset{K_a}{\rightleftharpoons} \underset{\text{conjugate base}}{CH_3COO^{\ominus}} + H^{\oplus}$$

which has a charge one unit less than that of the acid from which it is derived. Thus, acetic acid, which is electrically neutral, dissociates to a proton and its conjugate base, acetate ion, which has a charge of −1. An equilibrium is established between the acid and its conjugate base. The equilibrium constant, which is known as the acid dissociation constant (K_a), is a property of the acid in question. Because K_a values generally are exponential numbers, it is convenient to use $-\log K_a$ which is referred to as the pK_a of the acid. In water, the pK_a scale runs from 0 to 14 with the lowest values corresponding to the strongest acids. Refer to Chapter 17 for a more extensive treatment of this concept.

Basic groups require a pair of electrons, which are used to bond with a proton. This electron pair can be either an unshared pair or a formal negative charge. Bases such as ammonia or amines bond with protons using the lone unshared pair of electrons on the nitrogen atom. Other bases, such as hydroxide, use the electron pair made available by dissociation of the cation, to bond with protons. When a neutral base accepts a proton its charge increases by one unit and a new species is formed, called the *conjugate acid* of the base.

$$\underset{\text{base}}{:NH_3} + H^{\oplus} \overset{K_b}{\rightleftharpoons} \underset{\text{conjugate acid}}{NH_4^{\oplus}}$$

Ammonium ion (+1 charge) is the conjugate acid of ammonia; water (0 charge) is the conjugate acid of hydroxide ion. The equilibrium constant for base dissociation is called the K_b of the base. In water, the pK_b scale extends from 0 to 14 with low values representing the strongest bases. There is a relationship between the pK_a of an acid and the pK_b of its conjugate base in water.

$$pK_a \text{ (acid)} + pK_b \text{ (conjugate base)} = 14$$

A similar relationship holds for bases and their conjugate acids.

$$pK_b\text{(base)} + pK_a\text{(conjugate acid)} = 14$$

Acids are in equilibrium with their conjugate base forms. One of these species will be charged and the equilibrium ratio, therefore, will determine the extent to which the molecule is ionized in solution. This has profound implications in medicinal chemistry because the extent of ionization of a drug in the body will affect its transport from one compartment to another. Examination of the expression for acid dissociation shows that the equilibrium constant

$$K_a = [A^-][H^+]/[HA]$$

Taking the logarithm of both sides of the equation gives

$$\log K_a = \log [A^-] + \log [H^+] - \log [HA]$$

Multiplying both sides of the equation by −1 gives

$$-\log K_a = -\log [A^-] - \log [H^+] + \log [HA]$$

Substitution of pK_a for $-\log K_a$ and pH for $-\log [H^+]$ gives

$$pK_a = pH + \log [HA]/[A^-]$$

This is known as the Henderson–Hasselbalch equation and gives the relationship between the pK_a of an acid[5] and the ratio of its acid form to conjugate base form at a given pH. *It is important to remember that while pK_a is a property of the molecule, pH is a property of the medium (solvent).* In this case (for electrically neutral acids) the ratio $[HA]/[A^-]$ is the ratio of [nonionized]/[ionized] species.

A more general form of the equation can be expressed as

$$pK_a = pH + \log [\text{acid form}]/[\text{conjugate base form}]$$

This is easy to remember because the *base* goes in the *base*ment. For charged acids, such as conjugate acids of amines, the equation appears as

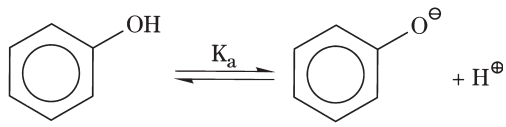
$$pK_a = pH + \log [BH^+]/[B]$$

Here, the ratio $[BH^+]/[B]$ equals the ratio of [ionized]/[nonionized] species.

The Henderson–Hasselbalch equation allows for calculation of the percent ionization of an acid at a given pH. This can be calculated as

$$\%\text{ ionization} = 100\,[\text{ionized}]/[(\text{ionized} + \text{non-ionized})]$$

An example of a Henderson–Hasselbalch calculation using phenol as the acid at pH 7.



phenol **phenolate ion**

[5]In medicinal chemistry only pK_a is recognized to eliminate confusion. Those compounds with a pK_a greater than pK_w are bases; the greater the pK_a, the stronger the base. Henceforth, only pK_a will be used.

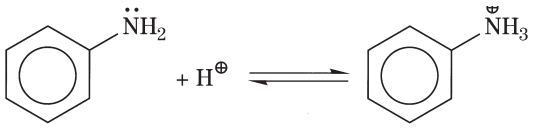
pK_a (phenol) = 9.9
$9.9 = 7 + \log [PhOH]/[PhO^-]$
$2.9 = \log [PhOH]/[PhO^-]$
$794 = [PhOH]/[PhO^-]$

Thus, the ratio of phenol to phenolate ion (PhO^-) at pH 7 is 794:1, the compound is largely non-ionized. The percent ionization is calculated to be

$$\% \text{ ionization} = 100[1/(1 + 794)]$$

$$\% \text{ ionization} = 0.126\% \text{ at pH } 7$$

A second example is provided for the extent of ionization of aniline at pH 7. Aniline ($PhNH_2$) is a base with a pK_a of 4.6 for the anilinium ion ($PhNH_2^+$). Using the Henderson–Hasselbalch equation gives



aniline ailinium ion

$4.6 = 7 + \log [PhNH_3^+]/[PhNH_2]$
$-2.4 = \log [PhNH_3^+]/[PhNH_2]$
$0.004 = [PhNH_3^+]/[PhNH_2]$

The ratio of ionized to non-ionized aniline at pH 7 equals 1:251. The percent ionization at pH 7 is

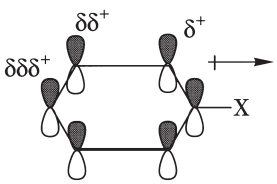
$$\% \text{ ionization} = 100\,[1/(1 + 251)]$$

$$\% \text{ ionization} = 0.\,4\% \text{ at pH } 7$$

Some compounds have several acidic or basic groups or a combination of acidic and basic groups. In these cases, the pK_a of the strongest acid is used for Henderson–Hasselbalch calculations because this is the group that will dissociate most readily. It also should be recognized that compounds that possess quaternary ammonium groups (N attached to four alkyl or aryl groups but not hydrogen) have a permanent +1 charge which is unaffected by the pH of the medium. Such compounds will *always* be 100% ionized and calculation of the extent of ionization of the molecule is unnecessary.

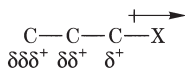
It was stated previously that in an aqueous environment hydrogen atoms attached to O, N, S, or P may be acidic and that an equilibrium is established between the acid form and its conjugate base. Groups that stabilize (lower the energy of) the conjugate base will drive the equilibrium farther to the right and thereby increase the strength of the acid. Such groups stabilize the conjugate base by providing a mechanism for the dispersal of any developing negative charge. Electronic effects from functional groups will therefore have an effect on the strength of nearby acidic and basic sites.

The electronic effects of functional groups can be divided into *field*, *inductive*, and *resonance* effects. The nature of these effects and how they are balanced, is the deciding factor for the type of electronic effect expressed by an individual functional group. *Field effects* are through-space effects on polarizability due to electronegativity differences.



field effect

Polarizability is the ease of distortion of the electron cloud. Attachment of a highly electronegative atom to a system will draw electron density toward that atom, thereby rendering other portions of the molecule positively charged. Field effects tend to decrease with increasing distance. *Inductive effects* are the polarization of bonds as a result of electronegativity differences.



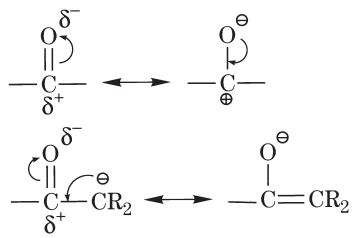
inductive effect

Thus an electronegative atom polarizes the bond attached to it by increasing the electron density in its vicinity. The opposite side of that bond acquires a degree of positive charge. This in turn polarizes the adjacent bond, and so on. These effects, which are transmitted through bonds, also decrease with distance from the electronegative atom.

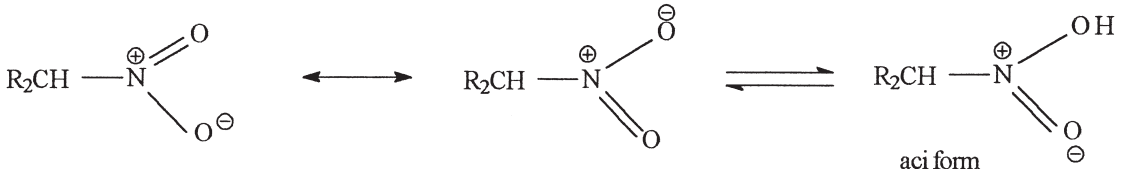
Resonance effects involve the actual movement of electrons through a π-bond system. The π-bond system acts as a conductor of electrons, much as wires conduct the flow of electricity, which can be moved in either direction depending on the needs of the system. This is especially prominent in conjugated systems (those with alternating double and single bonds). The movement of electrons through a conjugated system allows for charges to be dispersed over several atoms (delocalization). This lowers the energy of the system relative to an isolated charge. In contrast to field and inductive effects, resonance effects decrease much more slowly with distance. Stabilization increases as the number of atoms over which the charge is dispersed increases. Resonance effects generally contribute more extensively to the overall electronic effect of a functional group than do field or inductive effects.

Among the functional groups which are classified as being electron-withdrawing are the carbonyl-based groups (aldehydes, ketones, esters, carboxylic acids, amides, etc), nitro, nitrile (cyano), sulfinyl, sulfonyl, halo, quaternary ammonium, trifluoromethyl, vinyl, ethynyl, and phenyl. The relative contributions of field, inductive, and resonance effects to the overall electronic effect of these functional groups is discussed below.

The carbonyl group (=C=O) is an integral part of a large number of functional groups such as ketones, carboxylic acids, amides, esters, and carbamates. Field and inductive effects within this bond system arise because of the electronegativity difference between oxygen and carbon. Electrons in both the σ- and π-bonds are polarized so that the greater density occurs near oxygen. The carbon atom acquires a partial positive charge which can attract excess electrons from neighboring groups. If a negative charge develops adjacent to a carbonyl group, that charge is stabilized not only by electrostatic effects, but also by resonance, which can delocalize the negative charge onto the carbonyl oxygen.



Another powerful electron-withdrawing group is the nitro group ($-NO_2$). Although this group is electrically neutral overall, the nitrogen always carries a positive charge that is balanced by a negative charge on one of the oxygen atoms. Two resonance structures can be drawn which distribute the negative charge over both oxygen atoms. The positively charged nitrogen can stabilize an adjacent negative charge by electrostatic attraction as well as by resonance.



A nitrile possesses a carbon–nitrogen triple bond. The electronegativity difference between carbon and nitrogen results in carbon having a partial positive charge. The larger effect of this functional group however, comes from resonance stabilization of an adjacent negative charge onto the nitrogen.

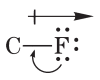
The difference between a sulfinyl and a sulfonyl group is that the former has one and the latter two S=O bonds. A major resonance form of the sulfinyl group has a S—O single bond with a formal positive charge on sulfur and a negative charge on oxygen. Sulfonyl has two such resonance structures. The preference for these structures over those with double bonds is a result of the relative inefficiency of *p*-orbital overlap due to the difference in size between sulfur and oxygen. Despite this, however, resonance stabilization of an adjacent negative charge does contribute to the electron-withdrawing capability of these functional groups.

sulfinyl

sulfonyl

The halides (F, Cl, Br, I) are much weaker electron withdrawing groups than might be expected. Fluorine, which is the most electronegative element, exerts strong field and inductive effects on an adjacent carbon atom. Additional electron density cannot be withdrawn by resonance because there are no available vacant orbitals. The lone-pair electrons on fluorine can however, be donated by resonance. As a result of this push–pull effect, the resonance and field (+ inductive) effects nearly cancel and fluorine usually exerts only a small electron-withdrawing effect.

electron-withdrawal by
field and inductive effects



electron-donation by
resonance

Chlorine is less efficient at donating electrons by resonance because of its size relative to carbon. It does exert substantial field and inductive effects, and therefore behaves as an electron-withdrawing group. The electronegativity difference between carbon and bromine is small, and electron-donation by resonance is inefficient. As a result, bromine generally behaves as a weak electron-withdrawing group. Iodine is weaker still because of decreased field and inductive effects.

Functional groups such as quaternary ammonium and trifluoromethyl exert their electronic effects primarily through field and inductive effects. The quaternary ammonium group has a permanent positive charge on nitrogen, which stabilizes an adjacent negative charge electrostatically. Because there are no lone-pair electrons or vacant orbitals, resonance with this group is not possible. Direct resonance with a trifluoromethyl group does not occur. The three highly electronegative fluorine atoms exert multiple field and inductive effects on the carbon atom to which they are attached, which can then in turn stabilize an adjacent negative charge in a similar fashion.

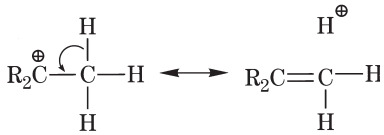
Unsaturated groups such as phenyl, vinyl or ethynyl can function as electron withdrawing groups by delocalizing any excess electron density throughout the π-system.

Functional groups, which are classified as being electron donating, include alcohols, ethers, amines, and alkyl groups. Each of these will stabilize a developing positive charge and, when attached to basic atoms, tend to increase the association constant.

Alcohols and ethers have similar inductive effects to those present in carbonyl groups but experience decreased field effects due to the lack of a polarizable π-bond. Although carbonyl groups have the ability to delocalize excess electron density onto the oxygen, this is not possible for alcohols and ethers. Unshared electrons on the oxygen, however, can be delocalized by resonance to help stabilize a developing positive charge. In the process a new C=O bond is formed and the charge is delocalized onto oxygen. Although it is unfavorable to place a positive charge on an electronegative atom, this is compensated by the formation of a new bond. The predominance of resonance over field and inductive effects is observed by the fact that alcohols and ethers behave as electron-donating groups.

A similar situation exists for amino groups where the lone-pair electrons can be donated to form a C=N bond and thereby delocalize an adjacent positive charge onto the nitrogen. Because nitrogen is less electronegative than oxygen, it can better tolerate the charge. Amino groups are generally stronger electron donating substituents than either alcohols or ethers.

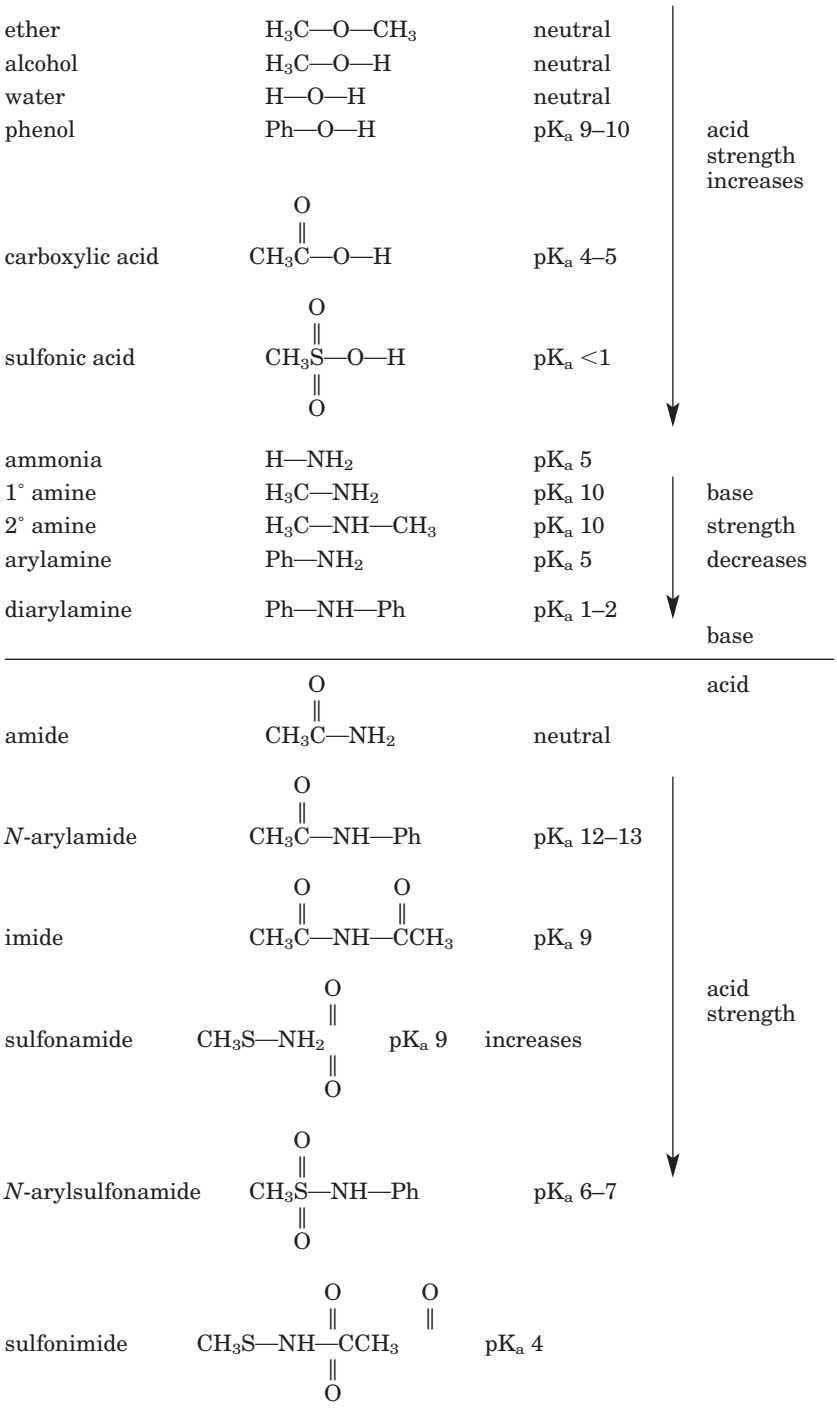
Alkyl groups, unlike alcohol or amino groups, do not have lone-pairs of electrons to donate. Instead, δ-bonding electrons, especially those from C—H bonds, can be donated in a process known as *hyperconjugation,* or *no-bond resonance.* Hyperconjugation allows an adjacent positive charge to be delocalized by resonance onto a proton. Such effects are greatest for methyl groups because the charge can be delocalized onto three different hydrogens. Methylene groups (CH_2), in contrast, allow for charge delocalization onto only two hydrogens.



hyperconjugation

It has been observed that in the absence of other factors, certain electron-withdrawing groups affect pK_a values of oxygen- and nitrogen-based functional groups in a predictable manner. A knowledge of such effects allows first-order predictions to be made of acid and base strength for a wide range of functional groups.

Some functional groups can be thought of as being derived from water by replacement of one or both hydrogens. Alcohols, for example, can be derived from water by replacement of one hydrogen by an alkyl group. Replacement of hydrogen by an aryl group (aromatic ring) gives a phenol. If both hydrogens are replaced by alkyl or aryl groups, an ether is formed. Water and simple alcohols are neutral (pK_a 14) with respect to their acid–base properties. Ethers are neutral by virtue of the fact that they have no hydrogen to donate. In contrast, unsubstituted phenols behave as moderate to weak acids in aqueous solution with pK_a values in the range of 9 to 10. Replacement of H by an aryl group increases acid strength relative to water by 4 to 5 pK_a units. Substitution by an alkyl group however, has a negligible effect on pK_a. If one of the hydrogens of water is replaced by an acyl group (carbonyl), a carboxylic acid is formed. Such compounds typically have pK_a values in the range of 4 to 5. An acyl group therefore lowers the pK_a by 9 to 10 pK_a units. Substitution of a sulfonyl group for H increases acidity by 14 to 15 pK_a units. The resulting compounds, called sulfonic acids, are nearly as acidic as sulfuric acid in aqueous solution. A listing of the *approximate* pK_a values for a number of organic compounds is presented below.



Electron-withdrawing substituents, when attached to a basic group, will decrease base strength by making it more difficult to donate lone-pair electrons for bonding with protons. Some nitrogen-containing functional groups can be thought of as being derived from ammonia by replacement of one, two, or three hydrogen atoms. Ammonia has a pK_a of about 9 and behaves as a moderately strong base in aqueous solution. Primary, secondary and tertiary alkyl amines can be formed from ammonia by replacement of one, two or three hydrogens, respectively, by alkyl groups. Such compounds have approximately the same base strength as ammonia in aqueous solution, indicating that the alkyl groups have little effect on pK_a.

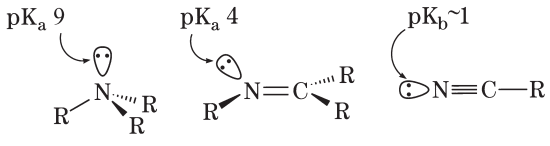
Replacement of one hydrogen of ammonia by an unsubstituted aryl group gives a very weak base with a $pK_a \approx 4$. A second aryl group further lowers the pK_a to about 2. A single aryl substituent therefore has an effect ($\approx$ 5 pK units), while a second such group displays an effect that is half again as great (2 to 3 pK units). The effect of a third group is not as easily quantified because of nonlinear effects such as steric hindrance.

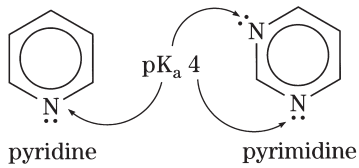
Replacement of one of the ammonia hydrogen atoms by an acyl group gives an amide. Such compounds are virtually neutral in aqueous medium, suggesting that the acyl group decreased the pK_a by 3 to 4 units, the same magnitude as it increased acid strength in the water model. The electron withdrawing carbonyl group restrains the lone pair electrons of the nitrogen atom to such an extent that it can no longer abstract protons.

Substitution of a second acyl group on ammonia gives an imide. Imides behave as acids in aqueous solution with pK_a values of about 9. The second electron withdrawing group not only makes donation of lone pair of electrons difficult, but weakens the N—H bond to the point that dissociation can occur. The resulting conjugate base is stabilized by the two carbonyl groups. It is to be noted that the second acyl group had about half the effect (5 pK units) of the first. A sulfonyl group, when substituted for hydrogen on ammonia, gives a sulfonamide, which is acidic with a pK_a of 9 to 10. A single sulfonyl group therefore alters the pK by 14 to 15 units.

Estimates of pK_a values can be made for functional groups derived from the water and ammonia systems. The data seen in Table 25-2 are useful. When two different substituents are attached to nitrogen, the group having the larger effect is taken as the first group and that with the smaller effect as the second group. Thus, *N*-methylaniline is calculated to have a pK_a of about 4 (using the first group value for the aryl substituent) and not pK_a of 5 to 6, as would be obtained if the methyl group were taken for the first group. *It is important to realize however, these estimates exclude steric and other electronic effects and may vary from the actual (experimental) values by several pK units.*

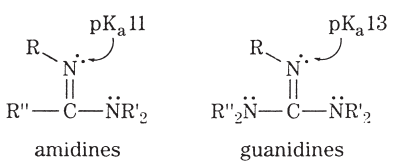
Hybridization also can affect base strength as observed in the series amine, imine, nitrile where the hybridization of nitrogen changes from sp^3 to sp^2 to sp. Although amines function as moderately strong bases ($pK_a \approx 9$), imines are much weaker with pK_a values near 4. Nitriles are essentially neutral ($pK_b \sim 1$). The effect of hybridization is to shorten the bond length and the general trend is that bond length decreases and electronegativity increases as the percent of *s*-character of the bond increases (25% for sp^3; 33% for sp^2; and 50% for sp). The shorter bond lengths and higher electronegativity associated with the nitrogen atom of nitriles results in the lone-pair being held much closer to nitrogen than it is for imines or amines. Since, basicity is a function of how readily the lone-pair is shared, it is reasonable that amines would be the most basic, and nitriles the weakest bases, within this series. Aromatic nitrogen atoms, such as found in pyridine and pyrimidine, are also sp^2 hybridized and are similar to imines with regard to their base-strength ($pK_a \approx 4$).





Two functional groups that are common in pharmaceuticals are amidine and guanidine. Refer to Appendix A of this chapter for a listing of functional groups and names. These can be considered as amino derivatives of imines. Amidines, which have a single amino group attached to the imine carbon, are strong bases with pK_a values near 11. Guanidines are even more basic ($pK_a \approx 13$) and have two amino groups attached to the imine carbon. The higher basicity of these functional groups as compared to imines is due to two factors: (1) the effect of the electron-donating amino nitrogen(s), which can increase electron density at the imino nitrogen by resonance, and (2) the conjugate acid form is stabilized by charge delocalization among each of the nitrogens again as a result of resonance. These effects are more pronounced for guanidines, which have an additional resonance structure available. In these functional groups it is the doubly-bound nitrogen that serves as the basic site. The single-bonded nitrogen is neutral due to the electron-withdrawing effect of the double bond and the lack of resonance stabilization for the conjugate acid form of this nitrogen. It is important to note, however, that if the amino nitrogen carries at least one hydrogen, tautomeric structures are possible in which either nitrogen can. be bonded to hydrogen, with the other then becoming the basic site.

Tautomers are structures that differ in the placement of one small group or atom, usually hydrogen. In amidines, hydrogen can shift rapidly back and forth between the two nitrogen atoms (with the consequent relocation of a pair of electrons) unless structural features favor a particular tautomeric structure.



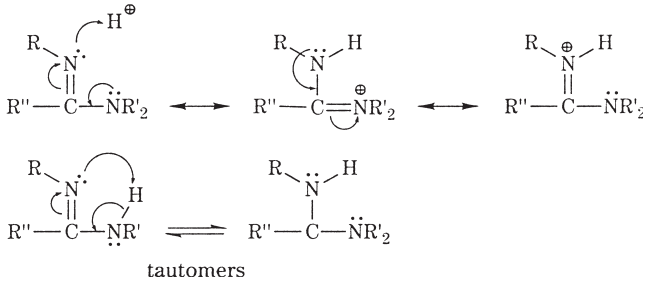
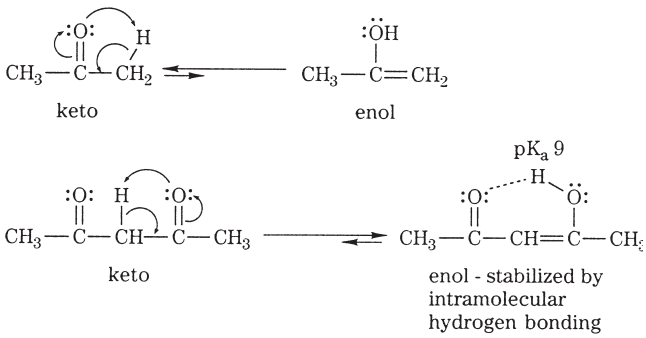


Table 25-2. pK Effect of Functional Groups as Substituents on H_2O and NH_3

FUNCTIONAL GROUP	EFFECT AS FIRST GROUP, PK UNITS	EFFECT AS SECOND GROUP, PK UNITS
H,Alkyl	0	0
Aryl, vinyl	4	2–3
Acyl	10	5
Sulfonyl	15	7–8

Another situation where tautomerization occurs involves protons on carbons adjacent to a carbonyl group. Ketones, for example, have two tautomeric structures known as the *keto* and *enol* forms. In the enol form, a hydrogen from an adjacent carbon migrates onto the carbonyl oxygen, with concomitant formation of a new C=C bond. The resulting hydroxyl group is acidic (when viewed as water with one hydrogen substituted by a vinyl group, a pK_a of 9 would be predicted). For ordinary ketones however, the equilibrium constant heavily favors the keto form and in aqueous solution ketones behave as neutral compounds. If a second carbonyl group is attached to a carbon with at least one hydrogen the situation changes. In such compounds the equilibrium constant favors a much higher percentage of the enol tautomer due to stabilization by hydrogen bonding with the second carbonyl group. Such 1,3-dicarbonyl compounds behave as weak acids in aqueous solution.



SUMMARY

With the ability of the modern computer to manipulate millions of bits of data in a trice, the prediction of many physical and chemical constants for known and potential chemical entities, solely based on data available in a library of known information has really come to the fore. There exist programs that predict quite accurate values for pK_a, log P (octanol–water partition coefficient), fragmentation patterns for compounds in mass spectra, the interpretation of IR and NMR spectra, and so on, coupled with extensive databases of experimentally derived constants. (One such program may be viewed at http://www.acdlabs.com/.)

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Appendix A Types of Organic Compounds

CLASS	EXAMPLES
Acetals	
RC(H or R)$(OR)_2$ (*cf* Ketals)	$CH_3CH(OCH_3)_2$ acetaldehyde dimethyl acetal (1,1-dimethoxyethane)$(CH_3)_2C(OC_2H_5)$ acetone diethyl acetal (2,2-diethoxypropane)
Acid Anhydrides	
1. Of Monocarboxylic Acids	
RCOOCOR	$(CH_3CO)_2O$ acetic (acid) anhydride
2. Of Dicarboxylic Acids	
RCOOCO	CH_2CH_2COOCO succinic (acid) anhydride
Acid Halides (Acyl Halides)	
RCOX	CH_3COCl acetyl chloride
Acids (Carboxylic) (other acids are listed under their characteristic names, eg, *Sulfonic Acids, Thio Acids,* etc)	
RCOOH	CH_3COOH acetic acid
Acyloins (α-Hydroxy Ketone)	
RCOCH(OH)R	$CH_3COCH(OH)CH_3$ acetoin $C_6H_5COCH(OH)C_6H_5$ benzoin
Alcoholates (Alkoxides)	
ROMetal	C_2H_5ONa
where R is aliphatic or alicyclic	sodium ethylate sodium ethoxide
Alcohols	
ROH	C_2H_5OH
where R is aliphatic or alicyclic	ethyl alcohol (ethanol) $CH_2(CH_2)_4CHOH$ cyclohexyl alcohol (cyclohexanol)

CLASS	EXAMPLE
Aldehydes	
RCHO	CH_3CHO acetaldehyde
Alkoxides (see *Alcoholates*)	
Alkylhalosilanes	
$R(SiH_2)_nX$	CH_3SiH_2Cl methylchlorosilane
where one or more H's may be substituted by additional R's or X's	
Alkylsilanes	
$R(SiH_2)_nH$	CH_3SiH_3 methylsilane $C_2H_5SiH_2SiH_2C_2H_5$ *sym*-diethyldisilane
where one or more H's may be substituted by additional R's	
Alkylsilanols	
Types here illustrated are limited to derivatives of silane; ie, (mono)-silane, SiH_4. There are similar derivatives of the di-, tri-, etc, silanes.	
$RSiH_2OH$ Alkylsilanols; $RSiH(OH)_2$ alkylsilanediols; $RSi(OH)_3$ alkylsilanetriols R_2SiHOH dialkylsilanediols; $R_2Si(OH)_2$ dialkylsilanols R_3SiOH trialkylsilanols	
Alkylsiloxanes	
Various linear and cyclic types. (see *Silicones*). A common linear type consisting of condensation polymers of dialkylsilanediols is shown.	$HO(SiR_2O)_nSiR_2OH$
Amides	
$RCONH_2$	CH_3CONH_2 acetamide
Amidines	
$RC(=NH)NH_2$	$CH_3C(NH)NH_2$ acetamidine

Appendix A Continued

CLASS	EXAMPLES
Amines RN(H or R)(H or R) RNH_2 types = Amino Compounds	CH_3NH_2 methylamine $(C_2H_5)_2NH$ diethylamine $CH_3N(C_2H_5)C_3H_7$ methylethylpropylamine
Amino Acids $R(NH_2)COOH$	$CH_2(NH_2)COOH$ aminoacetic acid
Ammonium Derivatives $[RH_3N]^+X^-$ *where X = OH or a salt anion and any or all H's may be R's. If N is a ring member, specific "ium" nomenclature is employed to denote the heterocycle.*	$[(CH_3)_4N]^+I^-$ tetramethylammonium iodide $[(C_2H_5)_2N^+H_2]Cl^-$ diethylammonium chloride (diethylamine hydrochloride) $[CH{=}CHCH{=}CHCH{=}N^+(CH_3)]Br^-$,1-methyl pyridinium bromide
Anilides RCONHR′ *where NHR′ is derived from aniline* *Note*—If NHR′ is derived from: toluidine xylidine anisidine phenetidine	$CH_3CONHC_6H_5$ acetanilide Compounds are termed: toluidides xylidides anisidides phenetidides
Anils (Schiff bases) RCH=NR	$C_6H_5CH{=}NC_6H_5$ *N*-Benzylideneaniline
Azides (Acyl Azides) $RCON{=}N^+{=}N^-$	$CH_3CON{=}N^+{=}N^-$ acetyl azide
Azido Compounds $RN{=}N^+{=}N^-$	$C_2H_5N{=}N^+{=}N^-$ azidoethane
Azines $R_2C{=}NN{=}CR_2$	$(CH_3)_2C{=}NN{=}C(CH_3)_2$ acetone azine
Azo Compounds RN=NR	$C_6H_5N{=}NC_6H_5$ azobenzene
Azoxy Compounds RN=N(O)R	$C_6H_5N{=}N(O)C_6H_5$ azoxybenzene
Benzils (Aromatic α-Diketones) RCOCOR *where R is aromatic*	*p*-$CH_3C_6H_4COCOC_6H_4CH_3$-*p* *p,p′*-dimethylbenzil
Benzoins (Aromatic α-Hydroxy Ketones) RCH(OH)COR *where R is aromatic*	*p*-$CH_3C_6H_4CH(OH)CO$-$C_6H_4CH_3$-*p* *p,p′* dimethylbenzoin or *p*-toluoin
Betaines $R_3N^+(CH_2)_nCOO^-$	$(CH_3)_3N^+CH_2CH_2COO^-$ β-alanine, trimethylbetaine
Borates (see *Esters*)	
Carbonates (see *Esters*)	
Carbylamines (see Isocyanides; Isonitriles) RNC	C_6H_5NC phenyl { carbylamine, isocyanide or isonitrile
Cynates ROCN	C_6H_5OCN phenyl cyanate
Cyanides (see *Nitriles*)	
Cyanohydrins RC(CN)(OH)(H or R)	$CH_3C(CN)(OH)CH_3$ acetone cyanohydrin

CLASS	EXAMPLE
Diazoamino Compounds (Triazene Derivatives) RN=NNHR	$C_6H_5N{=}NNHC_6H_5$ diazoaminobenzene or 1,3-diphenyltriazene
Diazo Compounds *Type A* RNNX *where X = OH or a salt anion* *Type B* RN=NOMetal (diazoates) *Type C* C(H or R)(H or R)-=$N^+{=}N^-$	$C_6H_5N{=}NCl$ benzenediazochloride $C_6H_5N{=}NONa$ sodium benzenediazoate $CH_2{=}N^+{=}N^-$ diazomethane
Diazonium Compounds $RN_2{}^+X^-$ *where X = OH or a salt anion*	$[C_6H_5N_2{}^+]OH^-$ benzenediazonium hydroxide
Epoxy Compounds $CH_2(CH_2)_nCH_2O$ *where n = zero or greater and any or all H's may be R's*	$\overline{CH_2CH_2O}$ epoxyethane $CH_3\overline{CHCH_2CH(CH_3)O}$ 2,4-epoxypentane
Esters (of Carboxylic Acids) RCOOR	$CH_3COOC_2H_5$ ethyl acetate

Esters (of Inorganic Oxy Acids)

The listing here is intentionally limited to esters of the more important oxy acids of nitrogen, phosphorus, sulfur, boron, silicon, and carbon. In each instance, the type formula shown is for the ester which results from the replacement of all acidic H's by R's. Where more than one R is present, acid esters (ie, esters still containing one or more unreplaced H's) are possible.

Nitrates	$RONO_2$	$C_2H_5NO_3$, ethyl nitrate
Nitrites	RONO	C_2H_5ONO, ethyl nitrite
(Ortho)phosphates	$(RO)_3PO$	$(C_2H_5)_3PO_4$, (tri)ethyl phosphate
Metaphosphates	$ROPO_2$	$C_2H_5PO_3$, ethyl metaphosphate
Pyrophosphates	$(RO)_2PO{-}O{-}PO(OR)_2$	$(C_2H_5)_4P_2O_7$, (tetra)ethyl pyrophosphate
(Ortho)phosphites	$P(OR)_3$	$(C_2H_5)_3PO_3$, (tri)ethyl phosphite
Hypophosphites *cf Phosphonic Acids*	$H_2P(O)(OR)$	$C_2H_5H_2PO_2$, ethyl hypophosphite
Sulfates	$(RO)_2SO_2$	$(C_2H_5)_2SO_4$, (di)ethyl sulfate
Sulfites	$(RO)_2SO$	$(C_2H_5)SO_3$, (di)ethyl sulfite
Orthoborates	$B(OR)_3$	$(C_2H_5)_3BO_3$, (tri)ethyl orthoborate
Metaborates	ROBO	$C_2H_5BO_2$, ethyl metaborate
Orthosilicates	$Si(OR)_4$	$(C_2H_5)_4SiO_4$, (tetra)ethyl orthosilicate
Metasilicates	$(RO)_2SiO$	$(C_2H_5)_2SiO_3$, (di)ethyl metasilicate
Orthocarbonates	$C(OR)_4$	$(C_2H_5)_4CO_4$, (tetra)ethyl orthocarbonate
Carbonates	$(RO)_2CO$	$(C_2H_5)_2CO_3$, (di)ethyl carbonate

CLASS	EXAMPLE
Ethers ROR	$CH_3OC_2H_5$ ethyl methyl ether

Appendix A Continued

CLASS	EXAMPLES
Fluorophosphates (see *Phosphorofluoridates*)	
Glycerides	
$RCOOCH_2CH(OCOR)CH_2$-OCOR	$C_3H_5(C_2H_3O_2)$ or $(CH_3COO)_3$-C_3H_5 glyceryl triacetate or triacetin
Glycols	
$HOCH_2(CH_2)_nCH_2OH$ *where n = zero or greater*	$CH_2(OH)CH_2OH$ ethylene glycol $CH_2(OH)CH_2CH_2OH$ trimethylene glycol
Guanidino Compounds	
$NH_2(C{=}NH)NHR$	$NH_2(C{=}NH)NHC_2H_5$ 1-ethylguanidine
Haloalkylsilanes	
$XR(SiH_2)_nH$ *where one or more of the H's in R may be substituted by additional X's and one or more of silicon hydrogens may be substituted to additional RX groups*	$ClCH_2SiH_3$ (chloromethyl)silane
Halohydrins	
XCH_2CH_2OH *where either or both of the CH_2's may be CHR or CR_2*	$ClCH_2CH_2OH$ ethylene chlorohydrin
Hemiacetals	
RC(H or R)(OR)(OH)	$CH_3CH(OC_2H_5)OH$ acetaldehyde ethylhemiacetal (1-ethoxyethanol)
Hydrazides	
$RCONHNH_2$	$CH_3CONHNH_2$ acetic acid hydrazide
Hydrazines	
RN(H or R)N(H or R)-(H or R)	$C_6H_5NHNH_2$ phenylhydrazine
Hydrazones	
R_2(or RH)$C{=}NNH_2$	$(CH_3)_2C{=}NNH_2$ acetone hydrazone $C_6H_5CH{=}NNH_2$ benzaldehyde hydrazone
Hydrocarbon Halides (Alkyl, Alkylene, Alkylidene, Alkenyl, Aryl, Arylene, etc Halides)	
RX_n *where n = valence of R*	CH_3Cl methyl chloride (chloromethane) $CH_2{=}CHBr$ vinyl bromide CH_3CHCl_2 ethylidene chloride C_6H_5I phenyl iodide (iodobenzene)
Hydroxamic Acids	
$RC(=NOH)OH$	$CH_3CH_2C(=NOH)OH$ propionohydroxamic acid
Hydroxy Acids	
RCH(OH)COOH	$CH_3CH(OH)COOH$ α-hydroxypropionic acid or lactic acid
Hypophosphites (see *Esters*)	
Imides (Carboximides)	
RCON(H or R)CO	$\overline{CH_2CH_2CONHCO}$ succinimide 1,2-ethanedicarboximide
Imidic Acids	
RC(NH)OH	$CH_3C(=NH)OH$ acetimidic acids
Imines	
R═NH	$\underline{CH_3CH_2}{=}NH$ ethylideneimine $\overline{CH_2CH_2NH}$ ethyleneneimine
Iodonium Compounds	
$[R_2I]^+X^-$ *where X = OH or a salt anion*	$[(C_6H_5)_2I]^+Br^-$ diphenyliodonium bromide

CLASS	EXAMPLE
Iodoso Compounds	
RIO	C_6H_5IO iodosobenzene
Iodoxy Compounds	
RIO_2	$C_6H_5IO_2$ iodoxybenzene
Isocyanates	
RCNO	C_6H_5NCO phenyl isocyanate
Isocyanide Dichlorides (Imidocarbonyl Chlorides)	
$RN{=}CCl_2$	$C_2H_5NCCl_2$ ethyl isocyanide dichloride, ethylimidocarbonyl chloride
Isocyanides (see *Carbylamines*)	
Isonitriles (see *Carbylamines*)	
Isothiocyanates (Isosulfocyanates; Thiocarbimides; Mustard Oils)	
RNCS	CH_3NCS methyl isothiocyanate, etc
Ketals	
$R_2C(OR)_2$ (Commonly treated as *Acetals, qv* above)	$(CH_3)_2C(OC_2H_5)_2$ acetone diethylketal (2,2-diethoxypropane)
Ketenes	
RC(H or R)═C═O	$(CH_3)_2C{=}C{=}O$ dimethyl ketene
Keto Acids (monobasic)	
$H(CH_2)_nCO(CH_2)_nCOOH$ *where n = zero or greater and any or all H's may be R's. May also be polybasic.*	CH_3COCH_2COOH 3-oxobutyric acid or acetoacetic acid $HOOCCH_2COCOOH$ ketosuccinic acid or oxalacetic acid
Ketones	
RCOR *where R's are aliphatic or alicyclic. If one or both R's are aromatic, compounds are termed Phenones.*	$CH_3COC_2H_5$ ethyl methyl ketone or 2-butanone $C_6H_5COCH_3$ acetophenone
Lactams	
$\overline{CH_2(CH_2)_nCONH}$ *where n = 2 or more and any or all H's may be R's.*	$\overline{CH_2CH_2CH_2CH_2CONH}$ δ-valerolactam (2-piperidone)
Lactides	
$\overline{CH_2COOCH_2COO}$ *where any or all of the H's may be R's*	$CH_3\overline{CHCOOCH(CH_3)COO}$ 2-hydroxypropionic acid lactide "lactide"
Lactims	
as per lactams except $\underline{CH_2(CH_2)_nCONH}$ becomes $\overline{CH_2(CH_2{}_nC(OH)=N}$	$\overline{CH_2CH_2CH_2CH_2C(OH)=N}$ δ-valerolactim
Lactones	
$CH_2(CH_2)_nCOO$ *where n = 2 or more and any or all H's may be R's*	$CH_2CH_2CH_2CH_2COO$ δ-valerolactone
Mercaptans (see *Thiols*)	
Mercaptides	
RSMetal	C_2H_5SNa sodium ethylmercaptide
Mercaptoles	
$R_2C(SR)_2$	$(CH_3)_2C(SC_2H_5)_2$ acetone diethylmercaptole
Morpholides	
$RCON(CH_2)_2OCH_2CH_2$	$CH_3\overline{CONCH_2CH_2OCH_2CH_2}$ acetomorpholide (4-acetylmorpholine)
Nitrates (see *Esters*)	
Nitriles (Cyanides; Carbonitriles)	
RCN	CH_3CH_2CN propionitrile, ethyl cyanide

Appendix A Continued

CLASS	EXAMPLES
Nitrites (see *Esters*)	
Nitro Compounds RNO_2	CH_3NO_2 nitromethane $C_6H_5NO_2$ nitrobenzene
Nitroso Compounds RNO	C_6H_5NO nitrosobenzene
Organometallic (Metallo-organic) Compounds *Note*—Restricted here to compounds having a direct metal–carbon linkage. Commonest types are: MR_V and $R_{(V-1)}MX$ *where* M = metal functioning with valence v *R = univalent* unsubstituted, or, substituted, hydrocarbon radical *X = univalent anion*	$(CH_3)_2Zn$ dimethylzinc $(C_2H_5)_4Pb$ tetraethyl lead CH_3MgBr methylmagnesium bromide $C_6H_5HgNO_3$ phenylmercuric nitrate; Ag_2C_2 silver acetylide
Osazones [Bis(phenylhydrazones)] (H or R)C(═NNHPh)-C(═NNHPh)(R or H) *where Ph = phenyl*	$C_6H_5C(═NNHPh)C(═NNHPh)C_6H_5$ benzil osazone [Benzil bis(phenylhydrazone)]
Oximes RC(H or R)═NOH	$CH_3CH═NOH$ acetaldoxime $(CH_3)_2C═NOH$ dimethylketoxime (acetone oxime)
Oxo Compounds (see *Aldehydes, Ketones, Quinones, Keto Acids*)	
Ozonides RCH-O-O-CH-R	$CH_3CHOOCHCH_3$ 2-butene ozonide
Peptides (Polypeptides) $NH_2(RCONH)_nRCOOH$	$NH_2(CH_2CONH)_2CH_2COOH$ glycine tripeptide glycylglycylglycine
Peroxides ROO(R or H)	$C_2H_5OOC_2H_5$ ethyl peroxide
Peroxy Acids RC(O)OOH	$CH_3C(O)OOH$ peroxyacetic acid
Phenolates (Phenoxides) ROMetal *where R is aromatic*	C_6H_5ONa sodium phenolate sodium phenoxide
Phenols ROH *where R is aromatic*	*p*-$CH_3C_6H_4OH$ *p*-methylphenol (*p*-cresol)
Phenones (see *Ketones*)	
Phenoxides (see *Phenolates*)	
Phosphates (see *Esters*)	
Phosphites (see *Esters*)	
Phospho Compounds RPO_2	$C_6H_5PO_2$ phosphobenzene
Phosphonic Acids $RPO(OH)_2$	$CH_3PO(OH)_2$ methylphosphonic acid or methanephosphonic acid
Phosphorofluoridates (Fluoro-phosphates) $FPO(OR)_2$	$FPO[OCH(CH_3)_2]_2$ diisopropyl phosphorofluoridate or diisopropyl fluorophosphate
Phosphorus Compounds (General) In addition to the compounds in this listing, phosphorus forms a very large number of types of compounds containing direct linkages between the phosphorus atom and halogens, cyanogen, nitrogen, and sulfur. Many of these contain also phosphorus-oxygen linkages. For a comprehensive presentation of organic compounds containing phosphorus, see the report entitled *Organic Compounds Containing Phosphorus,* which is available from *Chemical Abstracts Service.*	
Phthaleins, simplest type only $\overline{RC(R'OH)_2OCO}$ *where R is o-phenylene, R′ is p-phenylene and either or both may be substituted.*	$o\text{-}\overline{C_6H_4C(p\text{-}C_6H_4OH)_2OCO}$ phenolphthalein
Piperidides $RCON(CH_2)_4CH_2$	$CH_3CON\overline{CH_2CH_2CH_2CH_2CH_2}$ acetopiperidide (1-acetylpiperidine)
Quaternary Ammonium Compounds $[R_4N]^+X^-$ *where X = OH or a salt anion*	$[(CH_3)_4N]^+Cl^-$ tetramethylammonium chloride
Quinones O═R═O *where R is a quinoid cycle*	*p*-O═C_6H_4═O *p*-benzoquinone
Salts (Metal)	Formulas as for the acids except that the acidic H's are replaced by metal equivalent.
Semicarbazones RC(H or R)═NNHCONH$_2$	$(CH_3)_2C═NNHCONH_2$ acetone semicarbazone
Silicates (see *Esters*)	
Silicon Compounds (General) Because of its position in Group IV of the Periodic Table, it is not surprising that silicon enters freely into organic-type chemical combinations. Like carbon, although to a much lesser extent, silicon forms stable chain compounds containing —SiSi— linkages. Compounds which contain hydrogen as the only other element are termed silanes: eg, SiH_4, silane (silicane, silicomethane); Si_2H_6, disilane (disilicoethane) and Si_3H_8, trisilane. Cyclosilanes, $SiH_2(SiH_2)_nSiH_2$ are also well-known. These silicon-hydrogen compounds are analogous to the alkanes and cycloalkanes in the carbon family of compounds. They form various types of derivatives: eg, SiH_3OH, H_2SiO, HSiOOH, $HOSiH_2SiH_2OH$, $SiHCl_3$, $H_2Si═NH$, $(SiH_3)_2NH$, etc. These structures are analogous to carbon compounds. Silicon also shows a strong tendency to form stable-chain compounds containing —SiOSi— linkages which are the siloxanes: eg, $H_3SiOSiH_3$, disiloxane, $H_3SiOSi\text{-}H_2OSiH_3$, trisiloxane; etc. Analogous compounds containing the imino group instead of oxygen, are also well-known. These are the silazanes: eg, $H_3SiNHSiH_3$, disilazane; $H_3SiNHSiH_2$—NH-SiH_3, trisilazane; etc. It will be noted that none of the above types of compounds contain carbon and, in this sense, they are not organic compounds. However, the alkyl derivatives, which are very numerous, are organic in the same sense as alkyl derivatives of hydrogen compounds of other elements such as nitrogen and sulfur. Since	

Appendix A Continued

CLASS	EXAMPLES
the alkyl groups in the derivatives also may contain substituent functional groups, it readily is apparent that there are a great many types of organic silicon compounds. Only a few of the better known types are included in this listing.	
Silylalkanols (Silicoalcohols)	
Alcohols in which one (or more) of the CH hydrogens is replaced by silyl (SiH_3) or substituted silyl groups. In contrast to the silanols, compounds of this type contain hydroxyl in true organic combination. There are many subtypes.	$(C_2H_5)_3SiCH_2CH_2OH$ 2-(triethylsilyl)ethanol
Sulfamic Acids	
RNH(or R_2N)SO_2OH	CH_3NHSO_2OH methanesulfamic acid; $(C_2H_5)_2NSO_2OH$ diethylsulfamic acid
Sulfates (see *Esters*)	
Sulfenamides	
$RSNH_2$	$C_6H_5SNH_2$ benzenesulfenamide
Sulfenic Acids	
RSOH	C_6H_5SOH benzenesulfenic acid
Sulfenyl Halides	
RSX	C_6H_5SCl benzenesulfenyl chloride
Sulfides (Thio Ethers)	
RSR	$(CH_3)_2S$ (di)methyl sulfide (di)methyl thioether
Sulfimides	
RCONHSO$_2$	*o*-$C_6H_4CONHSO_2$ *o*-benzosulfimide (saccharin)
Sulfinamides	
$RSONH_2$	$C_6H_5SONH_2$ benzenesulfinamide
Sulfinic Acids	
RSOOH	C_6H_5SOOH benzenesulfinic acid
Sulfinyl Halides	
RSOX	C_6H_5SOCl benzenesulfinyl chloride
Sulfites (see Esters)	
Sulfonamides	
RSO_2NH_2	$C_6H_5SO_2NH_2$ benzenesulfonamide
Sulfones	
RSO_2R	$(C_2H_5)_2SO_2$ diethyl sulfone
Sulfonic Acids	
RSO_2OH	$C_6H_5SO_2OH$ benzenesulfonic acid
Sulfonium Compounds	
$[R_3S]^+X^-$ *where X is OH or a salt anion. If S is a ring member, specific "ium" nomenclature is employed to denote the heterocycle.*	$[(CH_3)_3S]^+I^-$ trimethylsulfonium iodide
$[\overline{CH_2CH_2CH_2CH_2CH_2S}^+$-$(C_2H_5)]PtCl_6^-$ 1-ethylhexahydrothiapyrylium chloroplatinate	
Sulfonyl Halides	
RSO_2X	$C_6H_5SO_2Cl$ benzenesulfonyl chloride
Sulfoxides	
RSOR	$(C_2H_5)_2SO$ diethyl sulfoxide
Sultams	
Analogous to Lactams, *qv* with —SO_2— replacing —CO—	
Sultones	
Analogous to Lactones, *qv* with —SO_2— replacing —CO—	
Thetins	
$R_2S^+CH_2COO^-$	$(CH_3)_2S^+CH_2COO^-$ *S,S*-dimethylthetin
Thio Acids	
1. Thiolic RCOSH	CH_3COSH thioloacetic acid ethanethiolic acid
2. Thionic RCSOH	CH_3CSOH thionoacetic acid ethanethionic acid
3. Thionothiolic RCSSH (Dithioic)	CH_3CSSH thionothioloacetic acid ethanedithioic acid
Thio Aldehydes	
RCHS	CH_2CHS thioacetaldehyde
Thiocyanates (Sulfocyanates; Rhodanates)	
RSCN	C_6H_5SCN phenyl thiocyanate, etc
Thio Ethers (see Sulfides)	
Thiols (Mercaptans, Acid Sulfides, Hydrosulfides; Sulfhydryl Compounds)	
RSH	C_2H_5SH ethanethiol ethyl { mercaptan / acid sulfide / hydrosulfide }
Thiones (Thio Ketones)	
RCSR	CH_3CSCH_3 propanethione dimethyl thioketone
Thionium Compounds (see *Sulfonium Compounds*)	
Thioureides-Ureides (*qv*) with the urea oxygen replaced by sulfur.	
Ureides, simplest types only	
acyclic RCONHCONH (H or COR)	$CH_3CONHCONH_2$ acetic acid ureide; acetylurea
cyclic RCONHCONHCO	$CH_2CONHCONHCO$ malonic acid ureide (malonylurea); (barbituric acid)
Urethanes (Carbamate Estes)	
NH_2COOR	$NH_2COOC_2H_5$ ethyl urethane (ethyl carbamate)

Appendix B Prefixes

ald- (or aldo-) refers to *aldehyde,* as aldoxime and aldohexose

allo- signifies a *close* (usually isomeric) *relationship,* as allocholesterol (coprostenol) is an isomer of cholesterol

anhydro- denotes *abstraction of water,* as anhydrohydroxyprogesterone

anti- equivalent to *trans, qv,* in certain geometric isomers, eg, *anti*-benzaldoxime

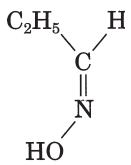
apo- usually signifies *formation from the compound* whose name is attached, as apomorphine may be formed (produced) from morphine

ar- abbreviation for *aromatic,* as aryl

as- abbreviation for *asymmetric*

bis- used instead of di-, meaning *two,* before complex expressions, as in bis(*m*-nitrophenyl)-

cis- refers to that *geometric isomer* in which the two groups are on the *same* side of a plane produced through rigid bonding, preventing free rotation (eg, unsaturation, ring formation, etc)



cyclo- indicates a *cyclic* structure, as cyclopropane

d- see *dextro-*

D- signifies a *structural relationship* to D-glyceraldehyde without any reference to direction of optical rotation, as D-glucose

de- (or des-) denotes *removal of something,* as hydrogen in dehydrocholic acid, and oxygen in desoxyephedrine

Δ (the capital Greek letter *delta*) used to indicate, or focus attention on, *double bonds,* as in Δ^2-butene [$CH_3CH{=}CHCH_3$]

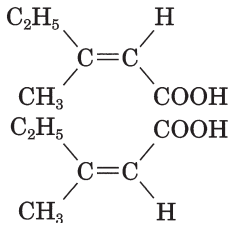
dehydro- see *de-*

desoxy- see *de-*

dextro- [or *d-* or (+)-] signifies *dextrorotatory* form, as *d*-glucose

***dl-* (or *d,l-*)** see *racemic*

E* and *Z *E* (entgegen), *Z* (zusammen); descriptors used to distinguish stereoisomers differing in the spatial distribution of groups about a doubly-bonded atom pair. *E* signifies that the group of higher priority (by the Cahn-Ingold- Prelog sequence) on one of the atoms and the group of higher priority on the other atom are on opposite sides of the double bond. *Z* signifies that these higher priority groups are on the same side of the double bond. For further discussion, see *J Am Chem Soc 90:* 509, 1968. Examples:



(*E*)-3-methyl-2-pentenoic acid

(*Z*)-3-methyl-2-pentenoic acid

epi- (or ep-) connotes a *difference in steric configuration,* as epicholesterol is the 3α-hydroxy epimer of cholesterol; also used to signify a bridge, as in epichlorohydrin and 1,3-epoxybutane.

epoxy- see *epi-*

gem- refers to *two groups attached to the same carbon atom,* as the *gem*-dimethyl grouping in 2,2-dimethylpropane or camphor

hetero- means *different,* or *not all the same,* as in heterocyclic

hom- (or homo-) indicates a *homolog* of another compound, as homatropine

hydro- (or hydr-) refers to *hydrogen,* as hexahydrobenzene and hydracrylic acid

hypo- signifies a *lower state of oxidation* in relation to another compound, as hypoxanthine

i- sometimes used instead of iso-

iso- (rarely, *i-*) denotes an *isomer* of another compound, as isobutane and isopropyl alcohol

levo [or *l-* or (−)-] signifies *levorotatory* form, as *l*-ephedrine

L- signifies a *structural relationship* to L-glyceraldehyde without any reference to direction of optical rotation, as L-glucose

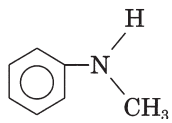
m- see *meta-*

meso- signifies *optical inactivity due to internal compensation, as mesotartaric acid*

meta- (or m-) indicates the *1,3-positions in benzene,* as in *m*-dihydroxybenzene

n- abbreviation for *normal,* as *n*-butyl alcohol

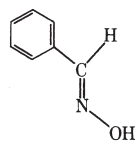
N a locant, indicating substitution on a nitrogen atom, as in *N*-methylaniline



nor- indicates a *relationship, usually through alkylation or isomerization,* between the compound whose name carries the prefix and the compound whose name does not. Examples: ephedrine is an *N*-methylated norephedrine; camphane is a trimethylated norcamphane; and leucine (2-amino-4-methylpentanoic acid) is an isomer of the normal form represented by norleucine (2-aminohexanoic acid).

Appendix B Continued

o-	see *ortho*-
ortho- (or *o*-)	signifies the *1,2- positions in benzene,* as in *o*-hydroxybenzoid acid
p-	see *para*-
para- (or *p*-)	signifies the *1,4- positions in benzene,* as in *p*-aminobenzoic acid
per-	signifies *maximum state of substitution or addition,* as in perchloroethane, C_2Cl_6; perchloroethylene, $Cl_2C{=}CCl_2$; perhydrobenzene, C_6H_{12}. Sometimes used synonymously with peroxy, *qv*
poly-	indicates a *union of several* identical molecules or molecular fragments, as in polymers and polysaccharides
R and *S*	*R* (rectus), *S* (sinistere); notations used in the Cahn-Ingold-Prelog convention to describe configuration about a chiral center. The system utilizes a set of rules to establish a priority rating for the substituent groups around a center and the rating is then applied to the structure to describe the configuration. Unlike the D-L system, the convention does not involve comparisons with reference compounds. For further discussion, see *J Chem Ed 41 (Mar):* 116, 1964.
racemic [or dl- or (±)-	signifies *optical inactivity due to equimolecular mixture of* (+)- and (−)- *forms*
s-	see *sym*-
S and *R*	see *R* and *S*
sec-	abbreviation for *secondary, as in sec*-butyl alcohol and *sec*-amines
sub-	denotes a *basic salt,* as in aluminum subacetate
sym- (or *s*-)	abbreviation for *symmetrical,* as in *sym*- dichloroethane, $ClCH_2CH_2Cl$; specifically signifies the 1,3,5 positions in benzene, as in *sym*-trinitrobenzene
syn-	equivalent to *cis, qv*, in certain geometric isomers, eg, *syn*-benzaldoxime
t-see *tert*-	
tert- (or *t*-)	abbreviation for *tertiary,* as in *tert*-butyl alcohol and *tert*-amines
tetrakis-	used instead of tetra, meaning *four,* before complex expressions (see bis-)
trans- (or *anti*)	refers to that *geometric isomer* in which the two groups are on *opposite* sides of a planar bond (see *cis*)



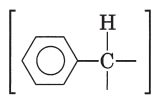
tris-	used instead of tri-, meaning *three,* before complex expressions (see *bis*-)
uns-	see *unsym*-
unsym- (or *uns*-)	abbreviation for *unsymmetrical,* as in *unsym*- dichloroethane, CH_3CHCl_2; specifically signifies the 1,2,4 positions in benzene, as in *unsym*-trihydroxybenzene
v-	see *vic*-
vic- (or *v*- or *adj*- or *a*-)	signifies the *1,2,3 positions in benzene* as *vic*-trimethylbenzene
Z and *E*	see *E* and *Z*

Appendix C Suffixes

-al	indicates an *aldehyde,* as methanal, HCHO
-ane	indicates *saturated hydrocarbon or saturated heterocycle* as ethane, androstane or furane
-ase	characteristic ending for *enzymes,* as zymase, amylase, polypeptidase, etc
-ate	characteristic ending for *salts and esters of acids* ending in -ic, as acetate, phosphate, etc
-ene	denotes *one double bond,* as ethane, butadiene, etc (see also *-ylene*)
-ine	characteristic ending for various *basic nitrogen compounds such as amines or alkaloids,* as histamine, epinephrine, morphine, etc
-ite	characteristic ending for *salts and esters of acids* ending in -ous, as phosphite, nitrite, etc
-oic	refers to the *—COOH group,* as in ethanoic, benzoic, etc, acids
-ol	characteristic ending for *alcohols, phenols, naphthols, etc,* as in ethanol, cyclohexanol, etc
-one	indicates a *ketone,* as in propanone, acetophenone, etc
-osan	generic ending for *polysaccharides,* as pentosans, hexosanes, etc
-ose	characteristic *carbohydrate* ending, especially for *sugars,* as dextrose, sucrose, etc
-oside	generic ending for *glycosides,* as glucoside, rhamnoside, etc
-oyl	characteristic ending for *acyl* radicals, as ethanoyl (for acetyl), carbamoyl, etc
-yl	indicates a *group* or *radical,* especially a *univalent hydrocarbon radical,* as methyl, phenyl, etc
-ylene	signifies a *bivalent hydrocarbon radical* or *group* with the free bonds on *different* carbon atoms, as in ethylene [—CH_2CH_2—] and *o*-phenylene

; used also to indicate a *double bond* in olefin hydrocarbons, as in ethylene [$CH_2{=}CH_2$]

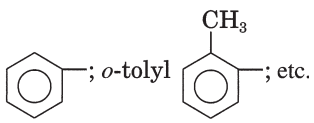
-ylidene	signifies a *bivalent hydrocarbon radical* or *group* with the free bonds on the *same* carbon atom, as in ethylidene [$CH_3CH{=}$] and benzylidene



-yne	denotes *one triple bond,* as in ethyne [CH≡CH], ethynyl [CH≡C—], etc

Appendix D Organic Groups and Radicals[a]

acetamido	CH_3CONH—
acetate	CH_3COO— or $C_2H_3O_2^-$
acetonyl	CH_3COCH_2—
acetoxy	see *acetate*
acetyl	CH_3CO—
acridinyl	$C_{13}H_8N$— (5 isomers)
acyl	generic term signifying an acid minus its OH group or groups as *acetyl,* CH_3-*CO*— *or carbonyl,* =CO
adipoyl	—$CO(CH_2)_4CO$—
alanyl	$CH_3CH(NH_2)CO$—
alkoxy	generic term signifying a radical consisting of an alkyl joined to oxygen as *methoxy,* CH_3O— and *ethoxy,* C_2H_5O—
alkyl	generic term signifying a saturated hydrocarbon radical with a valence of one as *methyl,* CH_3— or *ethyl,* C_2H_5—
alkylamino	generic term signifying RNH— wherein R is an *alkyl*
allyl	CH_2=$CHCH_2$—
amide (amido)	—$CONH_2$, see carbamoyl
amidino	H_2NC(=NH)—
amine (amino)	—NH_2
aminoacetate	H_2NCH_2COO—
aminobenzoate	$H_2NC_6H_4COO$— (*o*-, *m*- and *p*-isomers)
n-amyl (amyl)	see *pentyl*
tert-amyl	see *tert-pentyl*
anilino	C_6H_5NH—
anthryl	$C_{14}H_9$—, from anthracene (3 isomers)
aryl	generic term signfying an aromatic hydrocarbon radical as; phenyl



auro	Au—
azido	—N=N^+=N^-
azo	—N=N—
azoxy	—N(O)=N—
benzal	see *benzylidene*
benzamido	C_6H_5CONH—
benzenesulfonamido	$C_6H_5SO_2NH$—
benzenesulfonyl	$C_6H_5SO_2$—
benzhydryl	see *diphenylmethyl*
benzoate	C_6H_5COO— or $C_7H_5O_2^-$
benzoyl	C_6H_5CO—
benzoyloxy (benzoxy)	see *benzoate*
benzyl	$C_6H_5CH_2$—
benzylidene	C_6H_5CH=
biphenylyl	$C_6H_5C_6H_4$— (3 isomers)
bisulfate	$HOSO_2O$= or SO_4H^-
bisulfide	—SH; see *thiol*
bisulfite	$HOSOO$— or SO_3H^-
borate (orthoborate)	 or BO_3^{3-}
bromo (bromide)	Br—
brosyl	*p*-bromobenzenesulfonyl
n-butyl (butyl)	$CH_3(CH_2)_3$—
sec-butyl	$CH_3CH_2CH(CH_3)$—
tert-butyl	$(CH_3)_3C$—
butyrate (butanoate)	$CH_3CH_2CH_2COO$— or $C_4H_7O_2^-$
cacodyl	see *dimethylarsino*
carbamate (carbamoyloxy)	H_2NCOO—
carbamoyl	H_2NCO—, see amide
carbethoxy	see *ethoxycarbonyl*
carbomethoxy	see *methoxycarbonyl*
carbonyl	=CO
carboxyl (carboxy)	—COOH
cetyl	see *hexadecyl*
chloro (chloride)	Cl—
chloromercuri	ClHg—
cinnamoyl	C_6H_5CH=$CHCO$—
cinnamyl	C_6H_5CH=$CHCH_2$—
citrate	—$OOCCH_2C(OH)(COO$—$)CH_2COO$— or $C_6H_5O_7^{3-}$
cresyl	$CH_3C_6H_4O$— (3 isomers)
cyanato (cyanate)	N≡C—O—
cyan (cyanide)	—CN
cyclohexyl	C_6H_{11}—
cyclopentyl	C_5H_9—
cyclopropyl	C_3H_5—
n-decyl (decyl)	$CH_3(CH_2)_9$— or $C_{10}H_{21}$—
dialkylamino	R_2N— wherein R's are *alkyls*
diazo	—N(≡N)—
diazoamino	—N=N—NH=
diazonium	N^+(≡N)—
dimethylamino	$(CH_3)_2N$—
dimethylarsino	$(CH_3)_2As$—
diphenylmethyl	$(C_6H_5)_2CH$—
dodecyl	$CH_3(CH_2)_{11}$—
epoxy	—O— oxygen united to two different atoms already united in some other way
ethenyl	see *vinyl*
ethoxy	C_2H_5O—
ethoxycarbonyl	C_2H_5OCO—
ethyl	C_2H_5—
ethylamino	C_2H_5NH—
ethylene	—CH_2CH_2—
ethylenedioxy	—OCH_2CH_2O—
ethylidene	CH_3CH=
ethylthio	CH_3CH_2S—
ethynyl	HC≡C—
fluoro (fluoride)	F—
fluorophosphate	see *phosphorofluoridate*
formamido	HC(=O)NH—
formate	HCOO— or CHO_2^-
formyl	—CHO
furfuryl	OCH=CHCH=CCH_2— (two isomers, but1 used unqualified to refer specifically to the 2-form)
furfurylidene	OCH=CHCH=CCH= (two isomers, but used unqualified to refer specifically to the 2-form)
furyl	C_4H_3O— (2 isomers)
glucosyl	$C_6H_{11}O_5$—
glyceryl	—CH_2—CH—CH_2— or C_3H_5≡
glycinate	NH_2CH_2COO—
glycyl	NH_2CH_2CO—
guanidino	H_2NC(=NH)NH—
n-heptyl (heptyl)	$CH_3(CH_2)_6$—
hexadecyl	$CH_3(CH_2)_{15}$—
hexamethylene	—$CH_2(CH_2)_4CH_2$—
n-hexyl (hexyl)	$CH_3(CH_2)_5$— or C_6H_{13}—
hydrazino	H_2NNH—
hydrazo	—NHNH—
hydroxy (hydroxyl)	—OH
hydroxyamino	HONH—
hydroxyimino	HON=
hydroxymethyl (methylol)	$HOCH_2$—
imide	=NH, as in succinimide (cyclic)
imino	HN=
indolyl	C_8H_6N— (several isomers)
iodo (iodide)	I—
isoamyl	see *isopentyl*
isobutyl	$(CH_3)_2CHCH_2$—

Appendix D Continued

isocyanato (isocyanate)	O═C═N═
isocyano (isocyanide)	—NC
isonitrile (isonitrilo)	see *isocyano*
isopentyl	$(CH_3)_2CHCH_2CH_2$—
isopropoxy	$(CH_3)_2CHO$—
isopropyl	$(CH_3)_2CH$—
isothiocyano (isothiocyanato, isothiocyanate)	S═C═N— or NCS^-
keto	see *oxo*
lactate	$CH_3CH(OH)COO$— or $C_3H_5O_3^-$
malonyl	—$COCH_2CO$—
mandelate	$C_6H_5CH(OH)COO$—
menthyl	$C_{10}H_{19}$— (several isomers)
mercapto (mercaptan)	—SH; see *thiol*
mercuri	—Hg—
mesityl	2,4,6-$(CH_3)_3C_6H_2$—
methenyl	see *methylidene*
methoxy	CH_3O—
methoxycarbonyl	CH_3OCO—
methoxyphenyl	$CH_3OC_6H_4$— *o*-, *m*- and *p*-isomers
methyl	CH_3—
methylene	CH_2═
methylenedioxy	—OCH_2O—
methylidene	—CH_2—
methylidyne	HC≡
methylol	see *hydroxymethyl*
methylsulfonyl (methanesulfonyl)	CH_3SO_2—
methylthio	$\underline{CH_3S}$—
morpholino	$\overline{CH_2CH_2OCH_2CH_2N}$—
naphthyl	$C_{10}H_7$— (from naphthalene; α and β isomers)
neopentyl	$(CH_3)_3CCH_2$—
nitramino	O_2NNH—
nitrate	—ONO_2
nitrile	see *cyano*
nitrilo	≡N
nitrite	—ONO
nitro	—NO_2
nitroso	—NO
n-nonyl (nonyl)	$CH_3(CH_2)_8$—
n-octyl (octyl)	$CH_3(CH_2)_7$—
oleate	$CH_3(CH_2)_7CH$═$CH(CH_2)_7COO$— or $C_{18}H_{33}O_2^-$
oxalate (oxalato)	—$OOCCOO$— or $C_2O_4^{2-}$
oxalyl	—COCO—
oxo	O═
oxy	—O— as a connective
palmitate	$CH_3(CH_2)_{14}COO$— or $C_{16}H_{31}O_2^-$
n-pentyl (pentyl)	$CH_3(CH_2)_3CH_2$—
tert-pentyl	$CH_3CH_2C(CH_3)_2$— (1,1-dimethylpropyl)
perchlorate	O_3Cl—O— or ClO_4^-
perchloryl	O_3Cl—
peroxy	—O—O—
phenethyl	$C_6H_5CH_2CH_2$—
phenoxy	C_6H_5O—
phenyl	C_6H_5—
phenylene	C_6H_4═ (*o*-, *m*- and *p*-isomers)
phenylsulfonyl	see *benzenesulfonyl*
phosphate (orthophosphate)	PO_4^{3-}
phosphino	H_2P—
phospho	—PO_2
phosphono	$(HO)_2OP$—
phosphoro	—PP—
phosphoroso	—PO
phthalate	*o*-$C_6H_4(COO—)_2$
phthaloyl	*o*-$C_6H_4(CO—)_2$
picrate	2,4,6-$(NO_2)_3C_6H_2O$—
picryl	2,4,6-$(NO_2)_3C_6H_2$—
piperidino	$\underline{CH_2}CH_2CH_2CH_2CH_2N$—
piperidyl	2-, 3-, or 4-$C_5H_{10}N$—
pivaloyl	$(CH_3)_3CCO$—
propenyl	CH_3CH═CH—
propionate (propanoate)	CH_3CH_2COO— or $C_3H_5O_2$—
propionyl	CH_3CH_2CO—
propoxy	$CH_3CH_2CH_2O$—
n-propyl (propyl)	$CH_3\underline{CH_2}CH_2$—
propylene	CH_3—CH—CH_2—
pyranyl	C_5H_5O— (3 isomers)
pyrazolidinyl	$C_3H_7N_2$— (many isomers)
pyridyl	C_5H_4N— (3 isomers)
pyrimidinyl (pyrimidyl)	$C_4H_3N_2$— (3 isomers)
quinolyl	C_9H_6N— (7 isomers)
salicyl	*o*-$C_6H_4(OH)CO$—
salicylate	*o*-$C_6H_4(OH)COO$— or $C_7H_5O_3^-$
silyl	—SiH_3
stearate	$CH_3(CH_2)_{16}COO$— or $C_{18}H_{35}O_2^-$
stibo	O_2Sb—
styryl	C_6H_5CH═CH—
succinate	—$OOCCH_2CH_2COO$— or $C_4H_4O_4^{2-}$
succinoyl	—$OCCH_2CH_2CO$—
sulfamoyl	H_2NSO_2—
sulfanilamido	*p*-$H_2NC_6H_4SO_2NH$—
sulfanilyl	*p*-$H_2NC_6H_4SO_2$—
sulfate	—OSO_2O— or SO_4^{2-}
sulfhydryl	see *thiol*
sulfide	—S—; characteristic of thioethers as (*di*)*ethyl sulfide* (ethyl thioether), C_2H_5—S—C_2H_5
sulfinyl	—SO—
sulfite	—$OSOO$— or SO_3^{2-}
sulfo	see *sulfonic acid*
sulfonamido	—SO_2NH—
sulfonate	—SO_2O—
sulfone	see *sulfonyl*
sulfonic acid	—SO_2OH
sulfonyl (sulfone)	—SO_2—
sulfoxide	see *sulfinyl*
sulfuryl	see *sulfonyl*
tartrate	—$OOCCH(OH)CH(OH)COO$— or $C_4H_4O_6^{2-}$
tetradecyl	$CH_3(CH_2)_{12}CH$—
tetramethylene	—$CH_2(CH_2)_2CH_2$—
tetrazolyl	CHN_4— (isomers)
thenyl	$C_4H_3SCH_2$— (2 isomers)
thiazolyl	C_3H_2NS— (3 isomers)
thienyl	C_4H_3S— (2 isomers)
thio	see *sulfide*
thiocarbonyl	═CS
thiocyano (thiocyanato, thiocyanate)	—SCN
thiol (thiolo, mercapto)	—SH
thionyl	see *sulfinyl*
toloxy (tolyloxy)	$CH_3C_6H_4O$— (*o*-, *m*- and *p*-isomers)
toluenesulfonyl	$CH_3C_6H_4SO_2$— (*o*-, *m*- and *p*-forms)
tolyl	$CH_3C_6H_4$— (*o*-, *m*- and *p*-isomers)
tosyl	= *tolylsulfonyl, qv*
trimethylene	—$CH_2CH_2CH_2$—
trityl	$(C_6H_5)_3C$—
ureido	H_2NCONH—
valerate (pentanoate)	$CH_3(CH_2)_3COO$— or $C_5H_9O_2^-$
vinyl	CH_2═CH—
xanthenyl (xanthyl)	$C_{13}H_9O$— (5 isomers)
xenyl	see *biphenylyl*
xylyl	$(CH_3)_2C_6H_3$— (6 isomers)

[a]Anionic radicals have slightly different names than given here when present as ligands. Examples: acetate versus acetato; nitrite versus nitrito; thiol versus thiolo.

Appendix E Heterocycles in Official Drugs

3 C_2N

Aziridine (11)[a]
Example: *Thiotepa*

5 C_3OS

1,3-Oxathiole (133)
4,5-dihydro form
Example: *Nivirapine*

5 C_4N

1H-Tetrazole (61)
Examples: *cefamandole; Cefazolin.*

C_2N_2S

1,2,5-Thiadiazole (89)
Example: *Timolol.*

1,3,4-Thiadiazole (90)
Examples: *Acetazolamide; Cefazolin; Sulfamethizole.*

1,3,4-Thiadiazoline (90)
Example: *Methazolamide.*

C_3NO

Oxazolidine (119)
Example: *Paramethadione*

Isoxazole (118)
Examples: *Cloxacillin, Isocarboxazid; Sulfisoxazole.*

Isoxazolidine (118)
Example: *Cycloserine.*

C_3NS

Thiazole (122)
Examples: *Thiabendazole; Thiamine.*

C_3N_2

Imidazole (127)
Examples: *Azathioprine; Histamine; Pilocarpine.*

2-Imidazoline (127)
Example: *Phenytoin*

Imidazoline (127)
Example: *Nitrofurantoin*

3-Pyrazoline (124)
Example: *Antipyrine.*

Pyrazolidine (124)
Examples: *Phenylbutazone; Sulfinpyrazone.*

C_3O_2

1,3-Dioxolane (136)
Examples: *Ketoconazole; Propylene Carbonate.*

C_4N

Pyrrole (142)
Example: *Pyrvinium Pamoate.*

Pyrrolidine (142)
Example: *Methsuximide*

C_4O

Furan (145)
Example: *Nitrofurantoin*

2,5-Dihydrofuran (145)
Examples: *Ascorbic Acid; Digitoxin.*

Tetrahydrofuran (145)
Examples: *Polysorbate; Sorbitan; Streptomycin; Sucrose.*

C_4S

Thiophene (149)
Example: *Cefoxitin*

6 C_3NOP

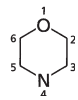
Tetrahydro-2*H*-1,3,2-oxazaphosphorine (7746)
Example: *Cyclophosphamide.*

C_3O_3

s-Trioxane (222)
Example: *Paraldehyde.*

C_4NO

Morpholine (239)
Examples: *Pramoxine; Timolol.*



C_4N_2

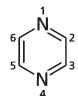
Pyrimidine (249)
Example: *Pyrimethamine.*

1,2,3,4-Tetrahydropyrimidine (249)
Example: *Propylthiouracil.*

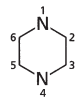
1,4,5,6-Tetrahydro form (249)
Example: *Oxyphencyclimine.*

Hexahydropyrimidine (249)
Examples: *All barbituric and thiobarbituric acids; Primidone.*

Pyrazine (250)
Example: *Amiloride.*



Piperazine: Hexahydropyrazine (250)
Example: *Prochlorperazine.*



C_5N

Pyridine (277)
Examples: *Cetylpyridinium Chloride; Niacinamide.*

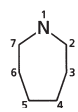
1,4-Dihydropyridine (4*H*-Pyridine) (277)
Example: *Propyliodone.*

Piperidine; Hexahydropyridine (277)
Example: *Meperidine.*

Tetrahydropyran (278)
Examples: *Lactose; Streptomycin.*

7 C_6N

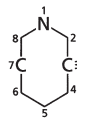
Hexahydroazepine (355)
Example: *Tolazamide.*



Appendix E Continued

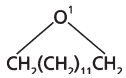
8 C_7N

Octahydroazocine (414)
Example: *Guanethidine.*



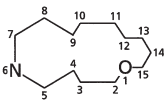
14 $C_{13}O$

Oxacyclotetradecane (534)
Example: *Erythromycin.*



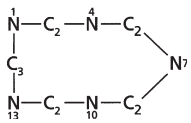
15 $C_{13}NO$

1-Oxa-6-azacyclopentadecane
Example: *Azithromycin.*



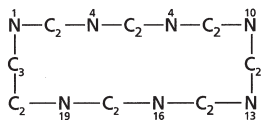
16 $C_{11}N_5$

1,4,7,10,13-Pentaazacyclo-hexadecane
Example: *Capreomycin.*



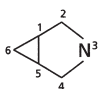
23 $C_{16}N_2$

1,4,7,10,13,16,19-Heptaazacyclotricosane (11705)
Examples: *Colistin; Colistimethate Sodium.*



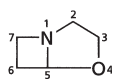
3,5 C_3-C_4N

3-Azabicyclo[3.1.0]hexane (690)
Example: *Trovafloxacin*



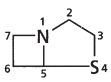
4,5 C_3N-C_3NO

4-Oxa-1-azabicyclo[3.2.0]heptane
Example: *Clavulanate Potassium.*



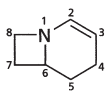
C_3N-C_3NS

4-Thia-1-azabicyclo[3.2.0] heptane (774)
Example: *Penicillins.*



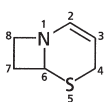
4,6 C_3N-C_5N

1-Azabicyclo [4.2.0] octane (810)
$\triangle^{2,3}$-form
Example: *Loracarbef*



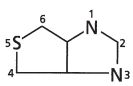
C_3N-C_4NS

5-Thia-1-azabicyclo[4.2.0]oct-2-ene (11757)
Example: *Cefotaxin*



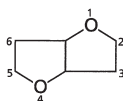
5,5 C_3N_2-C_4S

1*H*-Thieno[3,4-*d*]imidazole, hexahydro form (945)
Example: *Biotin.*



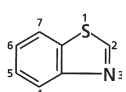
C_5O-C_5O

Furo[3,2-b]furan, hexahydro form (996)
Example: *Isosorbide Dinitrate.*

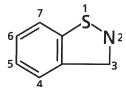


C_3NS-C_6

Benzothiazole (1152)
Example: *Ethoxzolamide.*

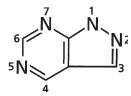


1,2-Benzisothiazole, 2,3-dihydro form (1150)
Example: *Saccharin.*

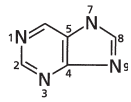


C_3N_2-C_4N_2

1*H*-Pyrazolo[3,4-*d*]pyrimidine (1174)
Example: *Allopurinol.*

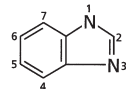


Purine[b] (1179)
Examples: *Caffeine; Dimenhydrinate.*



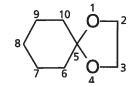
C_3N_2-C_6

Benzimidazole (1213)
Examples: *Cyanocobalamin; Droperidol; Thiabendazole.*



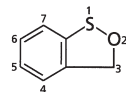
C_3O_2-C_6

1,4-Dioxaspiro[4.5]decane (1238)
Example: *Guanadrel.*



C_3OS-C_6

3*H*-2,1-Benzoxathiole (1222)
Example: *Phenolsulfonphthalein.*

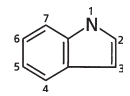


C_4N-C_5N

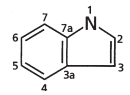
Nortropane (1281) or 8-azabicyclo-[3.2,1]octane
Examples: *Atropine; Cocaine.*

C_4NC_6

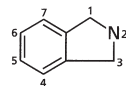
Indole (1286)
Example: *Indomethacin.*



Indoline (1286)
Example: *Indigotindisulfonate Sodium.*

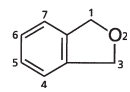


Isoindoline (1290)
Example: *Chlorthalidone.*



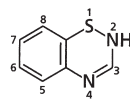
C_4O-C_5

Phthalan; (1,3-Dihydroisobenzofuran) (1330)
Example: *Phenolphthalein.*



6,6 $C_3N_2$5-C_6

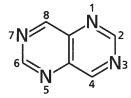
2*H*-1,2,4-Benzothiadiazine (8074)
Example: *Chlorothiazide.*



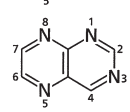
3,4-dihydro form (8074)
Examples: *Hydrochlorothiazide; Polythiazide.*

C_4N_2-C_4N_2

Pyrimido[5,3-*d*]pyrimidine (1585)
Example: *Dipyridamole.*

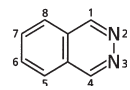


Pteridine (1587)
Example: *Methotrexate.*
1,4,5,6,7,8-hexahydro form.
Example: *Leucovorin.*

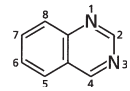


C_1N_2-C_6

Phthalazine (1628)
Example: *Hydralazine.*

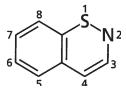


Quinazoline (1626)
Example: *Methaqualone.*

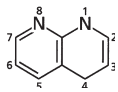


Appendix E Continued

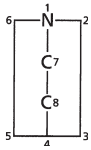
C_4NS-C_6
2*H*-1,2-Benzothiazine (1577)
Example: *Piroxicam.*



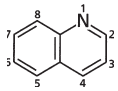
C_5N-C_5N
1,8-Naphthyridine, 1,4-dihydro form (1683)
Example: *Nalidixic Acid.*



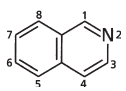
Quinuclidine (1690)
Examples: Clidinium Bromide; Quinine.



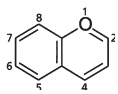
C_5N-C_5
Quinoline (1707)
Examples: *Chloroquine; Quinine.*



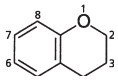
Isoquinoline (1708)
Example: *Papaverine.*
1,2,3,4-tetrahydro form
Example: *Emetine.*



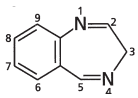
C_5O-C_5
2*H*-1-Benzopyran (1727)
Examples: *Dicumarol; Warfarin.*



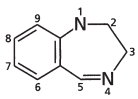
Chroman (Dihydrobenzopyran) (1727)
Example: *Vitamin E*



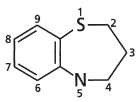
6,7 C_6-C_5N_2
3*H*-1,4-Benzodiazepine (1829)
Example: *Chlordiazepoxide.*



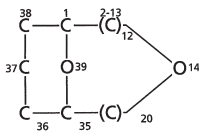
2*H*-1,4-Benzodiazepine, 1,3-dihydro form (12067)
Examples: *Diazepam; Oxazepam.*



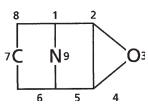
C_5-C_5NS
1,5-Benzothiazepine (1825)
1,2,3,4-Tetrahydro form
Example: *Dilitiazem*



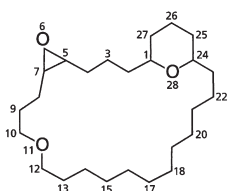
6,36 C_5O-$C_{34}O_2$
14,39-Dioxabicyclo[33.3.1] nonatriacontane
Example: *Amphotericin.*



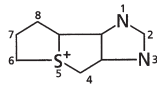
3,5,6 C_2O-C_4N-C_5N
3-Oxa-9-azatricyclo[3.3.1.$0^{2,4}$] nonane (2072)
Examples: *Methscopolamine Bromide; Scopolamine.*



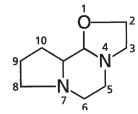
3,6,24 C_2O-C_5O-$C_{22}O_2$
6,11,28-Trioxatricyclo[22.3.1.$0^{5,7}$] octacosane
Example: *Natamycin.*



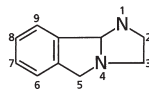
5,5,5 C_3N_2-C_4S-C_4S
Imidazo[4,5-c]thieno[1,2-*a*]thiolium or thieno[1′,2′:1,2]thieno[3,4-*d*] imidazol-5-ium, decahydro form (2215)
Example: *Trimethaphan Camsylate.*



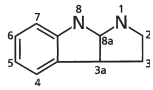
5,5,6 C_3NO_2-C_4N-C_4N_2
8*H*-Oxazolo[3,2-*a*]pyrrolo[2,1-*c*]-pyrazine, perhydro form (2319)
Example: *Ergotamine.*



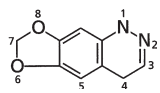
C_3N_2-C_4N-C_6
3*H*-Imidazo[2,1-*a*]isoindole, 2,5-dihydro form (2384)
Example: *Mazindol.*



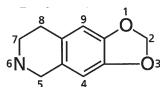
C_4N-C_4N-C_6
Pyrrolo[2,3-*b*]indole, 1,2,3,3a,8,8a-hexahydro form (2442)
Example: *Physostigmine.*



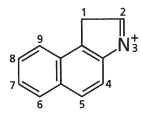
5,6,6 C_3O_2-C_4N_2-C_6
[1,3]-Dioxolo[4,5-*g*]cinnoline, 1,4-dihydro form (2806)
Example: *Cinoxacin.*



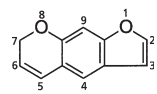
C_3O_2-C_5N-C_6
[1,3]-Dioxolo[4,5-*g*]isoquinoline, 5,6,7,8-tetrahydro form (2810)
Example: *Noscapine.*



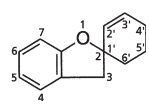
C_4N-C_5-C_6
1*H*-Benz[e]indolium (2933)
Example: *Indocyanine Green.*



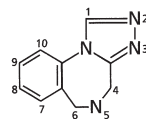
C_4O-C_5O-C_6
7*H*-Furo[3,2-*g*][1]benzopyran (2988)
Examples: *Methoxsalen; Trioxsalen.*



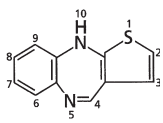
C_4O-C_6-C_6
Spiro[benzofuran-2(3*H*),1′-[2]-cyclohexene] (3028)
Example: *Griseofulvin.*



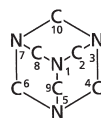
5,6,7 C_2N_3-C_6-C_5N_2
4*H*-[1,2,4]Triazolo[4,3-*a*][1,4] benzodiazepine
Examples: *Alprazolam, Triazolam.*



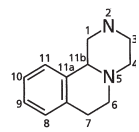
C_4S-C_6-C_5N_2
Thieno[2,3-*b*][1,5]benzodiazepine
Example: *Olanzapine*



6,6,6 C_3N_3-C_3N_3-C_3N_3
Hexamethylenetetramine (3237) or 1,3,5,7-Tetraazatricyclo [3.3.1^{3,7}] decane
Example: *Methenamine.*

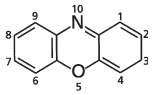


C_4N_2-C_5N-C_6
4*H*-Pyrazino[2,1-*a*]isoquinoline, 1,2,3,6,7,11b-hexahydro form (10470)
Example: *Praziquantel.*

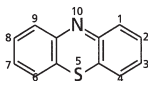


Appendix E Continued

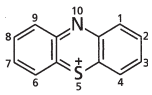
C_4NO-C_6-C_6
3*H*-Phenoxazine (3289)
Example: *Dactinomycin.*



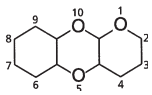
C_4NS-C_6-C_6
Phenothiazine (3314)
Examples: *Chlorpromazine; Prochlorperazine.*



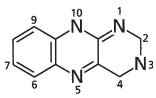
Phenazathionium (3315) or Phenothiazin-5-ium
Example: *Methylene Blue.*



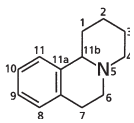
C_4O_2-C_5O-C_6
4*H*-Pyrano[2,3-*b*][1,4]benzodioxin, decahydro form (12687)
Example: *Spectinomycin.*



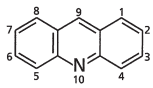
C_4N_2-C_4N_2-C_6
Benzo[*g*]pteridine, 2,3,4, 10-tetrahydroform (3340)
Example: *Riboflavin.*



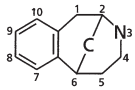
C_5N-C_5N-C_6
2*H*-Benzo[*a*]quinolizine, 1,3,4,6,7,-11b-hexahydro form (3487)
Example: *Emetine.*



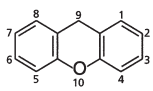
C_5N-C_6-C_5
Acridine[b] (3523)
Examples: *Acrisorcin; Quinacrine.*



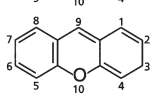
2,6-Methano-3-benzazocine, 1,2,3,4,5,6-hexahydro form (3535)
Example: *Pentazocine.*



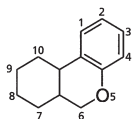
C_5O-C_6-C_6
Xanthene[b] (3571)
Example: *Propantheline.*



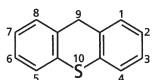
3*H*-Isoxanthene[b] (3569)
Examples: *Fluorescein Sodium; Rose Bengal Sodium.*



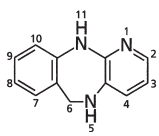
6*H*-Dibenzo[*b,d*]pyran, 6a,7,8, 10a-tetrahydroform (3581)
Example: *Dronabinol.*



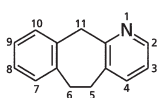
C_5S-C_5C_5
Thioxanthene[b] (3607)
Example: *Thiothixene.*



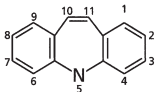
6,6,7 C_5N-C_5N-C_5N_2
Dipyrido[3,2-*b*:2′,3′,*e*][1,4]diazepine 5,11-dihydro form
Example: *Nivirapine*



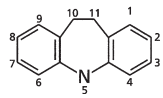
C_5N-C_6-C_7
5*H*-Benzo[5,6]cyclohepta[1,2-*b*]-pyridine 6,11-dihydro form
Example: *Azatadine.*



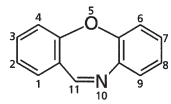
5*H*-Dibenz[*b,f*]azepine (3689)
Example: *Carbamazepine.*



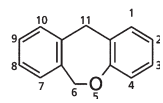
10,11-dihydro form (3689)
Examples: *Desipramine; Imipramine.*



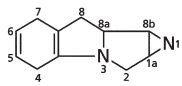
C_6C_6-C_5NO
Dibenz[*b,f*][1,4]oxazepine (3697)
Example: *Loxapine*



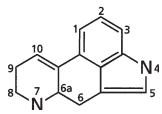
C_6C_6-C_6O
Dibenz[*b,e*]oxepine, 6,11-dihydro form (3697)
Example: *Doxepin.*



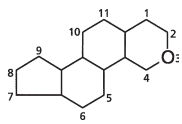
3,5,5,6 C_2N-C_4N-C_4N-C_6
Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole (12848),1,1a,2,8,8a,8b-hexahydro form
Example: *Mitomycin.*



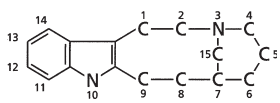
5,6,6,6 C_4N-C_5N-C_6-C_6
Indolo[4,3-*fg*]quinoline,4,6,6a,7,8,9-hexahydro form (4550)
Examples: *Ergonovine; Ergotamine.*



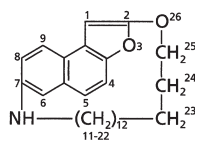
C_5O-C_6-C_6-C_6
Cyclopental[5,6]naphtho[1,2*c*]-pyran, perhydro form (4760)
Example: *Oxandrolone.*



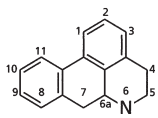
5,6,6,9 C_4N-C_5N-C_6-C_6N
10*H*-3,7-Methanoaza-cycloundecino-[5,4-*b*]indole, 1,2,4,5,6,7,8,9-octahydro form (13276)
Examples: *Vinblastine; Vincristine.*



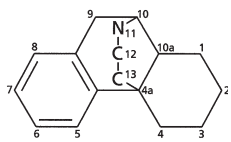
5,6,6,24 C_4O-C_6-C_6-$C_{22}NO$
2,7-(Epoxypentadecanimino) naphtho[2,1-*b*]]furan
Example: *Rifampin.*



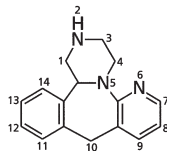
6,6,6,6 C_5N-C_6-C_6-C_5
4*H*-Dibenzo[*de,fg*]quinoline, 5,6,6a,7-tetrahydro form (5171)
Example: *Apomorphine.*



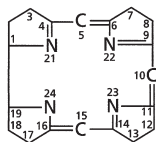
2*H*-10,4a-Iminoethanophenan-threne,[b] *cis*-1,3,4,9,10,10a-hexahydro form; morphinan (5180)
Examples: *Dextromethorphan; Levorphanol.*



6,6,6,7 C_4N_2-C_6-C_6-C_6N
Pyrazino[2,1-*a*]pyrido[2,3-*c*][2]-benzazepine, 1,2,3,4,10,14b-hexahydro form
Example: *Mirtizapine*

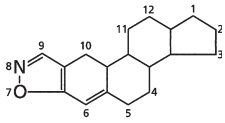


5,5,5,5,15 C_4N-C_4N-C_4N-C_4N-$C_{11}H_4$
Corrin[b] (5475)
Example: *Cyanocobalamin.*

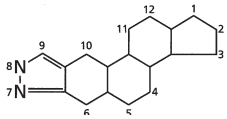


Appendix E Continued

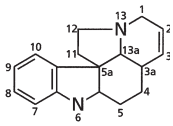
5,5,6,6,6 C_3NO-C_6-C_6-C_6-C_6
1*H*-Cyclopenta[7,8]phenanthro-[3,2-*d*]-isoxazole, 2,3,3*a*,-3*b*,4,5,10,10*a*,10*b*,11.12.12*a*-dodecahydro form (11036)
Example: *Danazol.*



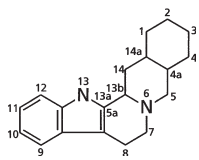
C_3N_2-C_5-C_6-C_6-C_6
8*H*-Cyclopenta[7,8]phenanthro-[3,2-*c*]-pyrazole, 1,2,3,3*a*,3*b*,-4,5,5*a*,6,7,10,10*a*,10*b*,11,12,-12*a*-tetradecahydro form (FKRBA)
Example: *Stanozolol.*



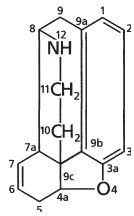
C_4N-C_4N-C_5N-C_6-C_6
1*H*-Indolizino[8,1-*cd*] carbazole, 3a,4,5,5a,6,11,12,13a-octahydro form (11605)
Examples: *Vinblastine; Vincristine.*



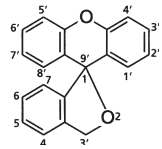
5,6,6,6,6 C_4N-C_5N-C_5N-C_6-C_6
Benz[*g*]indolo[2,3-*a*]quinolizine, 1,2,3,4,4a,5,7,13,13b,14,14a-dodecahydro form (5784)
Example: *Reserpine.*



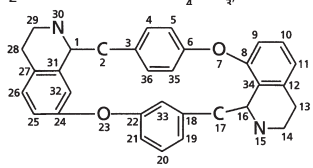
C_4O-C_5N-C_6-C_6-C_5
4a*H*-8,9*c*-Iminoethanophenanthro-[4,5-*bcd*]furan, 5922)
5,7a,8,9-tetrahydro form
Examples: *Codeine; Morphine; Nalorphine.*
5,6,7,7a,8,9-hexahydro form
Examples: *Hydrocodone; Hydromorphone.*



C_4O-C_5O-C_6-C_6-C_5
Spiro[phthalan-1,9′-xanthene] (5935) or Spiro[isobenzofuran-1-(3*H*), 9′] 9*H*]xanthene]
Example: *Fluorescein.*



6,6,6,6,6,6,18 C_5N-C_6-C_6-C_6-C_6-C_{16}-O_2
Octahydro form of Ring Index No 7408.
Examples: *Tubocurarine; Metocurine.*



[a] Characters in parentheses are either the *Ring Index* number or the *Parent Compound Identifier.*
[b] Exception to the numbering rule.

CHAPTER 26

Natural Products

Bill J Bowman, PhD, RPh
Robert Jordan

Natural products are used for a variety of purposes. This chapter will focus on those natural products that have a pharmaceutical importance (Table 26-1). Records show that in practically every country, certain foods and plants were the basis of early medicine.[1] More than 5,000 years ago, the Sumerians described well-established medicinal uses for such plants as laurel, caraway, and thyme.[2] The first Chinese "herbal" book dates back to ~2700 BC and lists 365 medicinal plants and their uses, including ma-huang, the source of ephedrine.[2] A substantial record of the use of herbs as medicine comes from the first Code of Hammurabi (~1770 BC), which is a series of tablets carved under the direction of the King of Babylon and mentions medicinal plants such as henbane, licorice, and mint.[3] The ancient Egyptians treated their sick by giving them what they thought to be suitable foods. For example, they prescribed liver, a rich source of vitamin A, for night blindness and used moldy breads on wounds.[4] Among the ancient Greeks, Hippocrates (~460–377 BC), who is considered the father of medicine in the Western cultures, based most of his protocols for the prevention and treatment of disease on what his patients ate and quoted the famous aphorism, "Food be thy friend and enemy."[5] However, the most significant Greek contribution is often considered to be the five-volume work entitled *De Materia Medica* written by Dioscorides (AD 40–90). This work described the preparation of approximately 1,000 simple drugs primarily from medicinal plants and is consider the prototype for future pharmacopoeias.[3]

As advances in science continued to improve man's understanding of physiology and the pharmacological effects of foods and herbals, these products remained an essential component in the management of disease around the world. By the early 1900s, it was well understood that many diseases were caused or aggravated by poor nutrition. In addition, the vitamins were discovered during studies on deficiency diseases such as pellagra (nicotinic acid, a B-vitamin, deficiency) and rickets (vitamin D deficiency). By the mid-1900s, vitamins were being isolated and synthesized and subsequently used as additives in other foods or to prepare vitamin supplements. In addition, most people in industrialized countries had achieved an adequate and nutritious food intake. Therefore, deficiency diseases all but disappeared, and as a result, there was little continued emphasis on the importance of foods and diet in health. At the same time, most industrialized nations also saw a rapid rise in drug development. Initially, many of these modern drugs had their origins in some herbal product. Most were just isolated, purified products from plant extracts that had been used for centuries such as morphine from the opium plant and digitalis leaf glycosides. Medicinal chemists then began to modify these extracted compounds producing new synthetic medications. Examples of these synthetic drugs include the opiate derivatives such as meperidine, the local anesthetics (novocaine, lidocaine) developed from cocaine, and the various ephedrine derivatives originally discovered in Ephedra species.[5]

This transition from the use of subtle foods and herbals to rapidly acting and specific synthetic vitamins and drugs in disease management, which took place primarily in the United States, occurred for several reasons. First, these new agents were more effective at curing and managing many diseases. Second, there was much disdain for "old-fashioned or folkloric medicine," especially after the hucksterism and quackery that took place at the turn of the century. Many fortunes were made during this era (known as the patent-medicine era) by those proclaiming that certain foods or herbs could "cure all ills."[5] This ultimately led to the formation of the FDA and later laws that regulate dietary supplements and pharmaceuticals based upon sound scientific evidence. Third, there was a belief that human trial and error over the past centuries had discovered most of the plants having medicinal value and little was left to be discovered. Lastly, many pharmaceutical companies felt that it was too costly to screen plants for useful drugs given the low success rate, especially once advances in science had made it easier and cheaper to design synthetic drugs, which are more easily patentable.[3]

However, by the end of the past century, we saw another major revolution in health care. Millions of people have begun eating healthier and using dietary supplements and herbal products to prevent disease and promote good health. A marketing survey reported that near the end of the 20th century "nutraceutical" (ie, foods, vitamins, supplements, herbal medicines, phytonutrients, etc.) sales were at $5.7 billion and that at least 40% of the population was paying for these products "out of pocket."[6] There are a number of reasons for the resurgence in popularity of these products: (1) it is now well recognized that diet and exercise alone can manage many disorders such as mature onset diabetes (Type II), cardiacvascular disease, and those of inborn errors of metabolism (eg, gout, galactosemia, phenylketouria)[5]; (2) many diseases have been conquered and only old age, degenerative disorders, which traditional medicine has had limited success with, remain[7]; (3) people are realizing that, although highly successful, traditional medicine, with its scientific basis, is emotionally hollow, esthetically meaningless, and spiritually empty; (4) many individuals have lost faith in science, which is being blamed for many ills such as pollution due to pesticides, carcinogens, and other environmental toxins; and (5) rising medical costs and managed health care have caused the public to lose trust in their health care providers, drug manufacturers, and the government.[7] As a result, people are taking a more active role in managing/preventing disease and searching for alternative ways to attain full health.

Table 26-1. Examples of Natural Products Having a Pharmaceutical Importance

NATURAL PRODUCT	OCCURRENCE	PHARMACOLOGICAL USE
Caffeine	Tea (the leaves of *Thea sinensis*—Ternstroemiaceae), cocoa beans (the seeds of *Theobroma cacao*—Sterculiaceae), and coffee beans (the seeds of *Coffea* spp. - Rubiaceae)	Stimulates mental activity
Morphine	Opium poppy, *Papaver somniferum* (Papaveraceae)	Analgesia
Pilocarpine	*Pilocarpus* spp. (Rutaceae)	Parasympathomimetic
Ephedrine	*Ephedra* spp. (Ephedraceae)	Peripheral vasoconstrictor
Theophylline	Tea (the leaves of *Thea sinensis*—Ternstroemiaceae), cocoa beans (the seeds of *Theobroma cacao*—Sterculiaceae), and coffee beans (the seeds of *Coffea* spp. - Rubiaceae)	Bronchodilator
Codeine	Opium poppy, *Papaver somniferum* (Papaveraceae)	Cough suppressant
Senna anthraquinones	*Cassia senna and Cassia angustifolia* (Leguminosae)	Laxative
Ergometrine	Ergot, a morbid growth formed when the fungus *Claviceps purpurea* develops on various plants of the Gramineae + Cyperacea families.	Uterine stimulation
Capsaicin	*Capsicum* spp. (Solanaceae)	Counter-irritant
Emetine	*Cephaelis ipecacuanha* (Rubiaceae)	Amoebic dysentery

While this trend toward self-awareness and increased participation in ones health is surely a good thing, there are also several concerns. Some individuals are abandoning traditional medicine completely, which ultimately leads them into irrational modes of thought such as occultism and mysticism. There is also much lacking, unsupported, and misinformation about herbals and other dietary supplements, and individuals have a tendency to be less than discerning or are not adequately educated to appropriately evaluate information regarding these therapies. Since the reemergence of herbals and dietary supplements is primarily consumer driven and lacks much scientific evidence, many health professionals have regarded it as mere faddism.[5] Unfortunately, this has caused many health care professionals to completely dismiss these products even though many of their patients use them for legitimate and useful reasons. This has resulted in a communication breakdown between patients and their health care providers. One study reported that 75% of individuals using nutraceuticals neglect to share this information with their physicians.[8] This is most concerning in light of the building evidence of serious herbal-drug interactions such as with St. John's Wort.

There is also major safety concerns with these products themselves. For example, early in 1998, a USP expert advisory panel determined that consumer use of comfrey could be harmful due to a lack of scientific evidence to support its safety and dispel the information on its hepatic toxicity.[9] An additional concern with the use of supplements or supplemented foods is that they tend to undermine the idea of healthy eating, which focuses on the whole diet and not just single ingredients. Healthy foods commonly contain several compounds with therapeutic activity or contain compounds that modify the effect of their active constituents on the body. Therefore, eating an orange is typically more beneficial than taking a vitamin C tablet. In addition, supplements may provide nutrients and active components in a potentially unbalanced and concentrated form, different than that used in research studies.[10] However, many of the functional compounds within foods are at too low of a concentration to exert a significant effect and the only rational way of getting the recommended amount is in supplement form or as a food additive, such as the stanol esters in the Benecol products. There are also legal and regulatory concerns on how to promote and market these products, to determine exactly which ingredients have a pharmacological activity, to standardize these products so that they will have known amounts of active principles with known activity, to determine actual efficacy, and to devise appropriate claims.[11] In addition, there appears to be a trend toward decreasing consumer confidence, which has been fuelled by the many negative outcomes portrayed in the media with these products, especially those of false labeled claims.

Although there are many concerns, modern research has strongly supported and further developed the idea that certain foods and herbals can help maintain good health or serve as medicines (Tables 26-2 and 26-3). The FDA also defines special classes of foods including Medical Foods, which have exact concentrations of nutrients and appropriate labeling for use in certain medical conditions (eg, certain hyperalimentations preparations),[14] and Foods for Special Dietary Uses (FSDU), which includes hypoallergenic foods, weight-reduction foods, foods for diabetics, reduced sodium foods, and infant formulas.[15] In addition, 80% of the world's population (primarily in developing countries) still rely on plant-derived medicines.[16] Therefore, quality health care needs to be a combination these "alternative" approaches with traditional therapies; both have a great utility in maintaining proper health and treating disease. With these factors in mind, it is certainly worthwhile for all of those in the health care arena to be aware of and take advantage of the fast flowing information regarding natural products to help decide which findings can be used to provide quality health care to all patients.

In addition to the use of natural products, such as foods and herbals, to prevent and manage disease, twenty-five percent of all drugs prescribed today are still based upon substances derived from plants or plant-derived synthetic analogs. In fact, in the former Federal Republic of Germany, six phytochemicals were among the top one hundred of the most prescribed drugs in 1990. Some 4.23 million prescriptions were written for standardized Ginkgo biloba preparation alone.[17] This maybe attributed to the Commission E, which was established in 1978 by a German federal agency (Bundesgeundheitsamt) to determine the safety and efficacy of herbal products. So far, the Commission E has produced about 400 monographs on various phytopharmaceuticals and combination products. These compendia probably represent the most complete and accurate modern body of scientific information on the subject today. Nature remains an extremely rich source of molecular diversity, and therefore, natural products continue to be used for drug discovery. In the past, collecting and processing natural com-

Table 26-2. Current FDA Qualified Health Claims

PRODUCT	PERMITTED QUALIFIED CLAIM
Dietary supplement containing selenium	Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer or Some scientific evidence suggests that consumption of selenium may produce anticarcinogenic effects in the body
Dietary supplements containing vitamin E and/or vitamin C	Some scientific evidence suggests that consumption of antioxidant vitamins may reduce the risk of certain forms of cancer.
Whole or chopped almonds, hazelnuts, peanuts, pecans, some pine nuts, pistachio nuts, and walnuts	Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts [such as *name of specific nut*] as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease.
Dietary supplements containing the omega-3 long chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA)	Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease.
Dietary supplements containing vitamin B6, B12, and/or folic acid	As part of a well-balanced diet that is low in saturated fat and cholesterol, folic acid, vitamin B6, and vitamin B12 may reduce the risk of vascular disease.
Dietary supplements containing soy-derived phosphatidylserine	Consumption of phosphatidylserine may reduce the risk of dementia in the elderly *or* Consumption of phosphatidylserine may reduce the risk of cognitive dysfunction in the elderly
Dietary supplements containing folic acid	0.8 mg folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form.

pounds was both difficult and costly, especially for compounds present in very low concentrations. However, this has been made easier by continued advances in extraction, concentrating, and identifying processes. Since natural products already have a function in nature, and therefore, typically already display pharmacological activity, they are seen as improving the odds of synthesizing a good drug compared to starting with a completely new structure. Such compounds are proving to be very useful as starting points for combinatorial chemistry and the synthesis of lead drug compounds.

The remaining portion of this chapter will focus upon the active constituents of natural products such as foods and herbals and provides a discussion of the fundamental characteristics of the following, essentially chemical, classes of naturally occurring products:

Carbohydrates and Glycosides
Proteins, Peptides, and Amino Acids
Lipids (Fixed Oils and Fats, Waxes, Phospholipids, and Prostaglandins)
Sterols and Saponins
Alkaloids
Phenols
Volatile Oils, Resins, and Miscellaneous Isoprenoids

CARBOHYDRATES AND GLYCOSIDES

Composition and Structure

Carbohydrates consist of carbon, hydrogen, and oxygen and include numerous aliphatic polyhydric alcohols and their condensation products. The aliphatic polyhydric alcohols are frequently termed *monosaccharides* (sometimes simply *saccharides* or simple sugars) and have either the primary alcohol function oxidized to an aldehyde or the secondary alcohol function oxidized to a ketone. They have the empirical formula $(CH_2O)_n$, where $n \geq 2$ for aldehydes and ≥ 3 for ketones. Monosaccharides may be subclassified into *aldoses* and *ketoses* according to whether they contain an aldehyde or a ketone group and into *dioses*, *trioses*, *tetroses*, etc. according to the number of carbon atoms they contain. For example, xylose may be considered an *aldopentose* (containing an aldehyde function and a total of five carbon atoms); similarly, fructose may be considered a *ketohexose* (containing a ketone function and a total of six carbon atoms).

The carbon skeleton of the common monosaccharides is unbranched and each carbon atom contains a hydroxy group except for the one containing the carbonyl oxygen that is combined in an *acetal* or *ketal* linkage. The total scheme for the aldoses and the ketoses is shown in Table 26-4 with the intermediate —CH(OH)— groups represented by horizontal lines drawn on the side to which the OH group is attached. Starting with the aldotrioses, the insertion of each —CH(OH)— group introduces a chiral center (asymmetric carbon atom), giving rise to an increasing number of stereoisomers. The enantiomorphs of each stereoisomeric pair are distinguished by the *configurational* notations D- and L-, referring respectively to whether the OH of the last inserted —CH(OH)— is on the right or left of the vertical axis when the formulas are drawn in the stick configuration as shown in Table 26-4. It is important to remember that the D- and L- notations have nothing to do with the direction of optical rotation and also that the actual demonstration of whether a given stereoisomer is D- or L- is a matter of extensive laboratory experimentation. It also should be noted that the prefixes D- and L- refer to the asymmetric carbon atom farthest removed from the carbonyl carbon atom. Two saccharides differing only in the configuration around the carbon atom adjacent to the carbonyl group are called *epimers* of each other. For example, D-glucose and D-mannose are epimers with respect to the second carbon atom.

Measurements of various characteristics, such as the propensity to function as reductants, the ability to form acetal derivatives, mutarotation, etc., have demonstrated conclusively that the open-chain formulas shown above do not represent the true structure of at least the higher monosaccharides such as the pentoses and hexoses. For example, in aqueous solution, many of the higher monosaccharides behave as if an additional chiral center is present. In reality, the structures are cyclic and may be looked upon as internal

Table 26-3. Popular Herbal Medicines—Their Bases and Source

HERBAL PRODUCT	SOURCE	ACTIVE INGREDIENT(S)	COMMON USES	COMMON SIDE EFFECTS	SUPPORTING EVIDENCE
Bilberry	*Vaccinium myrtillus*	Vitamins A & C, flavonoids, anthocyanin, and glucoquinine.	Improve eyesight, increase bloodflow, and treatment of diabetes	None known	Studies have indicated an improvement in eyesight, due mainly to the effects of vitamin A.
Black Cohosh	*Actaea racemosa* aka. *Cimicifuga racemosa*	Remifemin (brand name of standardized extract)	Menopausal symptoms, peripheral artery disease, and hypercholesterolemia	Overdose: nausea, dizziness, visual disturbances, nervous system abnormalities, increased perspiration and brachycardia. Large doses may induce miscarraige.	Studies have shown measurable effect on reproductive hormones. Studies have also shown that established breast tumor cell lines were not stimulated, leading scientists to consider Black Cohosh for studies as a substitute for hormone replacement therapy.
Cat's Claw	*Uncaria tormentosa*	Several alkaloids including: rhynchophylline, mytraphylline, gambirine, and hirsutine, also six quinovic acid glycosides	Inflammation, as an astringent, gastric ulcer, rheumatism, contraception, and cancer	Few to none.	Studies have verified; some anti-cancer claims, as well as some immunostimulant properties. The major effective ingredient, rhynchophylline may decrease blood pressure to the point of being hypotensive at certain doses.
Chamomile	*Matricaria recutita*	Bisabolol and flavanoids	Inflammation, GI spasms, and as a sedative	Persons allergic to the Compositae family may experience anything from contact dermatitis to anaphylaxis.	Anti-inflammatory and antipyretic claims are supported in animal models. Its main active ingredient, rhynchophylline, has also been shown to decrease blood pressure to the point of being hypotensive at certain doses.
Chaste Tree	*Vitex agnus-castus*	Monoterpene derivatives (limonene, 1,8-cineol, bornyl acetate, α- and β-pinene, sabinene), flavonoids (castican, orientin, isovitexin), and iridoid glycosides (agnuside, aucubin).	Menstrual irregularities, hormone imbalance, breast pain, uterine pain, and decreased sex drive in males	GI symptoms, rash, itching, headaches, and menstrual abnormalities can occur.	Progesterone/Estrogen balance was improved in studies. Its inhibition of prolactin release has also been supported, this can aid in the correction of luteal phase defects.
Cranberry	*Vaccinium macrocarpon*	Hippuric acid, although recent studies have suggested other alternatives.	Treatment, or prevention, of urinary tract infections	GI symptoms, such as diarrhea, can occur at very high doses.	Significant decrease in urinary pH has been observed in studies. However, treatment is still unproven as bacterial susceptibility and minimum effective dose were unclear.
Echinacea	*Echinacea augustifolia* (common); *E. purpuree* (commerce)	Isobutylamides	To decrease the length of cold or prevent its contraction	Those allergic to the daisy family should avoid due to immune response symptoms.	Some evidence points toward a shortening of duration for the common cold; however, prevention has been shown to be doubtful at best.
Evening Primrose	*Oenothera biennis*	Gamma-linolenic acid (GLA)	Breast disorders, PMS, breast pain, cardiovascular disease, rheumatiod arthritis, multiple sclerosis, atopic eczema, and other dermatologic disorders	None Known	Cholesterol—studies have shown that the active ingredient is successful in significantly lowering blood cholesterol; however, in the concentration found in primrose oil, such a decrease is substantially less, if any. Breast cancer—studies have indicated only a slight decrease in recurrence in those patients who have recovered from breast cancer. Premenstrual syndrome—studies have indicated a decrease in symptoms associated with primrose oil.

Table 26-3. Popular Herbal Medicines—Their Bases and Source *(continued)*

HERBAL PRODUCT	SOURCE	ACTIVE INGREDIENT(S)	COMMON USES	COMMON SIDE EFFECTS	SUPPORTING EVIDENCE
					Rheumatiod arthritis—studies have indicated a drop in NSAID usage among those taking primrose oil, suggesting some level of efficacy; however, disease modification has not been shown.
Feverfew	*Tanacetum parthenium*	Parthenolide	Fever, migraine prophylaxis, arthritis, manstrual pain, asthma, and dermatitis	Abrupt discontinuation can result in a withdrawal syndrome; increased heart rate has also been reported. Should not be used in children < 2 years old, or in pregnant or lactating women.	Severity and incidence of migraine headaches has been shown to be decreased in those taking feverfew.
Garlic	*Allium sativum*	Alliin[(+)-S-allyl-L-cysteine sulfoxide]	High blood sugar, hypercholesterolemia, and hyperlipidemia	None known	Garlic has been shown clinically to increase HDL, decrease LDL and total cholesterol. It has also been shown to have antioxidant properties and to decrease platelet aggregation.
Ginger	*Zingiber officinale*	Gingerols; shogaol	Prevent motion sickness, for cough, stomachache, and gallbladder disease.	In large amounts, CNS depression may occur. May affect cardiac function and anticoagulant activity.	Ginger has been shown to dramatically increase the amount of time needed to reach a state of motion sickness. It also decreases cardiac workload by increasing vasodilation. It has a strong antimicrobial effect.
Ginkgo	*Ginkgo biloba*	Flavonol and flavone glycosides (eg, of quescetin and kaempferol); rutin	Raynaud's disease, stress, tinnitis, dementia, cerebral insufficiency, anxiety, asthma, and circulation problems	Rare, but may include heart palpitations, dizziness, headache and dermatological reactions.	Ginkgo has been shown to increase cerebral blood flow and decrease cerebral deficiency. It has also been shown to decrease inflammatory response in the lungs reducing severity of asthma attacks. It also increases microcirculation and improvement in pathologic blood flow diseases has been observed.
Ginseng	*Panax quinque-folius*	Ginsenosides (triterpenoid saponin glycosides)	Decreased energy, cancer, immune support, and cardiovascular problems	Nervousness is the most common side effect; also some breast nodulation and vaginal bleeding have been reported.	An increase in CNS stimulatory and inhibitory effects has been observed in patients taking Ginseng. An increase in overall cognitive function has been established as well. However, no studies to date have linked ginseng and improved physical performance.
Goldenseal	*Hydrastis canadensis*	Isoquinolone alkaloids (hydrastine, canadine, and berberine)	Topical infections and as an anticatarrhal	Side effects are rare, but contraindicated in patients with hypertension or pregnancy. In very high doses, can cause nausea, anxiety and seizures.	Clinically, it has been shown to have modest antimicrobial activity, most effective topically.
Grape Seed	*Vitus vinifera*	Essential fatty acids and tocopherols	Nutritional supplement (fatty acid)	Hepatotoxicity in animal studies.	Clinically, it has been shown to have anti-enzyme properties resulting in a decrease in breakdown of compounds important for tissue structure, such as collagen, elastin, and hyaluronic acid.

(continues)

Table 26-3. Popular Herbal Medicines—Their Bases and Source *(continued)*

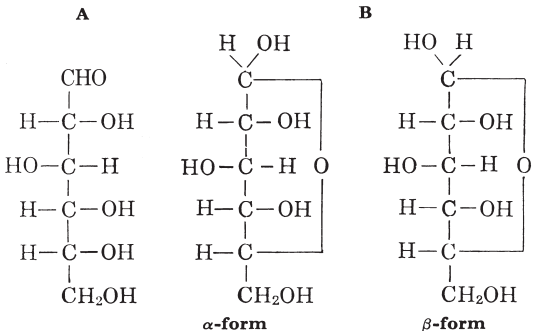
HERBAL PRODUCT	SOURCE	ACTIVE INGREDIENT(S)	COMMON USES	COMMON SIDE EFFECTS	SUPPORTING EVIDENCE
Green Tea	*Camellia sinensis*	Catechins and polyphenol components	Cancer, hyperlipidemia, prevention of dental carries, as an antimicrobial, antimutagenic, and an antioxidant	Caffeine in green tea may cause nervousness and increased heart rate, and should be avoided during pregnancy.	Clinically, it has been shown to decrease total cholesterol; however, triglycerides and HDL were unchanged. Also, antimicrobial activity has been shown especially against mouth flora. It also has been shown to inhibit the growth of some harmful GI pathogens, although the dose was 9 cups per day.
Hawthorn	*Crataegus laevigata*	Oligomeric procyanidins (epicatechin and flavonoids)	Hypertension, abnormal heart rate, artherosclerosis, angina pectoris, and as an antispasmodic and a sedative.	Hypotension and sedation can be experienced at high doses. May interfere with digoxin blood levels.	Studies have shown that hawthorn increases vasodilation and coronary artery flow, as well as to stabilize heart rate. It has also been shown to decrease lipid levels.
Horse Chestnut	*Aesculus hippo-castanum*	Aesculin	Edema, inflammation, and venous insufficiency	Use should be avoided due to classification as an unsafe herb by the FDA because of toxicity. Topical products containing this herb may also be carcinogenic.	Increased vascular resistance and tone has been indicated. A decrease in complaints and edema measures was shown in patients with peripheral edema. Anti-inflammatory properties have also been supported.
Kava Kava	*Piper methys ticum*	Kava lactones	Mild to moderate anxiety and as a sedative	Should not be used during pregnancy or by patients with depression. Use should be limited to 3 months to avoid habit-forming tendancies. Also, problems with vision and a condition similar to pellagra have been reported.	Studies have supported Kava's positive effect on patients with mild to moderate anxiety. It has also been demonstrated as an effective anticonvulsant. In addition, kava has an antithrombotic effect on platelet aggregation.
Licorice	*Glycyrrhiza uralensis*	Carbenoxalone	GI complaints	Lethargy and quadriplegia may result from long-term daily consumption.	Licorice has been shown to increase the lifespan of gastric epithelial cells. It has been demonstrated to be less effective than Cimetidine at treating gastric and duodenal ulcers.
Milk Thistle	*Silybum marianum*	Silymarins (flavano-lignanssilybin, isosilybin, dehy-drosilybin, silydianin, and silychristin)	Liver damage prophylaxis, antitoxin	Mild allergic reactions and mild GI symptoms.	Milk thistle has been shown to normalize liver enzymes; however, improvement in the evolution and mortality of cirrhosis is not supported.
Saw Palmetto	*Serenoa repens*	Probable active compounds are: phytosterols, fatty acids and their ethyl esters, and monoacylgly-cerides.	Symptoms associated with benign prostatic hyperplasia	Should be avoided during pregnancy, but no other side effects aside from mild GI symptoms.	Clinically, several symptoms associated with benign prostatic hyperplasia have been shown to decrease in those taking saw palmetto. It has not been shown to have any effect on prostate size or presence of prostate specific antigen in the blood.
St John's Wort	*Hypericum perforatum*	Hypericin, hyperforin, and related naptho-dianthrones	Depression and viral infection	Rare, but may include constipation, other GI symptoms, dry mouth, dizziness and photosensitivity. Mania and sexual disturbance occur even more rarely.	Clinical trials have shown that patients taking St. John's Wort have a significant decrease in serotonin reuptake as well as an increased dopamine function. Also, several viruses (influenza, herpes simplex 1 & 2 and some retroviruses) have susceptibility to this compound. St. John's Wort has also demonstrated potent antimicrobial activity.

Table 26-3. Popular Herbal Medicines—Their Bases and Source *(continued)*

HERBAL PRODUCT	SOURCE	ACTIVE INGREDIENT(S)	COMMON USES	COMMON SIDE EFFECTS	SUPPORTING EVIDENCE
Valerian	*Valeriana officinalis*	Valepotriates, valerenic acid, and valeranone	Restlessness and sleep disorders	Few to none.	Valerian has been demonstrated to improve sleep disorders very effectively. Also, antianxiety studies have indicated efficacy in treating those symptoms.

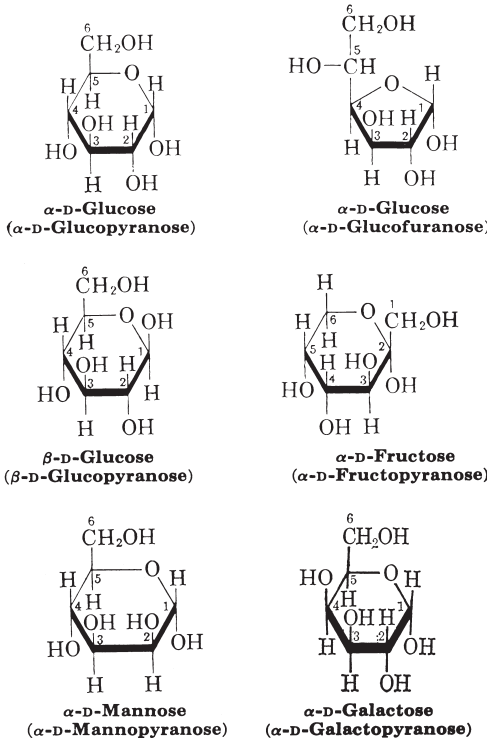
Data from DerMarderosian A, et al. *Guide to Popular Natural Products,* 2nd ed. St. Louis, MO: Facts and Comparisons, 2001; and *United States Pharmacopeia and National Formulary (USP 27–NF 22).* Rockville, MD: The United States Pharmacopeial Convention, Inc., 2003.

hemiacetals formed by condensation of the carbonyl oxygen atom and one of the alcoholic hydroxyls. Although such a reaction can involve any of the hydroxyl groups, theoretical considerations suggest that the γ- and δ-hydroxyl groups are situated more ideally to participate in the cyclization, thus giving rise to furanose (containing a furan ring) and pyranose (containing a pyran ring) structures. Experimental evidence indicates that the aldohexoses, in their normal monosaccharide states, exist largely in the more stable pyranose form. For example, the open-chain formula (**A**) for D-glucose gives way to the corresponding cyclic structures (**B**):

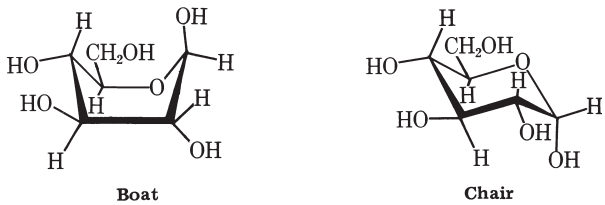


The two stereoisomeric forms of (**B**), conventionally distinguished by α- and β- nomenclature, arise because the cyclization automatically renders the former aldehyde carbon atom asymmetric. This isomerization occurs spontaneously in aqueous solution and causes the specific rotation to change until a final equilibrium value is reached. This process is termed *mutarotation.* Incidentally, both the α- and β-forms of D-glucose are well known with the commercial form (dextrose) being the α- variety. Isomeric forms of monosaccharides that differ from each other only in configuration of the chiral carbon atom derived from the carbonyl group are *anomers* and the newly formed asymmetric carbon atom is termed the *anomeric carbon.*

The two-dimensional representations of cyclic structures as in (**B**) have largely been superseded by the Haworth Projection models. In these models, the ring is usually represented as planar (although strict planarity is not implied), and the disposition of hydrogen atoms and substituents is portrayed by a vertical assignment upward or downward from the ring plane. Haworth structures for some selected hexoses are shown below, along with the conventional ring numbering. Note that the edge of the ring nearest the reader is represented by bold lines; thus, the plane of the ring is perpendicular to the page. For comparison, both the furanose and pyranose structures are shown for α-D-glucose.

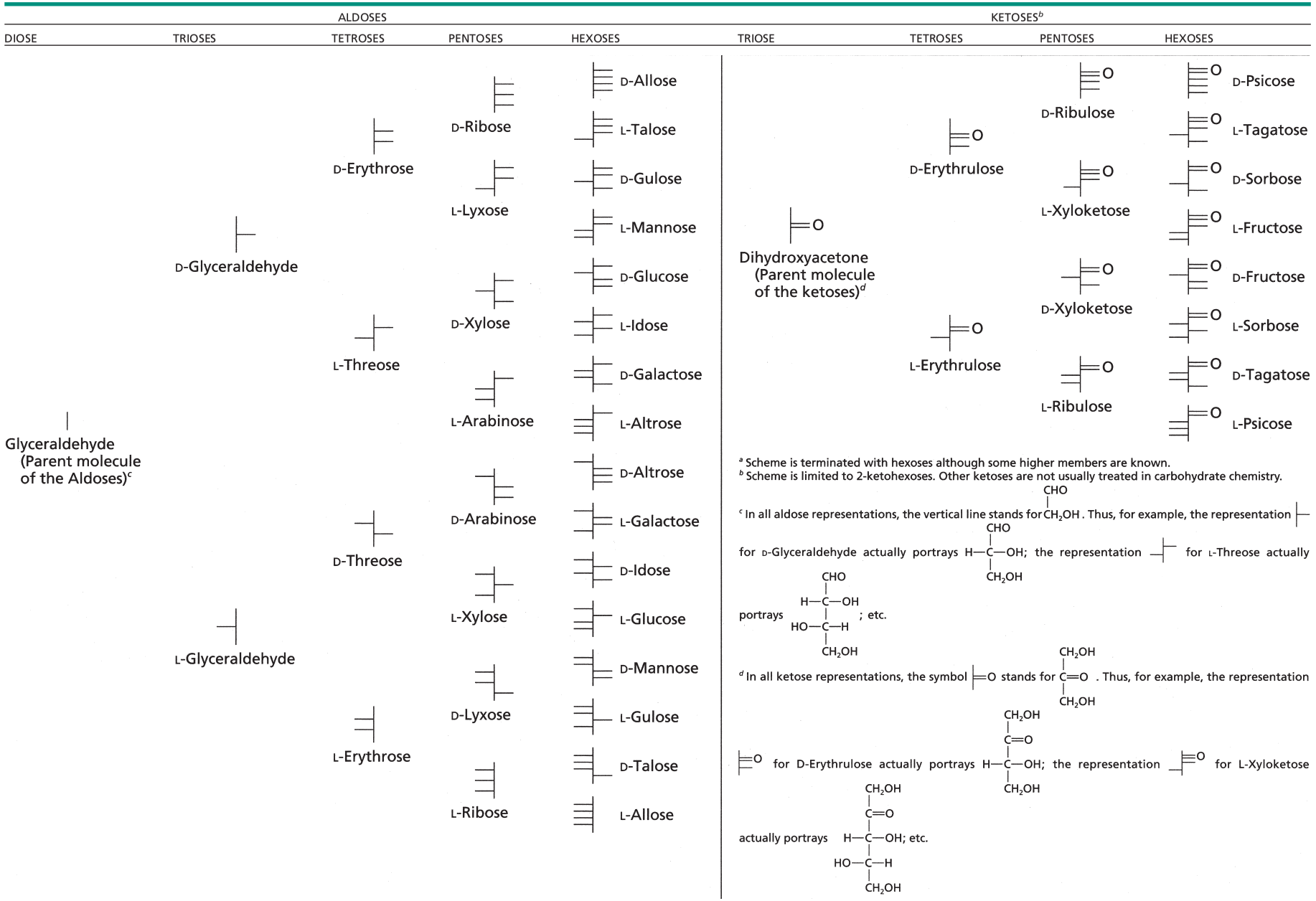


The Haworth projections are somewhat misleading, however, because they suggest that the five and six-member furanose and pyranose rings are planar, which is not the actual case. The pyranose rings exist in two conformations, the *chair* form and the *boat* form. The chair form of the pyranose ring, which is relatively rigid and much more stable than the boat form, predominates in aqueous solutions of hexoses. The substituent groups in the chair form are not equivalent geometrically or chemically; they fall into two classes, *axial* and *equatorial.* The equatorial hydroxyl groups of pyranoses are esterified more readily than axial groups.



The condensation products of the monosaccharides, whose fundamental structural units are either aldoses or ketoses, are

Table 26-4. Monosaccharides[a]



[a] Scheme is terminated with hexoses although some higher members are known.

[b] Scheme is limited to 2-ketohexoses. Other ketoses are not usually treated in carbohydrate chemistry.

[c] In all aldose representations, the vertical line stands for CH_2OH. Thus, for example, the representation for D-Glyceraldehyde actually portrays

; the representation for L-Threose actually portrays

; etc.

[d] In all ketose representations, the symbol =O stands for

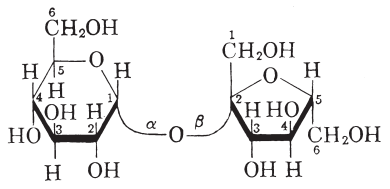
. Thus, for example, the representation =O for D-Erythrulose actually portrays

; the representation =O for L-Xyloketose actually portrays

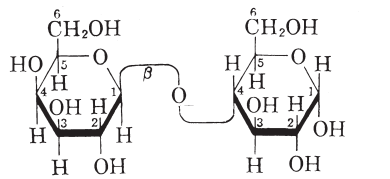
; etc.

sometimes referred to as *saccharide anhydrides.* They are subclassified into disaccharides, trisaccharides, etc. according to the number of monosaccharide units present. *Polysaccharides* contain many monosaccharide units joined in long linear or branched chains. Most polysaccharides contain recurring monosaccharide units of either a single or alternating type. The term *polysaccharide* may be used broadly to embrace all of the condensation products including the disaccharides or more restrictively excluding the disaccharides and sometimes the tri- and tetrasaccharides. In this case, the di- to decasaccharides may be grouped under the term *oligosaccharides* (from the Greek, *oligo, a few*).

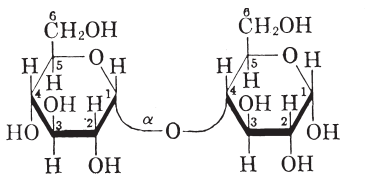
The structures and systematic names of the four best-known disaccharides are shown below. The systematic bracketed names identify precisely the location of the oxygen bridge joining the two monosaccharide residues. Also note that, in the case of sucrose, the stable furan conformation is shown as being dominant for the fructose portion of the molecule.



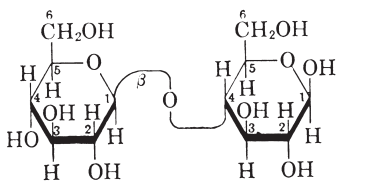
Sucrose
[β-D-Fructofuranosyl-α-D-glucopyranoside]



Lactose (α-Lactose)
[4-(*O*-β-D-Galactopyranosyl)-α-D-glucopyranoside]



Maltose
[4-(*O*-α-D-Glucopyranosyl)-α-D-glucopyranoside]



Cellobiose
[4-(*O*-β-D-Glucopyranosyl)-β-D-glucopyranoside]

The naturally occurring polysaccharides (eg, the starches, cellulose, glycogen, and inulin) are formed primarily from pentoses and hexoses but vary considerably in size and structure. For example, inulin is a relatively small polymer composed of approximately 30 fructose (fructofuranose) units; whereas, cellulose is a relatively large polymer probably containing no less than 1000 glucopyranose units. In some polysaccharides, such as cellulose, evidence is strong that the polymers are purely linear; in others, such as starch and glycogen observed experimental data requires that considerable branching is present along the chain. Polysaccharides often are classified on the basis of their monomers; for example, pentosans are polymers of pentoses and hexosans are polymers of hexoses. Frequently, such classification is rendered more specific. For example, cellulose is a glucosan (the hexose unit is D-glucose) and inulin is a fructosan (the hexose unit is D-fructose). The complete systematic names of carbohydrates are considered cumbersome and consequently find little use in ordinary chemical practice. Recognizing this, both IUPAC and *Chemical Abstracts* admit the commonly used trivial names.

Physical and Chemical Properties

The common monosaccharides, namely the pentoses and hexoses, are white, crystalline solids that usually melt rather sharply but with simultaneous decomposition. They are readily soluble in water, much less soluble in methanol or ethanol, and relatively insoluble in ether. The common disaccharides, all hexoses, also display these characteristics. The soluble, lower molecular weight carbohydrates are also characterized by a sweet taste but their relative sweetness varies considerably. For example, lactose is only about ⅙, maltose about ⅓, and glucose about ¾ as sweet as sucrose. Fructose, on the other hand, is about 1.7 times sweeter than sucrose. The higher polysaccharides such as starch, cellulose, and inulin are amorphous, do not melt sharply, and are much less water-soluble; however, they typically have the capacity to absorb significant amounts of water and often form gels.

All carbohydrates are optically active, and their specific rotations serve as one means of differentiation. Many display the phenomenon of *mutarotation*, a continuing change in the value of the rotation until a final fixed value is attained. For example, a freshly prepared aqueous solution of α-D-glucose has an $[\alpha]_D^{20}$ of +113°, but gradually changes to a final value of +52°. It has been frequently demonstrated that such changes in rotation are due to structural shifts and that the final value is quantitatively characteristic of the components present in the equilibrium mixture. In the case of glucose, this ultimate equilibrium value is derived from an aqueous solution containing about ⅓ of the α-D-form ($[\alpha]_D^{20} = +112.2°$) and about 2/3 of the β-D-form ($[\alpha]_D^{20} = +18.7°$). The attainment of the equilibrium state is hastened by acid and especially base. However, hastening the action of the equilibrium should be done with very dilute solutions of acids or alkali such as ammonia. Concentrated acids will yield other compounds such as 5-hydroxymethylfurfural from D-glucose and high concentrations of alkali or strong alkali themselves cause D-glucose to form D-fructose and D-mannose through enediol structures in an equilibrium reaction.

The chemical properties of the carbohydrates are, in general, those expected based upon their structural features previously described. They display all the chemical reactions characteristic of alcohol and carbonyl groups. The aldehyde group of an aldose and the terminal hydroxyl group are each capable of being oxidized to the corresponding mono- or dicarboxylic acid. The carbonyl function can also undergo reduction to a primary or secondary alcohol. Both aldoses and ketoses exhibit the usual addition reactions typical of the carbonyl function. For identification purposes, the carbonyl and adjacent alcohol functions will form phenylhydrazine derivatives known as *osazones*, which give characteristic melting points and exhibit definite crystalline structures. It should be noted that glucose, fructose, and mannose yield the same osazone because the differences in structure and configuration about carbon atoms 1 and 2 are abolished. Also, reactions with copper or silver ions under proper conditions, in which the metal ion is reduced in valence and the carbohydrate is oxidized, are employed to distinguish *reducing* from *nonreducing* sugars (as is the strong acid/substituted furfural reaction described above). The hydroxyl groups can be esterified or etherified, a process often used to decrease the polarity and thus increase volatility for identification and separation purposes, especially in gas and liquid chromatography and mass spectrometry.

All polysaccharides can be hydrolyzed to the simple monosaccharides of which they are composed. Either chemical (boiling with dilute acid) or enzymatic procedures can be employed with the latter showing much more specificity. In some instances, it is possible to hydrolyze only α-linkages or even cleave at a specific monosaccharidic linkage within the polymer

chain. Many microorganisms possess the ability to hydrolyze carbohydrates to simple alcohols, ketones, or acids, usually resulting in the production of carbon dioxide, by the process known as *fermentation*. Ethanol, acetic acid, citric acid, 2-butanone, and butyl alcohol are several of the products derived from sucrose by such a procedure. There are specific microorganisms used in quite efficient fermentation processes to transform l-sorbose, a glucose derivative, into ascorbic acid (vitamin C), which is actually the γ-lactone of a hexanoic acid having an enediol structure at carbon atoms 2 and 3.

Occurrence and Uses

Carbohydrates are the first products to arise from photosynthesis, and therefore, occur abundantly in nature. It has been estimated that more carbohydrate material occurs naturally than all other organic material combined. Although they are preponderantly important within the vegetable kingdom, carbohydrates also occur abundantly and have very important nutritional and biological roles in the animal world. Glucose and fructose are the only monosaccharides that occur in the free state to any important extent. They are present in the juices of many ripe fruits. Among the disaccharides, only sucrose (cane or beet sugar) and lactose (milk sugar) occur in important quantities. Prominent, naturally occurring, hexosan polysaccharides include cellulose (the primary structural material in the vegetable world), starch (the primary carbohydrate fuel reserve in the vegetable world; found primarily in seeds and underground roots in the form of granules or grains), and glycogen (the primary carbohydrate fuel reserve in the animal world; often dubbed as animal starch and found primarily in the liver). Pentosan polysaccharides occur abundantly in cereal straws and beans and yield the industrially important furfural upon suitable treatment with sulfuric acid.

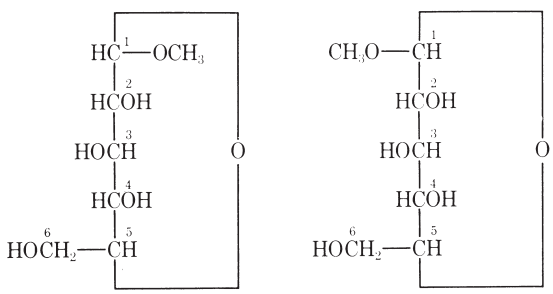
Carbohydrate derivatives (chemical combinations with noncarbohydrate substances or slightly altered carbohydrates) occur plentifully in nature. The monosaccharide phosphate esters, D-ribose and α-deoxyribose, are pentose constituents of RNA and DNA, respectively. Other classes include the gums and mucilages (in which the terminal groups have been oxidized forming uronic acid), pectins, glycoproteins, and glycolipids (cerebrosides). Chitin, a condensation polymer of *N*-acetyl-D-glucosamine (which contains NH_2 instead of OH in the 2 position), comprises the skeletal material of crabs, lobsters, and insects of the arthropoda class. This same acetylglucosamine is also present in hyaluronic acid, an important constituent of connective tissue. Many bacteria have been shown to produce complex carbohydrate materials and some are known to have immunological importance. A special class of derivatives, the *glycosides,* is discussed in a following section.

Due to their sweet taste, the soluble low molecular weight carbohydrates are often used as sweeteners by the food and pharmaceutical industries. Fructose, due to its significantly sweet taste, may be used as a sweetener in smaller quantities than other sugars; and therefore, is often used as a substitute for sucrose to lower the caloric content of certain foods. For this reason, fructose is frequently used to manufacture candies for persons suffering from diabetes. Lactose is commonly used as diluent for the preparation of solid dosage forms such as tablets and capsules. The ability of many polysaccharides to absorb water is a physical property that has found numerous uses. For example, cotton fibers (primarily cellulose) are used for various types of surgical dressings, starch is used as dusting powder, pectin and carrageen (a mixture of polysaccharides from algae) are used as gelling agents, and dextran (α,1,6-glucan) is used as a blood plasma replacement and matrix for column chromatography. Polysaccharides are also commonly used as suspending agents, tablet binders and disintegrants, emulsifiers, and film formers in the preparation of various pharmaceutical dosage forms. In addition, several polysaccharides may be used as therapeutic agents. For example, psyllium, from plantago seed, is commonly used as a laxative; acacia gum is used in lozenges as a demulcalent for cough, diarrhea, and throat problems; and the sodium salt of alginic acid, a polysaccharide from brown seaweed, is used for the treatment for GERD.

Glycosides

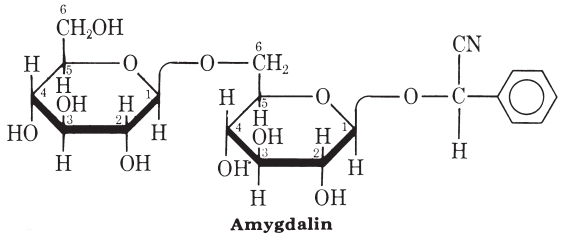
COMPOSITION AND STRUCTURE—*Glycosides* may be defined broadly as condensation products of saccharides with various kinds of organic hydroxy, and occasionally thiol compounds (usually noncarbohydrate in nature), with the added restriction that the OH of the hemiacetal portion of the carbohydrate must participate in the condensation. It is obvious that the polysaccharides also are encompassed in this broad definition. The nonsugar portion is termed an *aglycone* (or *aglycon*), or a *genin,* and a majority have cyclic structures. From a structural viewpoint, the glycosides may be looked upon as internal acetals. In modern terminology, the glycosides are usually classified according to their sugar moiety. For example, in glucosides, the sugar moiety is glucose; in fructosides, it is fructose; in galactosides, it is galactose, and so on (Table 26-5). The sugar in a large number of glycosides is D-glucose; therefore, in older literature, the term *glucoside* is used in a generic sense and is synonymous with the modern term *glycoside.* Classification according to the complexity of the sugar moiety is also employed frequently; for example, *monosides* are monosaccharide sugars, *biosides* are disaccharides, and *triosides* are trisaccharides. Classification on the basis of the aglycones, while feasible, is intricate because of the large variety of aglycones; however, with certain classes of glycosides (such as the cardiotonics) such subclassification is occasionally encountered in the literature.

Two series of stereoisomeric glycosides are known, the α- and β-glycosides. Taking the methyl-D-glucosides as a simple example, they are represented by:



α-Methyl-D-glucoside **β-Methyl-D-glucoside**

The glycosidic linkage is formed by dehydration involving a hydroxyl group of the aglycone (in the above example, methanol) and the hydroxyl group on the hemiacetal carbon of the sugar, thus forming an acetal type of structure. If the −OR (in the above example, $-OCH_3$) group is in the same steric sense as the CH_2OH group on C-5 (for D-family sugars), the glycoside configuration is designated as β-; if it is in the opposite steric sense, it is designated as α-. The great majority of naturally occurring glycosides are of the β- variety. For an illustration of how this relationship is reflected in the Haworth-type formulas, see amygdalin below, which is a typical β- glycoside, and therefore, the formula is written with the linking oxygen on the same plane as the CH_2OH group on C-5.



Amygdalin

Table 26-5. Selected Glycosides

NAME AND MOLECULAR FORMULA [a]	SOURCES [b]	AGLYCONE (GENIN)	SUGAR MOIETIES [c]
Amygdalin $C_{20}H_{27}NO_{11}$	Seeds of Amygdalaceae, Drupaceae, and Pomaceae; principally from almonds	D-Mandelonitrile → Benzaldehyde + HCN	Gentiobiose → 2 D-Glucose
Arbutin (Ursin) $C_{12}H_{16}O_7$	Leaves of plants of the Ericaceae and Rosaceae	Hydroquinone	D-Glucose
Coniferin (Abietin; Laricin) $C_{16}H_{22}O_8$	Plants of the Coniferae (ie, pine, spruce, and fir)	Coniferyl alcohol [4-Hydroxy-3-methoxycinnamyl alcohol]	D-Glucose
Cymarin $C_{30}H_{44}O_9$	Various species of Apocynum	Strophanthidin (a steroid)	Cymarose (3-Methyl-digitoxose)
Daphnin $C_{15}H_{16}O_9$	Bark and flowers of varieties of Daphne	7,8-Dihydroxycoumarin	D-Glucose
Digitoxin $C_{41}H_{64}O_{13}$	Leaves of *Digitalis lanata* and *purpurea*	Digitoxigenin (a steroid)	3 Digitoxose (Digitoxose is a 2,6-bisdesoxy-aldohexose)
Digoxin $C_{41}H_{64}O_{14}$	Leaves of *Digitalis lanata* or *Digitalis orientalis*	Digoxigenin (12-Hydroxydigit-oxigenin) (a steroid)	3 Digitoxose
Frangulin $C_{21}H_{20}O_9$	Seeds and barks of various species of Rhamnus, especially alder buckthorn	4,5,7-Trihydroxy-2-methylanthraquinone	Rhamnose
Lanatoside A $C_{49}H_{76}O_{19}$	Leaves of *Digitalis lanata*	Digitoxigenin (a steroid)	2 Digitoxose + Acetyldigitoxose + D-Glucose
Lanatoside B $C_{49}H_{76}O_{20}$	Leaves of *Digitalis lanata*	Gitoxigenin (16-Hydroxy-digit-oxigenin - a steroid)	2 Digitoxose + Acetyldigitoxose + D-Glucose
Lanatoside C $C_{49}H_{76}O_{20}$	Leaves of *Digitalis lanata*	Digoxigenin (a steroid)	2 Digitoxose + Acetyldigitoxose + D-Glucose
Ouabain (G-Strophanthin) $C_{29}H_{44}O_{12}$	Seeds of *Strophanthus gratus* and varieties of Acokanthera	Ouabagenin (a steroid)	Rhamnose
Phlorizin (Phlorhizin; Phloridzin) $C_{21}H_{24}O_{10}$	Roots and leaves of various plants of the Rosaceae	Phloretin [β-(p-Hydroxyphenyl)-2,4,6-trihydroxypropiophenone]	D-Glucose
Prunasin $C_{14}H_{17}NO_6$	Various parts of many Prunus plants	D-Mandelonitrile → Benzaldehyde + HCN	D-Glucose
Rutin (Melin, Eldrin, and others) $C_{27}H_{30}O_{16}$	Occurs in many plants. Chief source is the buckwheat plant, *Fagopyrum esculentum*	Quercetin [3,3′,4′,5,7-Pentahydroxyflavone]	Rutinose → L-Rhamnose + D-Glucose
Salicin $C_{13}H_{18}O_7$	Various Salix and Populus plants, especially the bark	Saligenin [o-Hydroxybenzyl alcohol]	D-Glucose
Scillaren A $C_{36}H_{52}O_{13}$	Bulbs of *Urginea maritima*	Scillaridin A (a steroid)	Scillabiose → L-Rhamnose D-Glucose
Sinigrin (Potassium Myronate) $C_{10}H_{16}KNO_9S_2$	Seeds of *Brassica nigra*, *Brassica juncea*, and other plants of the Cruciferae	$CH_2{=}CHCH_2N{=}C(SH)OSO_3K$ → $CH_2{=}CHCH_2NCS + KHSO_4$	D-Glucose
K-Strophanthin-β $C_{36}H_{54}O_{14}$	Seeds of *Strophanthus kombé*	Strophanthidin (a steroid)	Strophanthobiose → Cymarose + D-Glucose

[a] Shown as the anhydrous forms. As isolated, many glycosides are hydrated.
[b] Typical and well known, but not exclusive.
[c] Produced upon complete hydrolysis unless otherwise indicated.

This compound, like all other glycosides, contains several asymmetric carbon atoms and is optically active. In this instance the aglycone is also optically active due to the asymmetric carbon to which the phenyl, nitrile, hydrogen, and gentiobiose residues are attached.

The carbohydrate component of glycosides is frequently a di- or polysaccharide, such as amygdalin, digitoxin, and rutin (Table 26-5). In many instances it is possible, under carefully controlled hydrolysis, to cleave only a portion of the aglycone moiety of the natural (primary) glycoside to yield a derived substance that is still glycosidic. Amygdalin, for example, hydrolyzes under the influence of the enzyme amygdalase to yield glucose and prunasin (Table 26-5). Such derived glycosides are often referred to as *secondary glycosides.* The same enzyme is often able to hydrolyze different glycosides, but the α- and β-stereoisomers of the same glycoside cannot usually be hydrolyzed by the same enzyme. For instance, *Emulsin* has been found to hydrolyze only β-glycosides; therefore, those glycosides that are attacked by emulsin, such as amygdalin, are regarded as β-glycosides. Maltase hydrolyzes only α-glycosides.

PHYSICAL AND CHEMICAL PROPERTIES—The greater portion of the known glycosides, when pure, are colorless or white, optically active, and soluble in alcohol or diluted alcohol. The aglycones of the majority of glycosides are cyclic structures, and therefore, many have aromatic properties. The most characteristic chemical property of the glycosides is their susceptibility to hydrolysis, whereby they yield their sugar and nonsugar moieties. There are no simple identifying tests for

glycosides. It is through identification of the hydrolytic decomposition products that the composition of glycosides is commonly revealed. Methods for the detection of glycosides and for their quantitative determination involve the estimation of reducing sugars before and after hydrolysis by boiling with dilute acids or by the action of enzymes. Acid hydrolysis of glycosides is non-specific and occurs for both *alpha-* and *beta*-glycosidic linkages. On the other hand, enzymatic hydrolysis is often quite specific, as mentioned previously. It should be noted that there are two enzymes, namely emulsin of almond kernels and myrosin of black mustard seeds, each of which has the ability to hydrolyze a considerable number of different glycosides.

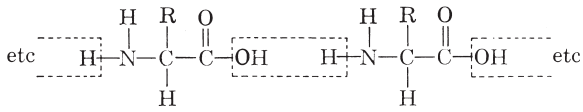
OCCURRENCE—Glycosides are distributed widely in the plant kingdom but rarely found in animals. Many fruits and other plant parts (ie, seeds, barks, and leaves) contain them. In addition, the pigments of flowers (anthocyanins) are of glycosidic character. Glycosides are extracted from the plant material by water, alcohol, or a mixture of the two. They occur in small amounts, and their isolation in a pure state is usually difficult and laborious. In addition, the enzymes responsible for hydrolyzing a particular glycoside frequently occur in the same plant along with the glycosides but usually in different cells. When the structure of the plant is destroyed by grinding or other means, the enzyme contacts the glycoside and soon exerts its hydrolytic action. Therefore, it is necessary to destroy any enzymes that are present before attempting to isolate glycosidal constituents. As a result, the processes used for glycoside production and purification vary according to the nature of the material and the glycoside. Many naturally occurring compounds not usually classed among the glycosides actually contain glycosidic linkages in their structures. Examples include gentamycin, amikacine, netilmicin, tobramycin, novobiocin, and streptomycin among the antibiotics, solanine and various other alkaloids (glucoalkaloids), and nucleosides (consist of a purine or pyrimidine base linked with D-ribose or D-2-deoxyribose). Certain glycosides will be covered in more detail within the following sections that pertain to their aglycone portion.

PROTEINS, PEPTIDES, AND AMINO ACIDS

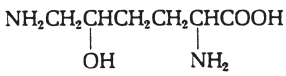
Composition and Structure

Unlike carbohydrates, proteins vary widely in composition, not only from one species to another but also among the various tissues and cellular fluids within a given species. These differences in composition result in different physical and chemical properties that are reflected in the diverse biofunctions in which proteins participate. The intimate roles these compounds play in the fundamental processes of tissue formation, regeneration, and function makes this class of substances the primary component of all living matter, and hence, the term *protein* (from the Greek, *first*). All proteins contain carbon, hydrogen, oxygen, and nitrogen. Nitrogen constitutes approximately 16% of most proteins, which leads to the rough factor of 6.25 generally employed to convert the amount of protein nitrogen found by analysis to the amount of total protein. Other elements such as sulfur, phosphorus, iodine, copper, iron, and occasionally zinc may be present.

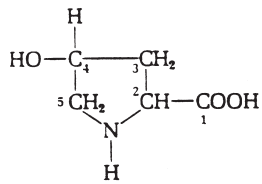
The fundamental structural units of proteins are α-amino acids, about 20 of which prominently participate in protein formation (Table 26-6). These building-block molecules contain at least one carboxyl group and one α-amino group, but differ in the structure of the remainder of the molecule. All except the simplest one, glycine, are capable of existing in both D- and L- configurations with respect to their α-carbon, but proteins contain only the L-enantiomers. The actual protein molecule consists of long-chain polymers that have resulted from condensation of the amino acids, thus producing amide or peptide linkages:



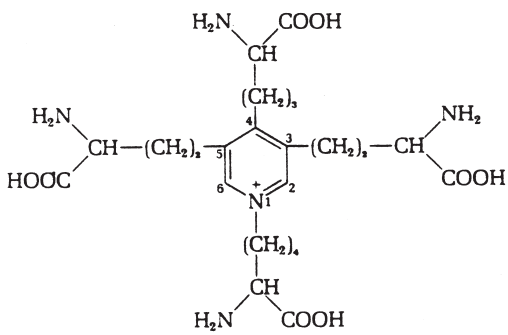
In addition to the 20 standard amino acids in Table 26-6, several others of relatively rare occurrence have been isolated from hydrolysates of some specialized types of proteins. All are derivatives of a standard amino acid. *Hydroxylysine*, the 5-hydroxy derivative of lysine, is present in collagen (as is *hydroxyproline*). *Desmosine* and *isodesmosine* occur in the fibrous protein *elastin*. As noted below, *desmosine* can be visualized as being formed from four lysine molecules with their side-chain moieties joined to form a substituted pyridine ring. Certain muscle proteins have been found to contain several *ε-N-methylated* analogs of *lysine* and *histidine*. β-*Alanine*, α-*aminobutyric acid, homocysteine, homoserine, citrulline, ornithine, canavinine, djenkolic acid,* and *β-cyanoalanine* are some naturally occurring amino acids that are not found in proteins. Some amino acids such as *γ-aminobutyric acid, α-aminoadipic acid, pipecolic acid, and δ-acetylornithine* exist only in the free state.



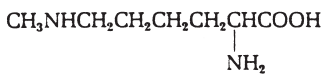
5-Hydroxylysine



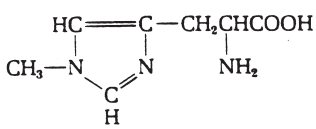
4-Hydroxyproline



Desmosine



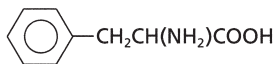
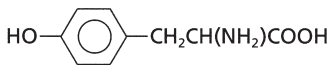
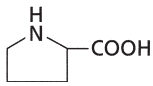
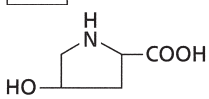
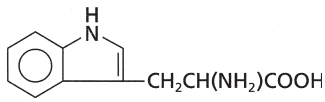
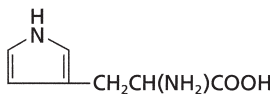
ε-*N*-Methyllysine



3-Methylhistidine

Proteins are macromolecules that differ from each other primarily in the number, type, and sequence of amino acid

Table 26-6. Prominent Protein Amino Acids

Neutral Aliphatic	
Glycine (Gly) aminoacetic acid	$CH_2(NH_2)COOH$
Alanine (Ala) 2-aminopropanoic acid	$CH_3CH(NH_2)COOH$
Serine (Ser) 2-amino-3-hydroxypropanoic acid	$CH_2(OH)CH(NH_2)COOH$
Threonine (Thr) 2-amino-3-hydroxybutanoic acid	$CH_3CH(OH)CH(NH_2)COOH$
Valine (Val) 2-amino-3-methylbutanoic acid	$CH_3CH(CH_3)CH(NH_2)COOH$
Leucine (Leu) 2-amino-4-methylpentanoic acid	$CH_3CH(CH_3)CH_2CH(NH_2)COOH$
Isoleucine (Ile) 2-amino-3-methylpentanoic acid	$CH_3CH_2CH(CH_3)CH(NH_2)COOH$
Neutral Thioaliphatic	
Cysteine (CySH) 2-amino-3-mercaptopropanoic acid	$CH_2(SH)CH(NH_2)COOH$
Cystine (CyS-SCY) 3,3′-dithiodi(2-aminopropanoic acid)	$SCH_2CH(NH_2)COOH$
Methionine (Met) 2-amino-4-(methylthio)butanoic acid	$CH_2(SCH_3)CH_2CH(NH_2)COOH$
Neutral Aromatic	
Phenylalanine (Phe) 2-amino-3-phenylpropanoic acid	
Tyrosine (Tyr) 2-amino-3-(p-hydroxyphenyl) propanoic acid	
Neutral Heterocyclic	
Proline (Pro) 2-pyrrolidinecarboxylic acid	
Hydroxyproline (Hyp) 4-hydroxy-2-pyrrolidinecarboxylic acid	
Tryptophan (Trp) α-aminoindole-3-propanoic acid	
Acidic	
Aspartic Acid (Asp) aminosuccinic acid	$HOOCCH_2CH(NH_2)COOH$
Glutamic Acid (Glu) 2-aminoglutaric acid	$HOOCCH_2CH_2CH(NH_2)COOH$
Basic	
Histidine (His) α-amino-4-imidazolepropanoic acid	
Lysine (Lys) 2,6-diaminohexanoic acid	$CH_2(NH_2)CH_2CH_2CH_2CH(NH_2)COOH$
Arginine (Arg) 2-amino-5-guanidinopentanoic acid	$NH_2C(=NH)NH—CH_2CH_2CH_2CH(NH_2)COOH$

residues present in the polymer chain. The number of amino acid molecules within proteins ranges from perhaps as few as 30 and up to tens of thousands. The term peptide is used in reference to very small hydrolytic fragments of proteins (generally having a MW less than 10,000). They typically contain anywhere from 2 to possibly 20 or so amino acids joined via amide linkages and are commonly subdivided into di-, tri-, etc, peptides according to the number of amino acid residues they contain. Collectively, higher molecular weight peptides are often termed as *polypeptides*. Various individual peptides have been isolated from protein hydrolysates or synthesized, such as oxytocin. With regard to classification or categorization, there is little distinction between peptides and polypeptides, except that the latter usually refers to compounds that carry a number of amino acid residues but usually do not involve a distinct upper limit of residues. For example, the polypeptide hormone prolactin carries 199 residues. The simplest naturally occurring peptides are the dipeptide *penicillins* and *cephalosporins*. The MW of proteins may be determined by various methods, such as diffusion, sedimentation, viscosity, x-ray analysis, light-scattering, ultracentrifugation, electron microscopy, and gel permeation. MW values for common proteins range from about 10^4 to about 10^7; the value found for a given protein often varies depending upon the determination method used.

As for the elucidation of protein composition, two fundamental problems exist, the quantitative assay of the individual amino acids and the determination of the amino acid sequence in the chain. Each is a highly specialized field of endeavor and

Table 26-7. Amino Acid Composition of Selected Proteins[a]

	IUPAC ABBREVIATION	GELATINS	MILK: MIXED PROTEINS	CASEIN	SERUM ALBUMIN*	γ-GLOBULIN	HEMOGLOBLIN: HORSE	INSULIN	CLOSTRIDIUM BOTULINIUM TOXIN
Alanine	Ala	9.2	...	3.0	6.2	...	7.4	4.5	3.9
Arginine	Arg	8.8	4.2	4.1	6.0	4.8	3.7	3.1	4.6
Aspartic Acid	Asp	6.3	...	7.1	10.3	8.8	10.6	6.8	20.1
Cystine	Cys-Scy	0.1	1.0	0.3	6.5	3.1	1.0	12.5	0.8
Glutamic Acid	Glu	11.7	21.5	22.4	17.0	11.8	8.2	18.6	15.6
Glycine	Gly	30.5	2.3	2.7	2.0	4.2	5.6	4.3	1.4
Histisdine	His	0.7	2.8	3.1	4.0	2.5	8.7	4.9	1.0
Hydroxyproline	Hyp	14.5	...	0	0	0?	0?	0?	...
Isoleucine	Ile	1.9	7.5	6.1	3.0	2.7	0?	2.8	11.9
Leucine	Leu	3.2	11.0	9.2	12.0	9.3	15.2	13.2	10.3
Lysine	Lys	5.1	8.7	8.2	12.7	8.1	8.5	2.5	7.7
Methionine	Met	0.9	3.2	3.4	1.3	1.1	1.0	0	1.1
Phenylalanine	Phe	2.1	5.5	5.0	7.0	4.6	7.7	8.1	1.2
Proline	Pro	6.3	...	11.3	5.1	8.1	8.5	2.5	2.6
Serine	Ser	3.8	4.3	6.3	7.0	11.4	5.8	5.2	4.4
Threonine	Thr	2.2	4.7	4.9	7.1	8.4	4.4	2.1	8.5
Tyrosine	Tyr	0.7	6.0	6.3	5.5	6.8	3.0	13.0	13.5
Tryptophan	Trp	0	1.5	1.2	1.0	2.9	1.7	0	1.9
Valine	Val	2.1	7.0	7.2	6.0	9.7	9.0	7.8	5.3

[a] The data in this table were taken from a more comprehensive table by Hawk et al. *Practical Physiological Chemistry,* 13th ed. New York: Blakiston, 1954. All values are in g/100 g of protein except those marked * which are in g/16 g total nitrogen.

relies upon modern techniques such as selective adsorption (ion- exchange, paper, thin-layer, high-performance liquid, and gas-liquid chromatography), electrophoresis, countercurrent distribution, and isotope-dilution methods. The amino acid composition of various selected proteins is presented in Table 26-7.[18] In view of the diverse analytical methods employed, slight variations in reported values are expected and often encountered in the literature. With simple (nonconjugated) proteins, the total mass of the amino acids exceeds the mass of the source protein because of the water that becomes fixed during hydrolytic cleavage of the peptide linkages. The precise sequence of amino acid residues is now known for a considerable number of proteins, including insulin, ribonuclease, tobacco mosaic virus, and many of the hemoglobins, immunoglobulins, and other specialized proteins.

Protein structure is typically divided into four levels:

Primary—The amino acid sequence, as determined by sequencing techniques.
Secondary—The folding of polypeptide chains into coiled structures as determined by X-ray diffraction, optical rotatory dispersion, and electron photomicrography.
Tertiary—The arrangement of chains into specific layers and/or fibers.
Quaternary—The organization of many monomeric units, each displaying primary, secondary, and tertiary structure, associated to form a quaternary structure.

A fifth level is believed to consist of aggregates of different proteins, each composed of the four fundamental structural levels. These macromolecular complexes are believed to be involved in fatty acid synthesis and electron transport.

Physical and Chemical Properties

A satisfactory practical classification of proteins based solely upon either composition or structure has not been achieved, partly because of their wide diversity and partly because of incomplete knowledge. Classifications in terms of occurrence and function are encountered frequently in the literature but these are designed for special purposes and usually do not embrace all proteins. A classification based primarily upon physical and chemical properties such as solubility, coagulability, conjugation, denaturation, and hydrolysis characteristics and having some practical utility has evolved gradually over the years and is presented below.

Simple proteins are naturally occurring proteins that yield only α–amino acids or their derivatives upon hydrolysis. They may be of several types and include:

Albumins, which are soluble in water and coagulated by heat; examples include ovalbumin in egg white and serum albumin in blood.
Globulins, which are insoluble in water but soluble in dilute salt solutions and coagulable by heat; examples include serum globulin in blood.
Glutelins, which are insoluble in water or dilute salt solution but soluble in dilute acid and alkali; examples include glutenin in wheat.
Prolamines, which are insoluble in neutral solutions but soluble in 80% alcohol; examples include zein in corn and gliadin in wheat.
Albuminoids, which are dissolved only by boiling in strong acids; examples include keratins in hair and horny tissue, elastins in tendons and arteries, and collagens in skin and tendons.
Histones, which are basic in reaction, soluble in water but insoluble in dilute ammonia, and not easily heat-coagulable; examples include thymus histone and hemoglobin.
Protamines, which are strongly basic in reaction and soluble in water, dilute acid, and ammonia; examples include salmin and sturin in fish sperm. They precipitate many other proteins.

Conjugated proteins are proteins that are combined in nature with some nonprotein substance. They are classified according to the nature of the prosthetic (nonprotein) group. The classes, which are not mutually exclusive, include:

Phosphoproteins, which contain a phosphoric acid moiety as the prosthetic group; examples include casein in milk and ovovitellin in egg yolk.
Nucleoproteins, which contain a nucleic acid as the prosthetic group; examples include nuclein in cell nuclei.
Glycoproteins, which are simple proteins united to a carbohydrate group; examples include mucins in vitreous humor and saliva.
Chromoproteins, which contain a colored prosthetic group; examples include hemoglobin in blood and flavoproteins.
Lipoproteins, which contain lipid materials, such as sterols, fatty acids, or lecithin.
Metalloproteins, which contain a metal as the prosthetic group; examples include enzymes such as tyrosinase, arginase, and xanthine oxidase.

In general, pure proteins are relatively odorless and tasteless and have varying colors. Many proteins have been obtained in crystalline form, but unlike crystalline substances in general, this is not necessarily evidence of homogeneity as some have been further resolved into two or more components through chromatographic, electrophoretic, and other procedures. Upon heating, proteins decompose with or without simultaneous liq-

uefaction and emit the characteristic odor of singed hair. In their normal biological environment, they are highly hydrated. Because proteins are polyelectrolyte macromolecules with multifunctional groups, they typically differ greatly in their physical properties such as solubilities in water, salt solutions, monohydric and polyhydric alcohols, and dilute acids and bases. Proteins often form colloidal solutions from which heat usually precipitates the protein in a coagulated form. Precipitation in an unaltered form is frequently accomplished, especially at their isoelectric point, by means of salt solutions such as sodium chloride and ammonium sulfate or by diluted ethanol. Dilution with acetonitrile is often sufficient to precipitate protein from extracted serum samples.

The exceptional vulnerability of proteins in general to chemical attack often requires careful control of reaction conditions; nevertheless, their chemical characteristics are quite in accord with those to be expected from the functional groups present. Peptides are readily soluble in water, noncoagulable by heat, and are not precipitated by saturation with ammonium sulfate. Precipitates are formed with amino acids on the addition of various reagents such as heavy metal salts, and certain acids such as picric, phosphotungstic, trichloroacetic, or sulfosalicylic acids.

In addition to the modern chromatographic, electrophoretic, and other procedures mentioned previously, the advent of post–column-derivatization techniques in which peptides and amino acids are made chromophoric by the use of such fluorescent derivatives as the fluorescamine derivative, the PTH amino acid derivatives, the derivative formed by reaction in the orthophthaldehyde method, and the *dansyl* and *dapsyl* derivatives makes it possible to determine the concentration of individual amino acids and small peptides in mixtures in the *nanomole* and *picomole* range. In addition, the hydrolysis of proteins yields amino acids that, upon treatment with *nitrous acid*, liberate nitrogen. This reaction along with other techniques forms the basis of Van Slyke's nitrogen distribution method, which has important uses in clinical chemistry. Amino acids and the free amino groups in proteins react with ninhydrin resulting in either yellow, pink, or violet color depending upon the amino acid. The presence of peptide linkages can be shown by means of the *Biuret* test. Numerous color tests are available for individual amino acids, including the *Ehrlich* and *Hopkins–Cole* tests for tryptophan, the *Sakaguchi* test for arginine, the *nitroprusside* test for cystine and cysteine, the *Millon* test for tyrosine, the *xanthoproteic* test for tyrosine and phenylalanine, the *Pauly diazo* test for histidine and tyrosine, and the *basic lead* test for the sulfur-containing acids.

Occurrence and Uses

Proteins are synthesized by the ribosomes in the cytoplasm and especially those associated with endoplasmic reticulum. Although proteins are present in all living matter, important differences in their distribution are clearly evident. In plants, for which the structural parts are essentially carbohydrate in nature, protein concentration is usually very much higher in the seed than in any of the other plant parts. No similar gross variation is observed in the animal world, but different tissues vary considerably in the approximate percentage of protein they contain (ie, skin—27%, skeletal muscle—21%, brain—11%, adipose tissue—5%).

Insoluble proteins are usually isolated simply by removing contaminating material by means of a suitable array of solvents. Débridement is often facilitated through the appropriate use of enzymes. Soluble proteins are usually obtained first as crude extracts in aqueous solutions and after subjecting the solution to dialysis to remove contaminating solutes, the protein is obtained either through precipitation by means of salt solutions or organic solvents or through lyophilization techniques. When first isolated, proteins are frequently mixtures. Separation into individual components was formerly accomplished only by means of tedious fractional precipitation operations. Currently, it is achieved much more conveniently and completely through chromatographic procedures using ion-exchange resins or various cellulose derivatives and preparative HPLC.

In addition to their role in nutrition and as building blocks of proteins, the amino acids are precursors of many important biomolecules, including various hormones, vitamins, coenzymes, alkaloids, and porphyrins. The aromatic amino acids are particularly versatile as precursors for many alkaloids, such as morphine, codeine, and papaverine and a number of hormones such as the thyroid hormone, thyroxine; the plant hormone, indoleacetic acid; and an adrenal hormone, epinephrine.

Hormonal polypeptides are produced in the mammalian hypothalamus and are stored in the posterior pituitary. Examples include the partially cyclic octapeptides oxytocin, vasopressin, argitocin, argipressin, and lypressin. The polypeptides *ACTH (adrenocorticotropic hormone), lipotropin, prolactin,* and *somatotropin* also originate in the pituitary. The hypothalamus produces the polypeptide hormones or factors corticoliberin (CRF), gonadorelin (GnRH), protirelin (TRH), and somatotropin-releasing factor (GHF), which are transported to the anterior pituitary. Glutathione is a peptide hormone that is present in nearly all living cells. Other peptides (nonhormonal) in the hypothalamus network are neurotensin (anorexiant), a tridecapeptide, and substance P, an undecapeptide. The nerve tissue prevalent calcitonin gene-related peptide (CGRP) (37 residues) is 1000 times more potent than acetylcholine or substance P. Cyclic polypeptides such as bacitracin and polymixin from *Bacillus* sp. act as antibiotics, as do the penicillins and cephalosporins mentioned previously.

LIPIDS

Lipids, also known as *lipins* or *lipoids,* are fat or fat-like substances that occur widely in plants (mainly fruits and seeds) and animals (special deposits and in complex, active tissues such as the brain and liver). They contain only carbon, hydrogen, and oxygen atoms except for complex lipids such as phospholipids. Like the carbohydrates and proteins, the lipids constitute a very important group of organic substances from a physiological standpoint. However, unlike the carbohydrates and proteins, the lipids comprise a rather heterogeneous group of substances in terms of chemical composition. In general, lipids are hydrophobic in nature, which is very important to their physiological/pharmacological activities, and are soluble in solvents such as ether and chloroform and insoluble in water. They may be divided into the following classes according to their chemical structure:

Fixed Oils and Fats—Esters of glycerol and fatty acids. An example is olive oil. Fixed oils that are solid at ordinary temperatures are commonly called *fats.* An example is lard.

Waxes—Esters of high-molecular-weight, monohydric alcohols and high-molecular-weight fatty acids. An example is spermaceti.

Phospholipids (Phosphatides)—Esters consisting of glycerol in combination with fatty acids, phosphoric acid, and certain nitrogenous compounds. Pharmaceutically, the most important members of this group are the lecithins.

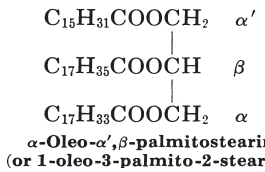
Prostaglandins—Essential fatty acids derived from prostanoic acid and having cyclic structures.

Fixed Oils and Fats

COMPOSITION AND STRUCTURE—*Fixed oils* and *fats* are mixtures of glyceryl esters of the higher-molecular-weight aliphatic acids, especially oleic, palmitic, and stearic acids. The natural fatty acids are nearly all straight-chain and contain an even number of carbon atoms (C_4 to C_{26}). The individual glyceryl esters themselves are frequently referred to as *glycerides.*

Mono-, di-, and triglycerides containing one, two, or three molecules of fatty acid esterified with one molecule of glycerol, respectively, have been prepared synthetically, but only the triglycerides occur commonly in nature. Three glycerides, *olein* (*glyceryl trioleate* [$C_3H_5(C_{18}H_{33}O_2)_3$]), *palmitin (glyceryl tripalmitate* [$C_3H_5(C_{16}H_{31}O_2)_3$]), and *stearin (glyceryl tristearate* [$C_3H_5(C_{18}H_{35}O_2)_3$]), are common to many fixed oils. Olein has a mono-unsaturated structure with the double bonds having a cis configuration. Palmitin and stearin have saturated structures.

The glycerides in a fixed oil may be simple or mixed. In *simple glycerides,* such as olein, palmitin, or stearin, all three fatty acid groups are identical. In the more frequently encountered *mixed glycerides,* more than one type of fatty acid is present. Because of the many possible combinations in the mixed glycerides, different fats having entirely different physical properties often show the same chemical analysis. The following formula illustrates a mixed glyceride:



α-Oleo-α′,β-palmitostearin
(or 1-oleo-3-palmito-2-stearin)

PHYSICAL AND CHEMICAL PROPERTIES—Fixed oils and fats are rather distinctive in their physical properties. They are greasy to the touch and leave a permanent oily stain upon filter paper. They are all lighter than water and insoluble therein, but are soluble in ether, chloroform, and some other water-immiscible solvents. A few of them, such as castor oil, are soluble in alcohol. When purified, they are nearly colorless and have a bland odor and taste that has little distinctiveness. The yellow color of fats is usually due to the presence of carotene, which is one of the provitamins A. Glycerides of unsaturated fatty acids have lower melting points than those of saturated acids with the same number of carbon atoms. Although most vegetable oils are liquid at room temperature and most animal fats are solids, there are notable exceptions, such as cocoa butter (solid) and cod liver oil (liquid). The difference in consistency between fixed oils and fats is caused by the relative proportions of liquid and solid glyceryl esters that are present. Fixed oils contain a relatively high proportion of liquid glycerides (polyunsaturated glycerides), such as glyceryl oleate; whereas, fats are relatively rich in solid glycerides (mostly saturated), such as glyceryl stearate. For example, *olein* is a liquid at ordinary temperatures but *palmitin* is a solid (melting point, 60°C). *Stearin* melts at 71°C. When heated moderately, fats liquefy and oils become less viscous. Upon aging, fixed oils often develop a precipitate of stearin that will reliquefy on warming.

Olein and glyceryl esters of other unsaturated acids may be converted into stearin in the presence of a catalyst such as finely divided nickel by *hydrogenation*. Liquid oils such as cottonseed, corn, soybean, and peanut are transformed (hardened) by this process into solid fats for commercial use. The proprietary cooking fat, Crisco (*Procter & Gamble*), is a well-known example. Through partial hydrogenation, the consistency of such hardened oils may be widely varied. However, this process, used in making many margarine preparations, is a mixed blessing because it produces some *trans* unsaturated fats, which may have unwanted health effects.

Fixed oils are to be distinguished sharply from *volatile oils*, also known as *ethereal* or *essential oils*. From a composition viewpoint, the volatile oils differ from fixed oils in that they do not contain glyceryl esters. Physically, fixed oils are nonvolatile under ordinary conditions (hence the name *fixed* oils). Fixed oils may be classified into drying and nondrying oils. The *drying oils,* when exposed to the air, undergo oxidation and resinify forming a tough, hard film. Linseed oil is an example of this class, which find their greatest use in the manufacture of paints and varnishes. The *nondrying oils,* when exposed to the air, remain sticky to the touch for an indefinite period, and therefore, cannot be used in paints and varnishes. Olive oil and expressed almond oil are examples. The drying quality of fixed oils is caused by the presence of characteristic unsaturated fatty acids, such as linoleic and linolenic acids.

When heated strongly, fats undergo decomposition with the production of acrid, flammable vapors; when ignited, they burn with a sooty flame. The acridity of an overheated fixed oil or fat is largely due to the formation of *acrolein* (*propenal*). The property common to all fats and fixed oils is their propensity to undergo hydrolysis to yield glycerol and the fatty acids representative of the fat or oil. Uncatalyzed, the reaction proceeds very slowly; however, it is usually accelerated by employing high temperatures and pressures and by the presence of either acids or alkalies. If alkalies are employed, the liberated acids are converted automatically into their corresponding metallic salts. Because such salts ordinarily are referred to as soaps, the alkali-catalyzed hydrolysis of fats and fixed oils is known as *saponification*. Many naturally occurring enzymes also catalyze fat and fixed oil hydrolysis. Such enzymes are termed *lipases*; steapsin in human pancreatic juice is an important example.

The analytical factors of greatest importance in identifying fixed oils and in judging their quality are:

Iodine Value (the number of grams of iodine monochloride, expressed as iodine, absorbed by 100 g of sample under prescribed conditions) measures the degree of saturation. Iodine is taken up at the double bonds, and therefore, unsaturated oils, such as the drying oils, typically have higher iodine values.

Saponification Value (the number of milligrams of potassium hydroxide required to neutralize the free acids and saponify or hydrolyze the esters in 1 g of sample).

Acid Value (the number of milligrams of potassium hydroxide required to neutralize the free acids in 1 g of sample).

The refractive index, specific gravity, color, odor, and congealing point of fixed oils and fats are of little value in determining their purity or quality. Some oils, such as cottonseed and sesame, are identifiable using specific tests, but the identification of most fixed oils is only inferentially possible after taking many physical and chemical factors into account. Gas chromatography (the FAME methods) is a useful means by which the identification of fixed oils may be accomplished. There are many gas chromatographic methods that bring about the separation of free fatty acids or fatty acid methyl esters and the resulting chromatographic pattern may be used to identify the fixed oil. Near IR spectroscopy may also determine the degree of saturation because the value is directly related to HC═CH stretch bands at 2130 nm.

OCCURRENCE AND USES—Generally, the biosynthesis of fatty acids requires acyl-CoA or fatty acyl carrier protein (ACP). In plants, this occurs in the mitochondria and chloroplasts; in animals, this occurs in the cytoplasm. Of all the fatty acids, oleic, palmitic, and stearic are the most widely distributed. Stearic acid is mostly found in animal fats, but it is occasionally an important constituent in vegetable oils. Saturated fatty acids lower than C_{12} are found in the milk of mammals; however, butter fat contains all of the even-numbered fatty acids from C_4 to C_{18} as well as oleic acid. Olein is the predominating constituent in many vegetable oils and the more fluid animal oils. Palmitin predominates in palm and coconut oil and stearin predominates in many of the solid fats.

Most fixed oils and fats are obtained from the plant or animal tissues in which they occur by *expression* and can be fractionated to some extent into glycerides. Generally, the source material is first ground and subsequently submitted to hydraulic pressure. Heat may also be used when necessary. The oils obtained by the first expression are usually of the highest commercial value. For example, virgin olive oil results from the first pressings of olives. Olein is separated and purified by cold expression; the other constituents are retained due to their lack of fluidity at low temperatures. Stearin may be separated by expression under controlled temperature conditions that re-

move the olein and palmitin. Sometimes the expressed oil from plant tissues is of crude quality and requires subsequent purification, as in the case of cottonseed oil. Fixed oils and fats are frequently bleached by treatment with Fuller's earth or similar clays and subsequently filtered. Some oils used for technical purposes are obtained by extraction using *volatile solvents* rather than expression. Animal fats and oils are usually separated from tissues by a process known as *rendering,* which consists of heating the tissues until the fat melts and separates.

Fats and fixed oils contain certain unsaturated fatty acids that are essential to human nutrition. Their absence in the diet produces eczematous skin conditions and, in experimental animals, has resulted in scaly skin, emaciation, necrosis, and premature death. Evidence exists to support the view that fats (oils) such as safflower, corn, cottonseed, and soybean, which are rich in lineoleic acid and other unsaturated acids, play an important role in the mobilization and utilization of serum cholesterol. It has been hypothesized that olive oil and canola oil (rapeseed) are even more effective in providing a favorable high-density lipoprotein/low-density lipoprotein (HDL/LDL) ratio. Combined with a controlled dietary fat intake, these oils can also ensure a favorable total serum cholesterol/HDL ratio. This is of particular interest in hypercholesterolemia, which is observed commonly in atherosclerosis. Peanut, almond, and sesame oils are used extensively as vehicles in the preparation of intramuscular injections. Theobroma oil found in cocoa butter is frequently used for the preparation of suppositories. Some derivatives of glycerides are soaps and related surface-active compounds, which are employed as detergents and germicides. A few oils are used medicinally. For example, castor oil is used as a cathartic, cod liver oil as an antirachitic, and olive oil as an emollient. Salts of several of the fatty acids are fungicidal, such as zinc undecylenate, which is prepared from the undecylenic acid in castor oil.

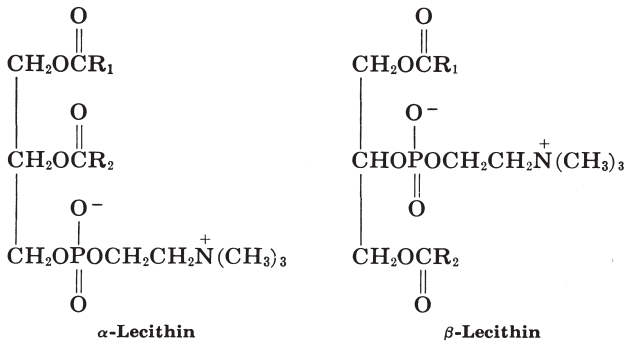
Waxes

Waxes, like fixed oils and fats, are esters of fatty acids. However, they differ in that the alcohol represented is *not* glycerol. In place of this trihydric alcohol is a sterol or one of the higher, even-numbered, monohydric alcohols from C_{16} to C_{36}. Therefore, they are typically solids and poorly water-soluble. In addition, unlike fats, which are primarily esters, waxes often contain significant amounts of free alcohols, sterols, and fatty acids (C_{24} to C_{36}); some of the waxes obtained from plants also contain paraffin hydrocarbons. The sterols and hydrocarbons presesnt in waxes are unsaponifiable. In addition, the esters are usually much more resistant to saponification than the glycerides of fats and fixed oils; they may only be saponified using alcoholic alkali. Therefore, waxes typically have high saponification values. Also, as a result of their free fatty acid content, they typically have high acid values. Conversely, iodine values are typically low. These characteristics have been exploited as a way to determine if waxes have been adulterated with fats. Waxes are frequently used to prepare pharmaceutical dosage forms. For example, wool fat is used as an emollient base for creams and ointments and beeswax and spermaceti are used to stiffen ointment preparations.

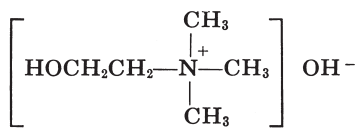
Phospholipids (Phosphatides)

CLASSIFICATION AND STRUCTURE—The *phospholipids* include all lipoidal constituents that contain phosphorus in their molecules and have been categorized as lecithins, cephalins, and sphingomyelins. Their chemical composition in all cases is revealed through quantitative measurement of the products resulting from hydrolysis under various conditions. They appear to be essential components of every plant and animal cell. The cis-double bond in the polyunsaturated fatty acids allows membrane lipids to remain mobile at relatively low temperatures. This is particularly critical for plants, which have no way of controlling their temperature. The only phospholipids having pharmaceutical applications are the lecithins.

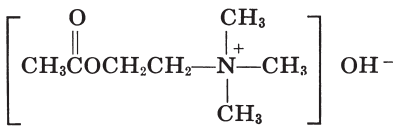
When completely hydrolyzed, each lecithin molecule yields two molecules of fatty acid and one molecule each of glycerol, phosphoric acid, and a basic nitrogenous alcohol compound (usually choline). The fatty acids obtained from lecithins are usually oleic, palmitic, and stearic. The phosphoric acid may be attached to glycerol in either a α- or β-position forming *α-glycerophosphoric acid* or *β-glycerophosphoric acid*, respectively, and producing the corresponding series of lecithins known as α- and β-lecithins. The representations below are in the *zwitterion* (internal salt) form; the naturally occurring lecithins are of the α-variety. *Choline,* a very strong base, is a member of the vitamin B complex. It functions in the body to prevent accumulation of fat in the liver; also, as the acetylated derivative *acetylcholine,* it is released at parasympathetic nerve endings when these nerves are stimulated and thus controls the transmission of impulses across cholinergic synapses.



α-Lecithin β-Lecithin



Choline

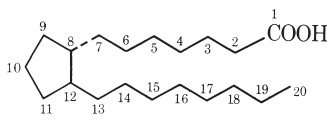


Acetylcholine

Lecithins oxidize readily and darken in color upon exposure to air. Commercially, lecithin is obtained by extraction processes. *Ovolecithin* (*vitellin*) from egg yolks, *vegilecithin* from soybeans, and purified lecithin from calves brains are used as emulsifiers, antioxidants, and stabilizers in foods and pharmaceutical preparations.

Prostaglandins

CLASSIFICATION AND STRUCTURE—The natural prostaglandins are unsaturated, hydroxylated fatty acids. They are derivatives of the parent compound, *prostanoic acid*, with nine principal groups or series of modifications being recognized, as listed in Table 26-8.



Prostanoic acid
5-Octylcyclopentaneheptanoic acid

The abbreviations in Table 26-8 often are shortened to the last letter, by dropping the PG prefix. A subscript following the ab-

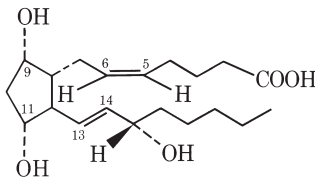
Table 26-8. Prostaglandins

	SUBSTITUENTS					
ABBREVIATION	C═C	>C═O	—OH	—O—O—	—OOH	—O—
PGA_1	10,13E	9	15S	—	—	—
PGB_1	8(12), 13E	9	15S	—	—	—
PGC_1	11, 13E	9	15S	—	—	—
PGD_1	13E	11	9α, 15S	—	—	—
PGE_1	13E	9	11α, 15S	—	—	—
PGF_1	13E	—	9α, 11α, 15S	—	—	—
PGG_1	13E	—	—	9α, 11α	15S	—
PGH_1	13E	—	15S	9α, 11α	—	—
PGR	See PGA series	—	—	—	—	—
PGI_2	5Z, 13E	—	11α, 15S	—	—	6, 9α

breviation pertains to the prostaglandin depicted in Table 26-8 or the following modifications:

Subscript 3—Two additional double bonds, at C-5 (*Z*) and C-17 (*Z*)
Subscripts α *or* β—indicate the configuration at C-9 and the same designation used for the steroids is employed; α is *down* and β is *up.* At C-15 the Cahn–Prelog–Ingold convention defines the chirality and the *S* configuration (α or dotted line) is found in most natural substances.

Thus, the compound $PGF_{2\alpha}$, or simply, $F_{2\alpha}$ (dinoprost, prostin F_2 alpha) is:



$PGF_{2\alpha}$

The subscript 2 depicts a *trans* (E) configuration at C-13 and *cis* (Z) at C-5, alpha hydroxyl at C-9, and a *cis* (α) diol at C-9 and C-11.

Prostaglandins are formed from the 20-carbon straight-chain carboxylic acid arachidonic acid and closely related fatty acids such as dihomo-γ-linoleic acid. The enzymatic process using vesicular extracts from sheep or bulls yields mainly the E series. Employing lung homogenates as the enzyme source, F_α compounds have been formed by a similar process. It has been suggested that the biological activity of the prostaglandin molecule is associated with a right-handed chirality, best visualized as a right-handed wedge in which all the hydrophilic functional groups are oriented to one side and the hydrophobic groups to the other side of the molecule while both ends are hydrophilic.

OCCURRENCE—Prostaglandins are associated with most mammalian tissues and have also been established as components of some higher plants. They can be extracted from most animal tissues with human seminal fluid containing the highest concentration and the greatest number of prostaglandins (31). However, the total prostaglandin production in the adult human is only of the order of 1 to 2 mg/24 hours. Many prostaglandins are characterized by both their generally short lifetime and multiplicity of effects. Metabolism occurs by hydroxylation, oxidation, and/or degradation of the carboxylic acid chain. The prostaglandins are perhaps the most versatile, ubiquitous, and powerful substances found in humans. They are involved in platelet aggregation, blood pressure, gastrointestinal motility, gastric acid secretion and *cytoprotection,* relief of glaucoma, pain and inflammation, nerve conduction, fetal development, uterine contraction (abortifacients and induce labor), thermoregulation and fever production, food intake, vasodilation and vasoconstriction, bronchodilation and bronchoconstriction, topical vasodilation, baldness, and the movement of fluid and electrolytes across membranes.

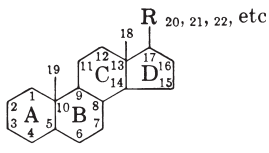
During the early stages of prostaglandin development, pharmacological studies were the major consumer of the natural materials. The small amounts required were supplied fairly rapidly by biosynthesis. The need to find compounds that were more selective and more stable than the natural prostaglandins led to an overwhelming outburst of synthetic activity in the late 1960s that continues today.[19, 20] Currently, prostaglandins are on the market or are under clinical investigation for potential applications in treating fertility problems, as oxytocic agents, as bronchodilators, and in a variety of uses in animal husbandry. In addition, prostacyclin is used to prevent blood clotting in cardiopulmonary bypass operations and to protect the stomach mucosa against rebound ulceration during the use of nonsteroidal anti-inflammatory agents (NSAIDs) employed for arthritis.

It was thought for a long time that the mechanism of action of the prostaglandins in anti-ulcer therapy was the inhibition of gastric acid secretion. However, a recent study shows that the anti-ulcer effect may result from both antisecretory and cytoprotective properties of the prostaglandins. PGE_1 has been introduced for a rare but frequently life-saving application. In certain instances of congenital heart disease, the normal closure of the *ductus arteriosus* is undesirable until corrective surgery has guaranteed the passage of blood to the lungs. Such surgery is more likely to be successful if PGE_1 is infused into the blood of the infant to prevent closure of the ductus until after successful surgery. Although the general implication is that prostaglandins are too irritating to be used as potent ocular hypertensive agents for glaucoma by direct ocular application, some success has been obtained with latanoprost.[21] Table 26-9 shows the structures of some representative prostaglandin derivatives currently marketed and under investigation.

STEROLS AND SAPONINS

Sterols

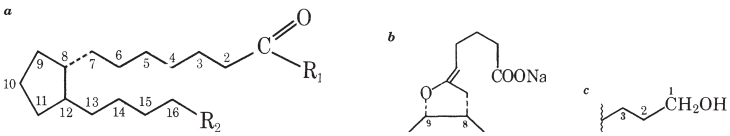
The *sterols* are alcohols structurally related to the *steroids,* naturally occurring compounds obtained from plants and animals that contain the partly or completely hydrogenated 17*H*-cyclopenta[*a*]phenanthrene nucleus. Typical examples include the familiar cholesterol and ergosterol. In addition to the sterols, the naturally occurring steroids include various other substances, such as compounds of adrenal origin, certain alkaloids, antirachitic vitamins, bile acids, cardiac glycosides, saponins, sex hormones, and toad poisons. The general formula for the basic structure of these compounds may be represented below.



General steroid formula

Table 26-9. Structures of Representative Prostaglandins

NAME	FORMULA	OH	DOUBLE BONDS	R_1	R_2	OTHER
Alprostadil	$C_{20}H_{34}O_5$	11α, 15α	13—14	—OH	n-C_4H_9	9-oxo
Carboprost (Prostin/15 M) (Tromethamine salt)	$C_{21}H_{35}O_5$	9α, 11α, 15α	5—6 cis, 13—14	—OH	n-C_4H_9	15β-CH_3—
Cloprostenol Sodium	$C_{22}H_{28}ClNaO_6$	9α, 11α, 15α	5—6, 13—14	—OH	m-ClC_6H_4O	—
Dinoprost (Prostin F_2) (Tromethamine)	$C_{20}H_{34}O_5$	9α, 11α, 15α	5—6, 13—14	—OH	n-C_4H_9—	—
Dinoprostone (Prostin E_2)	$C_{20}H_{32}O_5$	9α, 15α	5— 6, 13—14	—OH	n-C_4H_9-	9-oxo
Enprostil	$C_{23}H_{28}O_6$	11α, 15α	4— 5—6 (allene)	—OCH_3	—O · C_6H_5	9-oxo
Epoprostenol Sodium (Prostacyclin)	$C_{20}H_{31}NaO_5$	11α, 15α	13— 14[a]	—ONa	n-C_4H_9-	15β-CH_3
Latanoprost	$C_{26}H_{40}O_5$	9α, 11α, 15α	5—6 cis	$OCH(CH_3)_2$	$CH_2C_6H_5$	—
Misoprostil	$C_{22}H_{38}O_5$	11α, 16β	13—14	—OCH_3	n-C_4H_9	9-oxo, 16β-CH_3
Nocloprost	$C_{22}H_{37}ClO_4$	11α, 15α	5—6 cis, 13—14	—OH	n-C_4H_9	9β-Cl, 16-di-CH_3
Rioprostil	$C_{21}H_{38}O_4$	11α, 16β (1—OH)[b]	13— 14	(footnote[b])	n-C_4H_9	9-oxo
Rosoprostol Sodium	$C_{18}H_{33}NaO_3$	9β	—	—ONa	-C_2H_5	—
Vapiprost HCl	$C_{30}H_{39}NO_4$	11β	4— 5	—OH	n-C_4H_9	(footnote[c])
Viprostol	$C_{23}H_{36}O_5$	11α, 16β	5—6 cis, 13—14	—OCH_3	n-C_4H_9	9-oxo, 16β-vinyl



In actual conformation, however, the structure is not planar. The rings are lettered and numbered conventionally as indicated. Usually one or more rings are completely saturated and several centers of asymmetry are present. This, plus restricted rotations due to ring fusions, results in rather complex stereochemical relationships. In the naturally occurring compounds, substitutions in the rings occur most frequently on C-3, C-17, and C-11; C-18/C-19 may or may not be present (ie, CH_3). The direction in which a substituted group located at centers of asymmetry projects from the plane of the ring system is commonly indicated by the use of α- and β-. A α-substituent is viewed as projecting beneath the ring plane and is represented by a broken line; a β-substituent is viewed as projecting above the ring plane and is represented by a solid line.

The prefixes *cis* and *trans* are often employed (but *not* in standardized nomenclature) to distinguish the α- and β- members of a pair of compounds that are otherwise stereochemically identical. However, this requires the selection of a substituting group to serve as a reference point in the steroid molecule; a *rule* frequently used is that the nearest angular (branching off at a ring fusion) methyl group is selected. For example, in the case of the sterols, the angular methyl group nearest to the 3-hydroxyl group is the one at C-10 and is represented as having the β-configuration. Thus, 3-β-hydroxycholestane becomes *cis*-3-hydroxycholestane and 3-α-hydroxycholestane becomes *trans*-3-hydroxycholestane. Most naturally occurring sterols have the 3-hydroxyl group in the β-, or *cis-,* position. The prefix *epi-* is often employed to specifically designate the corresponding epimers. In this case, the epimer contains the 3-hydroxyl group in the α- or trans- position; examples are epicholesterol and epicoprosterol.

Different investigators use slightly different methods of classifying the steroids. One method is to divide them into five classes according to the type of substituent group at carbon 17 (ie, group R):

Sterols—R is an aliphatic side chain. They contain one or more OH groups attached in an alicyclic linkage.

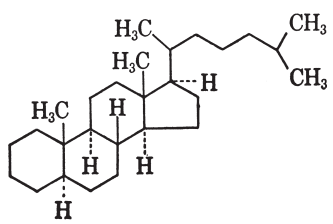
Sex Hormones—C-17 bears a ketonic or hydroxyl group and frequently carries a two-carbon side chain.

Cardiac Glycosides—R is a lactone ring. The glycosides also contain carbohydrates linked through oxygen in other parts of the molecule. Hydrolysis yields this carbohydrate and the *cardiac aglycone*.

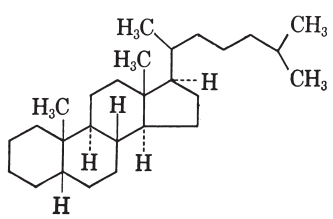
Bile Acids—R is a five-carbon side chain terminating in a carboxylic acid group.

Sapogenins—R contains an oxacyclic (ethereal) ring system.

The parent hydrocarbon of natural sterols is cholestane, which exists in two forms depending on the configuration of the hydrogen atom at C-5. These are drawn below and labeled with their standard (IUPAC) names and, in parentheses, their trivial names:

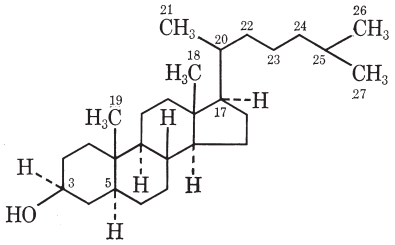


5α-Cholestane (Cholestane)

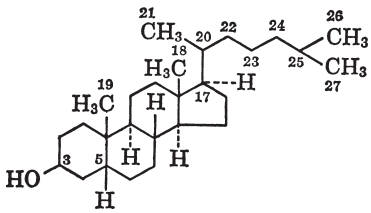


5β-Cholestane (Coprostane)

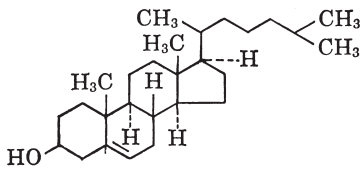
As mentioned previously, the characteristic function of natural sterols is the 3-hydroxyl in the *beta-* orientation. Thus, 5α-cholestan-3β-ol and 5β-cholestan-3β-ol are looked upon as the parent sterols. Other sterols may be named as derivatives of them, although most have commonly accepted trivial names such as cholesterol, ergosterol, and stigmasterol. These parent sterols are shown below along with their various names. The two cholesterols are also illustrated. Note that in the cholest-5-enols, there is no H at C-5 and thus no α- or β- accompanies the numeral 5.



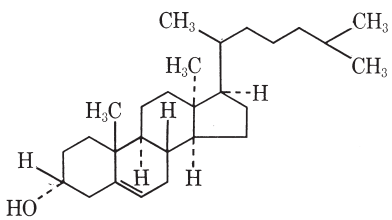
5α-Cholestan-3β-ol
3β-Hydroxy-5α-cholestane
(Cholestanol)



5β-Cholestan-3β-ol
3β-Hydroxy-5β-cholestane
(Coprostanol)



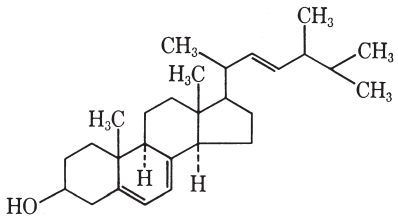
Cholest-5-en-3β-ol
3β-Hydroxycholest-5-ene
(Cholesterol)



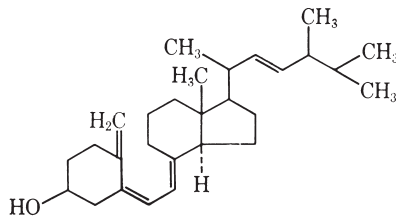
Cholest-5-en-3α-ol
3α-Hydroxycholest-5-ene
(Epicholesterol)

Several empirical color reactions have been developed for steroid identification. Most prominently cited are the Salkowski, Liebermann–Burchard, and Rosenheim reactions. For discussion of these, consult reference texts in biochemistry. Sterols occur abundantly in nature and often constitute a sizable fraction of the total unsaponifiable portion of lipoidal extractive matter from animal and vegetable tissue. The 3β-hydroxysteroids readily form sparingly soluble molecular complexes with the glycoside digitonin. These complexes are referred to as *digitonides,* and they find extensive application in various research operations involving isolation and characterization of the individual steroids.

Several sterols undergo intramolecular rearrangement under the influence of controlled ultraviolet radiation resulting in compounds that display antirachitic (vitamin D) activity. For example, ergosterol, a mycosterol occurring abundantly in yeast and ergot, is readily converted with good yield to ergocalciferol (vitamin D_2). The structure shown below emphasizes the locus of scission of the cyclic nucleus.

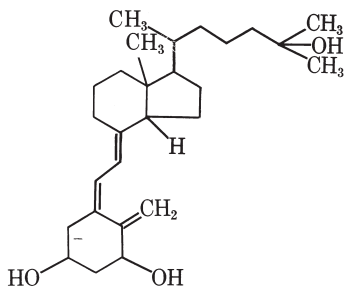


Ergosterol
5,7,22*E*-Ergostatrien-3β-ol

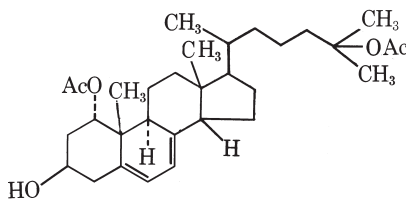


Ergocalciferol (vitamin D_2)
9,10-Seco-5*Z*,7*E*,10(19),22*E*-ergostatetraen-3β-ol

In a similar fashion, the natural vitamin D_3 metabolite, 1α,25-dihydroxycholecalciferol (calcitriol), is formed by ultraviolet conversion, hydrolysis, and heat isomerization from 1α,25-diacetoxy-7-dehydrocholesterol. Calcitriol (Rocaltrol, *Roche*) is used for the hypocalcemia associated with chronic renal dialysis.



Calcitriol
(1α,2β,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol



1α,25-diacetoxy-7-dehydrocholesterol

Saponins

The saponins are a group of amorphous, colloidal glycosides that are readily soluble in water and that produce froth when the aqueous solution is agitated. Two general types are well known, namely *steroid* (typically tetracyclic triterpenoids) as in digitonin, and *pentacyclic triterpenoids* as in aesculin. Both of these types have a glycosidic linkage at C-3 and are biosynthesized via mevalonic acid and isoprenoid units. Saponins have a

high molecular weight and polarity with many conforming to the general formula $C_nH_{2n-8}O_{10}$. The aglycones, usually freed by acid-catalyzed hydrolysis, are termed *sapogenins.*[22] The saponins are distributed widely in the botanical kingdom with the steroidal type less distributed than the pentacyclic triterpenoid types. Steroidal saponins are found in both mono- and dicotyledons and the pentacyclic triterpenoid saponins are abundant in dicotylendonous plants but rare in monocotylendons.[23] Pentacyclic triterpenoid saponins are typically classified into three groups, α-amyrin, β-amyrin, and lupeol.

Saponins are generally acrid in taste and in powder form cause sneezing. They are excellent emulsifying agents, and the aqueous solutions of some of them, such as *quillaja* bark, were used formerly as detergents to replace soap. In addition, many of the saponins are markedly toxic (*sapotoxins*) and usually exert a powerful hemolytic action on red blood corpuscles. However, when taken orally they are comparatively harmless. For example, sarsaparilla is rich in saponins but is widely used in the preparation of nonalcoholic beverages. Steroidal saponins are of great pharmaceutical importance due to their relationship with other steroidal compounds such as the sex hormones, cortisone, diuretics, and vitamin D. Much of the research conducted on the saponin-containing plants was motivated by the attempt to discover precursors for cortisone. It would appear that the most outstanding plant steroids for cortisone production are diosgenin and botogenin from the genus *Dioscorea* and hecogenin, manogenin, and gitogenin from a species of *Agave.* In addition, some naturally occurring steroidal saponins are used therapeutically themselves. For example, the roots of *Panax ginseng* (Araliaceae) contain numerous steroidal and triterpenoid saponins classified as ginsenosides and panaxosides that are responsible for its therapeutic activity. Ginseng has gained popularity in the West in recent years for improvement in concentration and as an adaptogenic (resistance to stress and disease).

A very important group of steroidal glycosides, characterized by their physiological action, are the cardioactive glycosides. Numerous Angiosperm plants contain C23 and C24 sterodial glycosides that exert a slowing and strengthening effect on the heart. Two types of cardioactive glycosides, cardenolides and bufadienolides, have been distinguished based upon the presence of a five or six membered ring, respectively. The cardenolide group is most pharmaceutically important. Digitalis, the dried leaves of *Digitalis purpurea* (Scrophulariaceae), has been the most extensively studied natural source of cardenolide cardiac glycosides. Digitoxin and gitoxin are the main active components of the dried leaves. The leaves of *Digitalis lanata* (Scrophulariaceae) have been almost exclusively used for the preparation of digoxin, one of the most widely used drugs for the treatment of congestive heart failure. Cardiac glycosides similar to those of digitalis are also found in the oleander plant *(Nerium oleander)* and the lily of the valley (*Convallaria majalis)*.

The commercial product saponin is a mixture of pentacyclic triterpenoid saponins prepared from the yucca plant or from the bark of species of *Quillaja* (Rosaceae). Licorice, which consists of the dried unpeeled roots and stolons of *Glycyrrhiza glabra* (Leguminosae), contains glycyrrhizin (the potassium and calcium salts of glycyrrhizinic acid, a pentacyclic triterpenoid saponin). These compounds are responsible for the sweet taste and use of licorice as a flavoring agent. Glycyrrhizinic acid has also been shown to possess deoxycorticosterone effects thus enabling its use to treat rheumatoid arthritis, Addisons's disease, and various inflammatory conditions.[24]

ALKALOIDS

Composition and Structure

These basic compounds at first were called vegetable alkalies; later these were renamed *alkaloids,* meaning alkali-like. All alkaloids contain carbon, nitrogen, and generally oxygen (a typical exception is nicotine) but members of this group are classified as alkaloids based upon chemical properties of a basic nitrogen, which confers their alkali-properties. However, the group is very varied in regards to their physiological role, taxonomy, and biogenesis. In addition, there is no clear-cut distinction between alkaloids and naturally occurring complex amines because they typically contain one or more nitrogen atoms, usually wholly or partly in a hetercyclic ring. Therefore, alkaloids have been classified in a variety of ways such as botanical source, chemical structure, and pharmacological action. Any attempt at comprehensive chemotaxonomic classification is far beyond the scope of this text; for such a treatment, consult the continuing encyclopedic work of Brossi (see the bibliography).

A partial classification that includes most of the more important pharmaceutical alkaloids is presented in Table 26-10. As in all such condensed classifications, caution must be exercised in interpreting the entries under *Nucleus*. Different hydrogenated forms of a given nucleus are often present in different alkaloids; thus, nicotine contains a pyridine ring; whereas, piperine contains a hexahydropyridine ring (piperidine). Also, some alkaloids contain more than one nucleus. For example, quinine contains both quinoline and quinuclidine. In many instances, the nuclei shown in Table 26-10 are merely the best-known fragment of the total fused ring system actually present in the alkaloid. For example, while it is true that each of the ergot alkaloids contains an indole ring in its nucleus, the indole is actually a fragment of the fused tetracyclic ring system, indolo[4,3-*fg*]quinoline, which constitutes the total nucleus. In addition to their basic nitrogen moiety, alkaloids usually contain one or more chemically functional groups. For example, cocaine contains two ester functions, quinine contains both a secondary alcohol and aromatic methoxy functions, and ergonovine contains a substituted amide function. Some alkaloids such as solanine and tomatine actually occur as glycosides.

Physical and Chemical Properties

Most of the nonvolatile alkaloids are solid and mainly crystallizable, though a few are amorphous. The volatile ones, such as nicotine, are mainly liquid under ordinary conditions and these often contain no oxygen. They are generally white. However, berberine is yellow and sanguinarine, itself colorless, yields red salts. They are either insoluble or sparingly soluble in water, with a few exceptions, such as caffeine and colchicines, but soluble in alcohol, chloroform, benzene, some in ether, and a few in petroleum ether. Their salts, formed by reaction with acids, behave conversely in the matter of solubility. Alkaloids unite with acids to form substituted ammonium salts. The stability of these salts toward hydrolysis and formation of the free base varies with the basic strength of the alkaloid and the nature of the acid used. With the exception of the xanthine alkaloids, most have pK values less than 7. The alkaloids are freed from their salts by the addition of alkali. In the same manner, *alkaline salts* such as the *acetates*, *carbonates*, *citrates*, *benzoates*, *salicylates*, and *basic phosphates* of sodium, potassium, and ammonium will precipitate the free alkaloid or, in some instances, will convert it to a less-soluble salt. As a general rule, alkaloids are incompatible with *oxidizing agents,* some undergoing oxidation readily upon exposure to air. Various antioxidants such as sodium metabisulfite are effective in retarding this deterioration. Oxidation is more rapid in alkaline solution and buffers are commonly used to maintain a suitable pH to prevent degradation. The rate of hydrolysis of ester and glycosidic alkaloids is also pH dependent.

Various kinds of tests have been devised to identify known alkaloids. Their effective use, however, usually requires some relevant knowledge of the history of the sample under examination. In general, these tests involve combinations of two or more of the following: melting points of the alkaloid and at least one of its salts or other derivatives; specific rotation; solubility

Table 26-10. A Partial Classification of Alkaloids

NUCLEUS	PLANT GENERA	ALKALOIDS
Benzazulene	*Aconitum, Delphinium*	Aconitine, delphinine, delsoline
Diterpenoid	*Taxus*	Cephalomannine β-hydoxybaccatn, taiwanxan, taxagafine, taxine, taxol
Imidazole	*Pilocarpus*	Pilocarpine, pilocarpidine, pilosine, pseudopilocarpine, pseudojaborine, isopilocarpinea
Indole	*Peganum, Psilocybe, Stropharia, Evodia, Corynanthe, Claviceps, Physostigma, Strychnos, Rauwolfia*	Brucine, ergonovine, ergotamine, harmine, physostigmine, psilocybin, reserpine, strychnine, yohimbine
Isoquinoline	*Hydrastis, Papaver, Corydalis, Berberis, Chondodendron, Ipecacuanha, Sanguinaria*	Anhalonine, bebeerine, berberine, cephaeline, codeine, corydaline, cotarnine chloride, emetine, erythramine, erythroidine, hydrastine, menispermine, morphine, papaverine, sanguinarine, tubocurarine chloride
Phenylalkylamine	*Ephedra, Lophophora*	Ephedrine
Purine	*Guarana, Cola, Coffea, Thea, Theobroma*	Caffeine,[a] theobromine,[a] theophylline[a]
Pyridine	*Anabasis, Areca, Conium, Lobelia, Piper, Punica, Ricinus, Nicotiana*	Anabasine, aphylline, arecaidine, arecoline, coniine, guvacine, lobeline, nicotine, pelletierine, piperine, ricinine, trigonelline
Quinoline	*Cinchona, Cusparia*	Cinchonine, cinchonidine, cusparine, ethylhydrocupreine, quinacrine, quinine, quinidine
Quinolizine	*Anagyris, Laburnum, Lupinus, Sophora*	Anagyrine, cytisine, lupanine, lupinine, matrine, sparteine
Spirobenzylisoquinoline	*Fumaria, Corydalis*	Corpaine, fumaricine, fumariline, fumaritine, ochrobirine, ochrotensimine, ochrotensine, sibiracine
Steroidal[b]	*Solanum, Veratrum, Lycopersicon, Holarrhena, Schoenocaulon*	Cevadine, cevine, conessine, jervine, rubijervine,solanidine, solanine, tomatidine, veratramine, eratridine
Tropane	*Erythroxylon, Atropa, Datura, Hyoscyamus, Scopola*	Atropine, benzoylecgonine, cocaine, eucatropine, homatropine, hygrine, hyoscyamine, scopolamine

[a] Some authors do not classify these relatively feebly basic compounds as alkaloids.
[b] Various nuclei are represented in this group. In general, they have some resemblance to the steroid (cyclopentanophenanthrene) nucleus.

in various solvents; color producing reactions with specified reagents; and microscopic examination of the crystals obtained by the action of suitable precipitants under controlled conditions. Closely related alkaloids such as morphine and codeine do not differ sufficiently in their absorption of ultraviolet light to permit differentiation on the basis of their respective spectrograms. However, the infrared spectrum of an alkaloid is individual and identification can be made with certainty. Modern high-resolution NMR techniques make possible even more definitive identification.

Occurrence and Uses

The building blocks of the alkaloids are presumed to be amino acids and their metabolic degradation products. Formaldehyde sources (ie, glyoxylic and formic acids) are also available and biological processes of deamination, decarboxylation, and oxidation are operative. Various genera of 158 botanical families have yielded compounds with alkaloidal properties. A few are obtained from cryptogams (flowerless plants) but the majority are extracted from the phanerogams (flowering plants), most of them being from dicotyledons. Among the monocotyledons, some useful alkaloids are found in species of the Amaryllidaceae and Liliaceae families. Alkaloids are also found in some fungi (ie, lysergic acid derivatives), the skins of amphibians, and some mammals (ie, indole and isoquinoline).

Phytochemists estimate that less than 5% of the known flowering plants have been investigated for possible alkaloid content. Specific alkaloids of complex structures are ordinarily confined to specific plant families (ie, *hyoscyamine* in Solanaceae and *colchicine* in Liliaceae). However, the occurrence of ergot alkaloids in the fungus *Claviceps purpurea* and certain *Ipomoea* species (Convolvulaceae) is an exception, which may be attributed to either parallel or conversion evolution of certain complex biochemical pathways. In their native environment, alkaloids usually exist in the form of salts, frequently of the simple organic acids such as lactic, malic, tartaric, or citric. Unusual, often distinctive, acids are also encountered, such as quinic with cinchona alkaloids, and meconic with opium alkaloids.

Alkaloids may be recovered from their parent plant material by extraction. In a representative type of processing, the crude, milled plant material is moistened with an aqueous alkali such as sodium carbonate, sodium bicarbonate, or lime to liberate the alkaloids from their salts and percolated with benzene, ether, or some other suitable water-immiscible solvent. The solvent layer is extracted with dilute acid to convert the alkaloids into salts and to bring them into the aqueous phase. The free alkaloids are precipitated by the addition of alkali and separated by appropriate means. The specific operations involved are based upon the physical and chemical properties of the alkaloids sought. Purification is usually accomplished by the crystallization of the alkaloidal salts but distillation and other procedures may also be employed. In some cases, when the alkaloid content of a plant is low and large volumes of dilute aqueous solutions are obtained, it is advantageous to adsorb the alkaloids on ion-exchange resins. If the alkaloids adsorbed onto a resin differ sufficiently in basicity, it may be possible to effect at least a partial separation of the alkaloids during the course of the elution from the resin. An excellent example of the problems encountered and of some of the techniques employed in the separation of a complex mixture of alkaloids is provided by the review of researchers on the *Vinca* alkaloids.[25]

Most alkaloids are physiologically active, some being extremely poisonous, although typically harmless to plants. In the majority of instances, they are responsible for the pharmacological actions of the plants from which they are derived. Notwithstanding the many extremely valuable synthetic medicinal and antibiotic agents that have been added to the list of weapons against disease, the alkaloids still constitute an indispensable and most potent group of substances for the treatment and mitigation of functional disturbances and relief from suffering. It is for this reason that some of the larger pharmaceutical firms maintain continuing programs for the pharmacological screening of alkaloids, both new and old. For example, reserpine, much valued for its antihypertensive and

psychotherapeutic actions, emerged from such a program in the 1950s, and an intensive effort with the *Vinca* (*Catharanthus*) alkaloids yielded some oncolytic drugs of value in the treatment of certain types of cancer. A number of naturally occurring alkaloids are made synthetically and there are also a number of synthetic drugs having an alkaloidal character.[25] Distinction should be made between *total synthesis,* in which the end product is the result of chemical processes that employ only materials that can be built up from the elements (carbon, hydrogen, oxygen, etc), and *partial synthesis* in which the end product is produced from a naturally occurring complex substance that is already closely related structurally to the desired end product (ie, the synthesis of ergonovine from lysergic acid).

Major Classes of Alkaloids

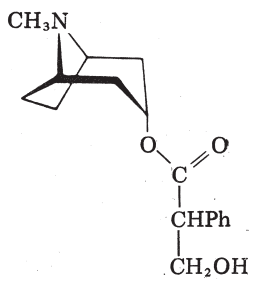
As mentioned previously, various alkaloidal classification systems have been employed. Each system has its advantages and disadvantages and more needs to be learned about the occurrence, composition, and physiological actions of the alkaloids before a comprehensive classification having maximum practical utility can be produced. We will classify the pharmaceutically relevant alkaloids based upon their biosynthesis from a particular amino acid derivative and discuss each of the following classes individually:

- Ornithine-derived alkaloids—The ornithine derivatives, proline and putrescine constitute the basic structures
- Phenylalanine-, tyrosine-, and dihydroxyphenylalanine-derived alkaloids
- Tryptophan-derived alkaloids
- Miscellaneous alkaloids—Not biosynthesized from amino acids or biosynthesis has not been fully established.

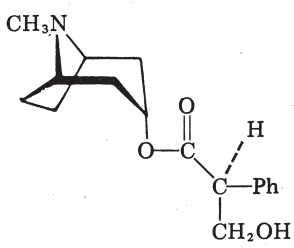
ORNITHINE-DERIVED ALKALOIDS

The **tropane alkaloids** will be considered in two groups: (1) atropine and related alkaloids and (2) cocaine. They are grouped together because all are derivatives of tropane. The alkaloids of the atropine group are closely related chemically (Table 26-11). Most of the natural alkaloids are esters of *mandelic acid* or *tropic acid* with *tropine* or *scopine*. Scopine is epoxytropine, the only difference being the 6,7-oxygen bridge. Esters of tropine are called *tropeines* (ie, tropine mandelate is mandelyltropeine). *Atropine* is a racemic variety of tropine tropate, *hyoscyamine* is the levorotatory enantiomorph of

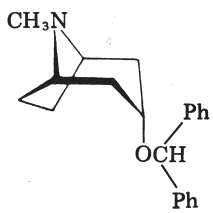
Table 26-11. Atropine and Related Alkaloids and Derivatives



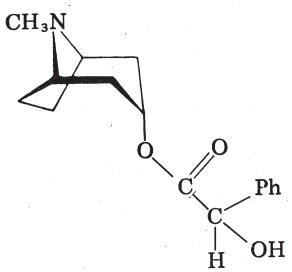
Atropine
(Tropine(±)-Tropate)



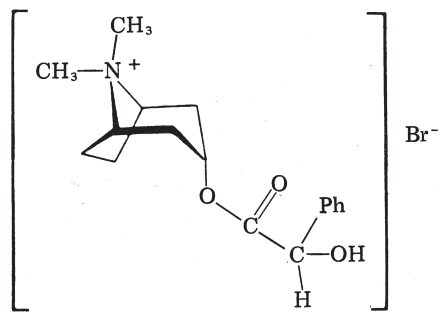
Hyoscyamine
(Tropine(–)-Tropate)



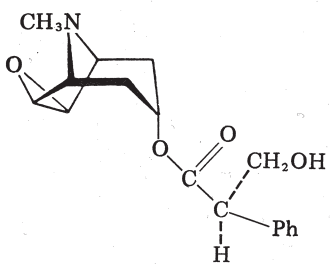
Benztropine



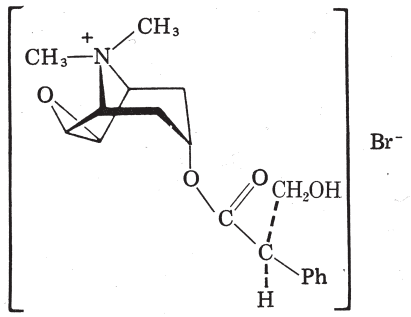
Homatropine



Novatropine
(Homatropine Methylbromide)

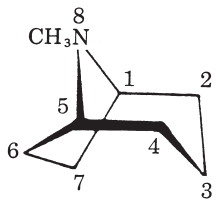


Scopolamine
(6β,7β-Epoxyhyoscyamine)

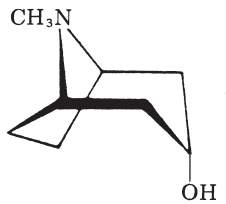


Methscopolamine
Bromide

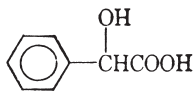
tropine tropate, and *scopolamine* is scopine tropate. These esters may be hydrolyzed by heating in water.



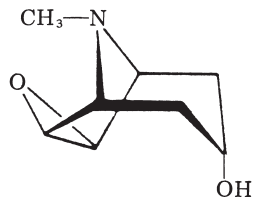
Tropane



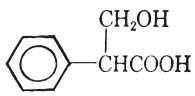
Tropine (*endo*-8-Methyl-8-azabicyclo[3.2.1]octane-3-ol)



Mandelic Acid



Scopine ([7(*S*)-(1α,2β,4β,5α,7β)]-9-Methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonan-7-ol)



Tropic Acid

Eumydrine is also related closely; it is 8-methylatropinium nitrate, a quaternary ammonium salt. Homatropine is tropine mandelate and novatropine is 8-methylhomatropinium bromide. Benztropine is the benzhydryl ester of tropine (Table 26-11).

Atropa belladonna (nightshade), *Hyoscyamus niger* (henbane), and *Datura stramonium* (jimson weed) all yield mydriatic alkaloids, characteristic of the Solanaceae family. There are also many other plants of this family that are being used largely in the manufacture of the various alkaloids. Atropine rarely occurs as such in any of the plants but is always the product of the racemization of the levo-isomeride hyoscyamine, which is converted into atropine by the action of weak alkalies. This racemization involves the conversion of the (−)-tropic acid moiety of hyoscyamine to (±)-tropic acid. The most characteristic physiological property of the Solanaceous alkaloids is their mydriatic effect (pupil dilation of the eye). This property is the basis for their most sensitive identification test. As little as one drop of a 1 in 25,000 solution will cause a distinct dilation of the pupil of a cat's eye. Atropine also simulates the CNS and causes a decrease in secretions; hyoscyamine does not stimulate the CNS and is used as a sedative for motion sickness.

Table 26-12. Ecgonine Derivatives

R	R′	NAME OF DERIVATIVE
H	H	Ecgonine
CH_3	C_6H_5CO-(benzoyl)	Cocaine
H	CH_3	Methylecgonine
H	$C_6H_5CH{=}CHCO$-(cinnamoyl)	Cinnamoylecgonine
H	C_6H_5CO	Benzoylecgonine

The cocaine group of tropane alkaloids is distinguished chemically from the atropine group by the presence of an *exo*-carboxyl (or esterified carboxyl) at the 2-position and by the *exo*-configuration (instead of *endo*-) of the 3-ester function. Therefore, they become derivatives of ecgonine ([1R-(*exo*,*exo*)]-3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid) having the general structure:

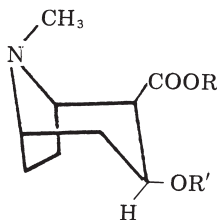


Table 26-13. Classification of Opium Alkaloids

Benzylisoquinoline Group	Codamine [$C_{20}H_{25}NO_4$][a]	Narcotine [$C_{21}H_{21}NO_7$][e,c]
	Gnoscopine [$C_{22}H_{23}NO_7$][b,c]	l-Narcotine [$C_{22}H_{23}NO_7$][b,c]
	Laudanidine [$C_{20}H_{25}NO_4$][a]	Oxynarcotine [$C_{22}H_{23}NO_8$][b,c]
	dl-Laudanine [$C_{20}H_{25}NO_4$][a]	Papaverine [$C_{20}H_{21}NO_4$][e]
	Laudanosine [$C_{21}H_{27}NO_4$][a]	Xanthaline [$C_{20}H_{19}NO_5$][e]
	Narceine [$C_{23}H_{27}NO_8$][d]	
Phenanthrene Group	Codeine [$C_{18}H_{21}NO_3$][f]	Neopine [$C_{18}H_{21}NO_3$][g]
	Morphine [$C_{17}H_{19}NO_3$][f]	Thebaine [$C_{19}H_{21}NO_3$][h]
	ψ-Morphine [$(C_{17}H_{18}NO_3)_2$][f]	
Tetrahydroisoquinoline Group	Hydrocotarnine [$C_{12}H_{15}NO_3$][b]	
Quinoline Group	Aporeine [$C_{18}H_{17}NO_2$][i]	
Cryptopine Group	Cryptopine [$C_{21}H_{23}NO_5$][j]	Protopine [$C_{20}H_{19}NO_5$][h]
Alkaloids of Unknown Structure	Lanthopine [$C_{23}H_{25}NO_4$]	Papaveramine [$C_{21}H_{25}NO_6$]
	Meconidine [$C_{21}H_{23}NO_4$]	Rhoeadine $C_{21}H_{21}NO_6$]
Derivatives of Natural Alkaloids	Apomorphine[k]	Metopon (methyldihydromorphinone)
	Dionine (ethylmorphine)	Nalorphine (N-allylnormorphine)
	Heroin (diacetylmorphine)	Naloxone
	Hydrocodone (dihydrocodeinone)	Oxymorphone
	Hydromorphone (dihydromorphinone)	Oxycodone

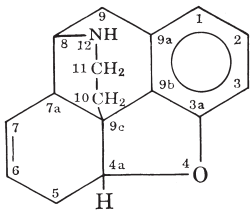
[a] 1,2,3,4-tetrahydroisoquinoline; (1708).
[b] 5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinoline; (2810).
[c] 1,3-dihydroisobenzofuran (phthalan); (1330).
[d] 2,3-dihydrobenzofuran (coumaran); (1328).
[e] isoquinoline; (1708).
[f] 5,7a,8,9-tetrahydro-4a*H*-8,9c-iminoethanophenanthro[4,5-*bcd*]furan; (5922).
[g] 5,6,8,9-tetrahydro-4a*H*-8,9c-iminoethanophenanthro[4,5-*bcd*]furan; (5922).
[h] 8,9-dihydro-4a*H*-8,9c-iminoethanophenanthro[4,5-*bcd*]furan; (5922).
[i] 6,7,7a,8-tetrahydro-5*H*-benzo[*g*]-1,3-benzodioxolo[6,5,4-*de*]quinoline; (5846)
[j] 6,7,12,13,14,15-hexahydrobenzo[*e*]-1,3-dioxolo[4,5-*l*][2]benzazecine; (4874).
[k] 4*H*-dibenzo[*de, g*]quinoline; (5171).

Table 26-12 portrays the identities of R and R‘ for the common ecgonine derivatives. Alkaloids within this group are commonly found in cocoa leaves. They have local anesthetic properties but also have highly addictive properties, and therefore, they are only used for ophthalmic, ear, nose, and throat surgery.

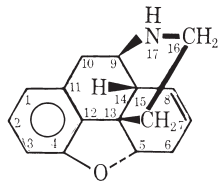
The **tobacco alkaloids** derived from ornithine are represented by nicotine, which consists of a pyridine moiety associated with a pyrrolidine ring. Nicotine is derived from the genus *Nicotiana* and is present in tobacco smoke and some insecticides. Nicotine has also been used in chewing gums, nasal sprays, and transdermal patches for smoking cessation.

PHENYLALANINE-, TYROSINE-, AND DIHYDROXYPHENYLALANINE-DERIVED ALKALOIDS

OPIUM ALKALOIDS—*Opium* is the latex obtained by incision of the unripe capsules of the opium poppy, *Papaver somniferum* (Papaveraceae). The many alkaloids obtained from the opium poppy are divided into the following chemical groups: *Benzylisoquinoline, Phenanthrene, Tetrahydroisoquinoline, Quinoline, Cryptopine, Alkaloids of Unknown Structure,* and *Derivatives of Natural Alkaloids* (Table 26-13). It will be observed that the pharmaceutically important alkaloids displayed in Table 26-14 derive from the so-called benzylisoquinoline (papaverine) and phenanthrene (morphine/codeine) groups. The parent heterocycle of the phenanthrene group is 4a*H*-8,9*c*-iminoethanophenanthro[4,5-*bcd*]furan. In the hexahydro state characteristic of codeine and morphine, its *Ring Index* (IUPAC) orientation and numbering are shown below. The specific stereoisomer present in these alkaloids is shown at the right in *Chemical Abstracts* format, which treats it as a 4,5α-epoxymorphinan and numbers it by the familiar Cahn–Robinson sequence.

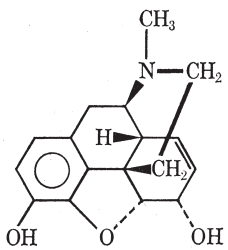


IUPAC

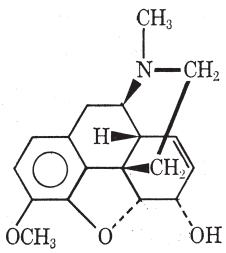


Chemical Abstracts

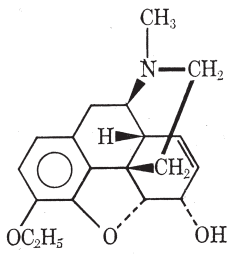
Table 26-14. Opium Alkaloids and Derivatives



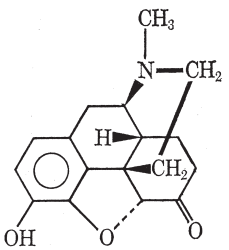
Morphine



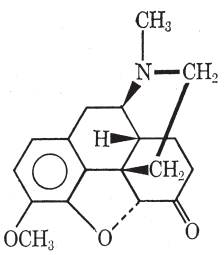
Codeine



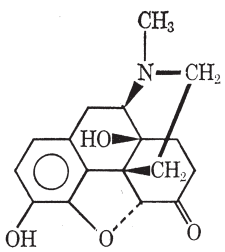
Ethylmorphine



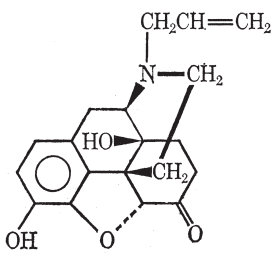
Hydromorphone



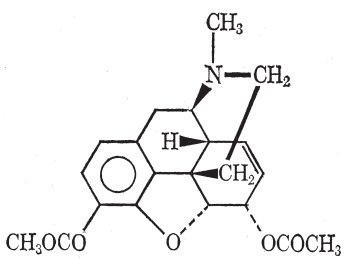
Hydrocodone



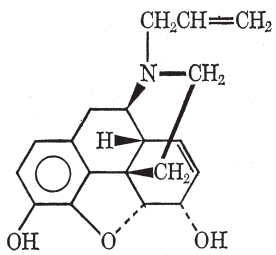
Oxymorphone



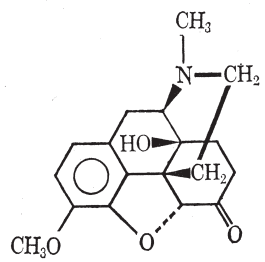
Naloxone



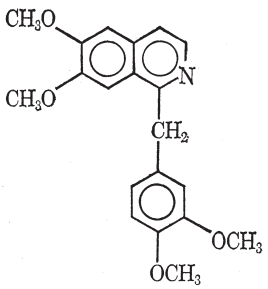
Heroin



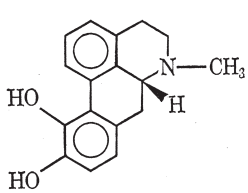
Nalorphine



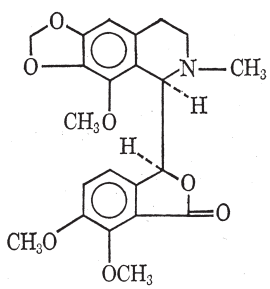
Oxycodone



Papaverine



Apomorphine



Noscapine (*l*-Narcotine)

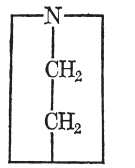
Papaverine is a very weak base and slightly toxic. Morphine is a stronger base, alkaline to litmus, and highly toxic. Morphine and codeine have been used to treat pain, as hypnotics, and to treat diarrhea. Codeine has also been used as a cough suppressant.

Additional pharmaceutically relevant, phenylalanine-, tyrosine-, and dihydroxyphenylalanine-derived alkaloids include the following:

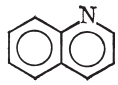
- Ephedrine and pseudoephedrine are derived from various species of *Ephedra* (Ma-huang) (Ephedraceae) and used for a variety of therapeutic actions including the relief of asthma.
- Colchicine is derived from the seed or corn of *Colchicum autumnale* (Liliaceae). It is an amorphous, yellowish-white solid that darkens upon exposure to light. It is a weak base that results in a yellow color when mixed with strong mineral acids. It is soluble in water, alcohol, and chloroform and slightly soluble in ether. It is used therapeutically to relieve gout.
- Emetine is derived from the root of *Cephaelis ipecacuanha* (Rubiaceae) and used as an expectorant and emetic.
- Tubocurarine is derived from *Chondrodendron tomentosum* (Menispermaceae) and used as a muscle relaxant. Such "curare" alkaloids are found in South American arrow poisons.

TRYPTOPHAN-DERIVED ALKALOIDS

***Cinchona* Alkaloids**, such as the quinoline alkaloids (quinine and quinidine, a pair of diastereoisomers) and their 6-demethoxy derivatives (cinchonine and cinchonidine), are derived from the dried bark of the stem or root of various species of *Cinchona* (Rubiaceae). The structural formulas in Table 26-15 indicate the close relationships between the various members of this group of alkaloids. Examination of the formulas of these compounds shows that they all contain a *quinoline* ring attached through a hydroxymethylene group to a *quinuclidine* ring.



Quinuclidine



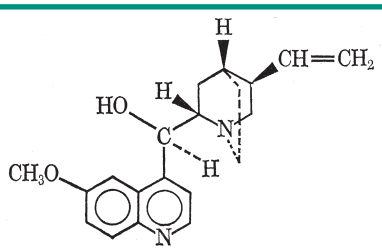
Quinoline

By altering the side chains attached to these rings and by esterifying and/or oxidizing the alcohol group, a large number of compounds have been produced and investigated.

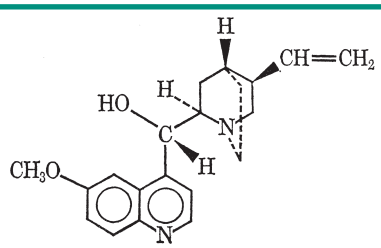
Both *Quinine* and *quinidine* have a *methoxy* group attached to the quinoline ring and a *vinyl* group attached to the quinuclidine ring. Each has the same four chiral centers, but the diastereoisomerism involves only the configurations at the carbinol and 2-quinuclidine carbon atoms. *Cinchonine* and *cinchonidine* differ from these two alkaloids in that they do not have a methoxy group on the quinoline ring. Quinidine and cinchonine are dextrorotatory; whereas, quinine and cinchonidine are levorotatory. *Hydroquinine,* obtained from quinine by reduction with hydrogen and a catalyst, has the same structure as quinine except the vinyl group is reduced to an ethyl group. *Cupreine,* another naturally occurring *Cinchona* alkaloid, has an OH group in place of the methoxy group and *hydrocupreine* is cupreine with an ethyl group instead of a vinyl group. Therefore, quinine is the 6-methyl ether of cupreine and hydroquinine is the corresponding ether of hydrocupreine. Woodward and Doering first synthesized quinine in 1944 but the process is too costly for commercial use.

The salts of the alkaloids are typical amine salts. Since there are two nitrogen atoms present in the molecules of the *Cinchona* alkaloids, it is possible to form salts containing one or two equivalents of acid, such as mono- and dihydrochlorides. Quinine and its diastereoisomer, quinidine, are characterized

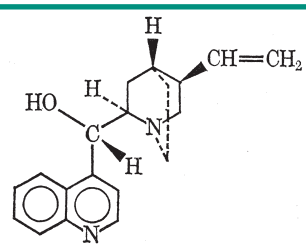
Table 26-15. Cinchona Alkaloids and Derivatives



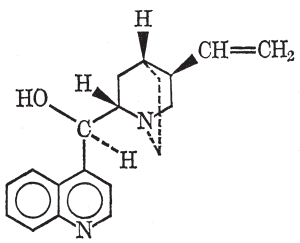
Quinine



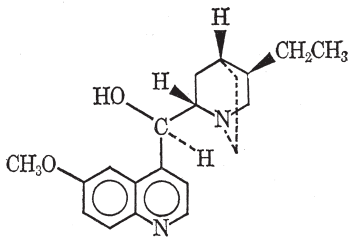
Quinidine



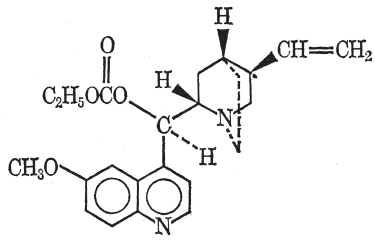
Cinchonine



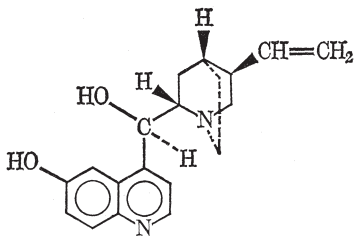
Cinchonidine



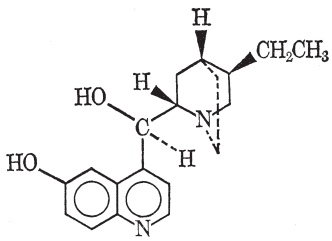
Hydroquinine



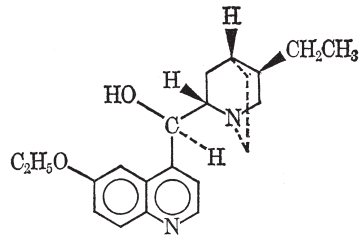
Quinine Ethylcarbonate



Cupreine



Hydrocupreine



Ethylhydrocupreine

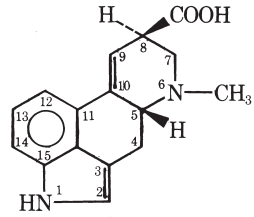
by the blue fluorescence of their solutions in dilute sulfuric or other oxyacids and by the *thalleioquin reaction.* The addition of two drops of bromine TS to 5 mL of a saturated solution of quinine or quinidine or a 1:1000 solution of their salts, followed by 1 mL of ammonia TS, produces an emerald green color due to the formation of thalleioquin. Quinine and quinidine are differentiated by their optical rotations and by their behavior toward alkali tartrate. In neutral or slightly acid solutions, quinine is precipitated by this reagent, but quinidine is not. On the other hand, quinidine, in moderately dilute solutions, is precipitated by soluble iodides but quinine is not affected. The same differences are exhibited by cinchonidine and its diastereoisomer, cinchonine; the former is levorotatory and, like quinine, is precipitated by alkali tartrates but cinchonine is dextrorotatory and unaffected by the reagent.

Other than quinine, quinidine, cinchonine, and cinchonidine, 18 other alkaloids have been isolated from cinchona barks. Some of these, such as cupreine, are found in only one kind of bark and some are doubtlessly split products (ie, not existing naturally in the bark but the result of the action of chemical agents upon them). The acids present are *quinic acid (hexahydro-1,3,4,5-tetrahydroxybenzoic acid), quinotannic acid,* and *quinovic acid (3β-hydroxyurs-12-ene-27,28-dioic acid).* Also present are α-*quinovin* (a glycoside), *cinchona-red*, other coloring matter, and a volatile oil. The quinine and total alkaloid content is highest in the bark from the cultivated variety. Java bark, representing a highly cultivated plant, contains 7 to 10% of total alkaloids, of which about 70% is quinine. In the bark from the uncultivated plant, cinchonine and cinchonidine predominate.

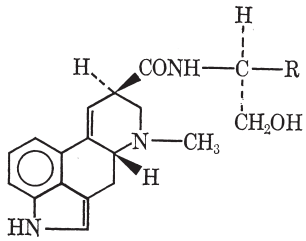
Quinine was used as a treatment for malaria until the advent of synthetic anti-malarials during WWII. Quinidine also has anti-malarial properties and is used as a prophylaxis for cardiac arrhythmias and a treatment for arterial fibrillations. Java bark is infrequently used in the US but is employed elsewhere as a cheap substitute for quinine. It shares the *antimalarial*, *antipyretic*, and *analgetic* actions of quinine, but the alkaloidal salts are to be preferred to the galenical preparations. One of the principal difficulties in preserving its galenical preparations arises from the alteration and precipitation that the cinchotannic acid and its compounds undergo on storage. Glycerin has proved to be very useful by dissolving and holding these in solution, and hence it is present in nearly all of the preparations.

Ergot Alkaloids are derived from *Ergot*, a morbid growth formed when the fungus *Claviceps purpurea* develops on various plants of the *Gramineae* (grass) and *Cyperaceae* (sedge) families such as rye, wheat, oats, barley, and rice. If the infestation of the plant occurs naturally, the resulting ergot is called *natural* ergot; if the infestation is brought about artificially (ie, wholly or partly by human intervention), the resulting ergot is referred to as *cultivated* ergot. Ergots from different plants vary in composition, and therefore, they are not medicinally equivalent. It is for this reason that rye is stipulated as the source of official ergot. Ergot has yielded 12 different, well-defined alkaloids, each of which is an *N*-monosubstituted amide of either *normal* or *iso*lysergic acids. The substituting group on the amide nitrogen is commonly referred to as the *peptide moiety* of the alkaloid because it always contains one or more peptide (amide) linkages. In addition to alkaloids, ergot contains various carbohydrates, glycerides, sterols (ie, ergosterol and fungisterol), amino acids (ie, histidine, leucine, and tyrosine), amines (ie, histamine and tyramine), quaternary ammonium compounds (ie, choline and betaine), and coloring principles.

As mentioned, ergot alkaloids are all substituted amide derivatives of lysergic acid, which is shown below along with the official compounds and the important, but unofficial, diethylamide. It is the lysergic acid group that is their important medicinal constituent. Ergometrine, known in the US as ergonovine, produces an oxytocic effect (induces/assists with labor) and has been used as an analgesic for migraine headaches. Ergonovine, simpler by far than any of the other ergot alkaloids, is commercially available both as the natural alkaloid and as a synthetic compound. It is soluble in water and dilute alcohol.



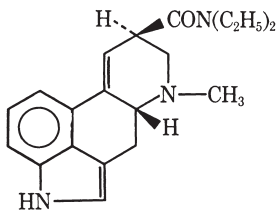
Lysergic Acid
(9,10-Didehydro-6-methylergoline-8β-carboxylic Acid)



Ergonovine (R = CH_3)
Methylergonovine (R = CH_2CH_3)

An understanding of the ergot alkaloids requires knowledge of the isomerism of lysergic acid, which exists in two diastereoisomeric forms depending on the spatial configuration of the carboxyl group relative to the 5β-hydrogen. In the *normal* lysergic acid (commonly called lysergic acid), this relative configuration is of the *cis* variety (carboxyl in β-configuration); in the *iso*lysergic acid, it is of the *trans* type (carboxyl in α-configuration). *Chemical Abstracts* treats lysergic and isolysergic acid compounds as derivatives of ergoline, which is the 4,6,6aβ,7,8,9,10,10aα-octahydro form of indolo[4,3-*fg*]quinoline, *Ring Index* No 4550.

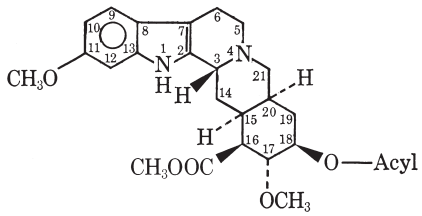
N,*N*-Diethyl-D-lysergamide, a compound of considerable interest, does not occur in nature. The physiologically active isomer is the (+)-enantiomorph of the *N*,*N*-diethylamide of normal lysergic acid and is commonly referred to as LSD-25 or simply LSD. Methods for its synthesis from lysergic acid have been developed. In normal subjects, LSD elicits a temporary combination of physiological and psychological effects that collectively mimic syndromes characteristic of psychotic states such as schizophrenia. LSD has been the subject of intense clinical investigation since the mid-1960s. There are no established therapeutic applications at present but it has found some application as a tool in psychopharmacology and in psychiatric diagnosis. Discovery of the psychotogenic activity of LSD has led to extensive research with various types of lysergic acid derivatives. It also has given rise to serious social problems.



***N*,*N*-Diethyl-D-lysergamide (LSD)**

***Rauwolfia* Alkaloids,** such as reserpine, are obtained from several *Rauwolfia* species. Interest in the remarkable therapeutic properties of these powerful agents became so keen that reserpine alkaloid injections and tablets were admitted to the *USP XV* (by the 1959 supplement). Rescinnamine soon followed in *NF XI* in 1960 and syrosingopine gained *NF XII* recognition in 1965. Currently, only reserpine has official status. The general structure of these three alkaloids is shown below. *Chemi-*

cal Abstracts uses the familiar Barger-Scholz numbering. It will be observed that they are all esters of methyl reserpate with the only difference being in the identity of the acyl represented in the ester group at locus 18 of the heteronucleus. By the *Chemical Abstracts* system, methyl reserpate is the methyl ester of 18β-hydroxy-11,17α-dimethoxy-3β,20α-yohimban-16β-carboxylic acid and yohimban is the 4aβ,13bα,14aα stereoisomer of the 1,2,3,4,4a,5,7,8, 13,13b,14,14a-dodecahydro form of *Ring Index* No 5874, benz[*g*]indolo[2,3-*a*]quinolizine. Reserpine and rescinnamine occur naturally; syrosingopine is synthetic.

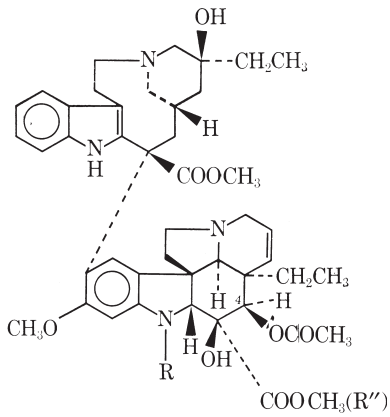


Alkaloid	Acyl
Reserpine	3,4,5-trimethoxybenzoyl
Rescinnamine	3,4,5-trimethoxycinnamoyl
Syrosingopine	carbethoxysyringoyl

The genus *Rauwolfia,* natural order *Apocynaceae,* contains almost 50 species that grow in tropical and semitropical regions (India, Burma, Ceylon, Java, etc). The most extensively investigated species are *Rauwolfia serpentina* Benth, *R canescens* Linn, *R vomitoria* Afzel, and *R heterophylla* Roem. In ancient literature, mention is made of the use of *Rauwolfia* as a remedy for snakebites and scorpion stings, as a febrifuge, and as a cure for dysentery. The sedative action of the drug was also noted, for it was considered useful in *moon's disease* (lunacy), to induce sleep in children, and in hypochondria. Despite this long history, very few pharmacological and chemical studies were undertaken on *Rauwolfia* until the Indian investigators Bose and Sen reported successful clinical trials with the drug in 1941; the Indian chemists Siddiqui and Siddiqui isolated the first crystalline alkaloid from the plant in 1931. At present, at least 25 substances have been reported from *Reserpentina* alone, which, when assayed as directed, contains not less than 0.15% of reserpine-rescinnamine group alkaloids, calculated as reserpine. *Rauwolfia* preparations (known collectively as Rauwolfia) are available in the form of powdered whole root, extracts, selected alkaloidal fractions, the pure crystalline alkaloids *reserpine* and *rescinnamine,* and the synthetic *syrosingo pine.* The most prominent actions of its alkaloids are upon the cardiovascular and central nervous systems. They are widely employed as *antihypertensive agents* and as *adjuncts in psychotherapy.*

***Vinca* Alkaloids—**During the late 1950s, pharmacological inquiries into the purported antihyperglycemic activity of principles contained in *Vinca rosae* Linn (Madagascan periwinkle of the Apocynaceae family) led to the initial discovery that two of the alkaloidal constituents, vincaleukoblastine (vinblastine) and leurocristine (vincristine), possessed certain demonstrable kinds of oncolytic (antitumor) activity. The overall result of these discoveries has been that the plant has been the subject, for several decades, of one of the most intensive phytochemical studies on record. Over 70 different alkaloids have been demonstrated to be present and more than half of these were recognized as new chemical compounds. The complete structure for most of the isolated compounds has been determined. An excellent review of the accomplishments during the first 7 years of intense research on the *Vinca* alkaloids is available.[25]

The therapeutic efficacy of vincaleukoblastine and leurocristine as antineoplastic agents has been established. The structures of these two closely related alkaloids are portrayed below. The four-ring heterosystem is a stereospecific hydrogenated form of 10*H*-3,7-methanoazacycloundecino[5,4-*b*]indole, *Ring Index* No 13276, and the five-ring system is a similar form of 1*H*-indolizino[8,1-*cd*]carbazole, *Ring Index* No 11065.



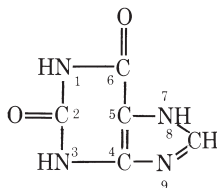
Vinblastine (vincaleukoblastine), R = CH$_3$
Vincristine (leurocristine), R = CHO
Vinglycinate, R = CH$_3$, R′ = OCOCH$_2$N(CH$_3$)$_2$
Vindesine, R = CH$_3$, R′ = OH, R″ = CONH$_2$

The costliness of vinblastine and vincristine provided increased interest in producing them synthetically. The five-ring indoline system is known to be available from other natural alkaloid sources. Vinglycinate and vindesine are additions wherein the structure has been modified synthetically.

An additional pharmaceutically relevant tryptophan-derived alkaloid is physostigmine, which is derived from calabor seeds, the dried ripe fruit of *Physostigma venenosum* (Leguminosae) and used to contract pupils and oppose the effect of mydriatics.

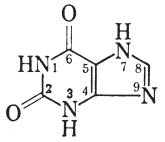
MISCELLANEOUS ALKALOIDS

The purine base alkaloids, better known as the **xanthine alkaloids**, have three medicinal important agents. They are secondary metabolites and are all methylated derivatives of 2,6-dioxypurine (xanthine). Three alkaloids, caffeine (1,3,7-trimethylxanthine), theophylline (1,3-dimethylxanthine), and theobromine (3,7-dimethylxanthine), comprise the bulk of this group. The structural relationships of the purine or xanthine alkaloids are portrayed in Table 26-16; purine is the parent molecule of each. The common practice of portraying the two-dimensional structure in box form is still primarily used. For example, the xanthine structure can be represented by:

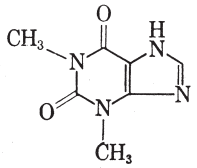


Other bases closely related to purine are *hypoxanthine*, *adenine*, and *guanine*, all of which are found normally in animal tissues. The primary significance of the last two bases is the fact that they are constituents of nucleic acids and nucleoproteins that are found in cell nuclei and that hypoxanthine is produced in the body during the first stage of adenine oxidation. Subsequent oxidation yields *xanthine* and, finally, *uric acid*. In humans, the end product of protein metabolism is *urea*. In certain animals, the end product is *allantoin*, which is formed by further oxidation of uric acid. The two-dimensional structures of these compounds are illustrated in Table 26-16. The oxygen-containing compounds are depicted here in keto form but they often are shown in texts in enol form, as illustrated below with xanthine. The presence of oxygen in several of these structures also causes a slight alteration in the position of unsaturation because of the tautomerization that can occur. The enol forms often are named specifically to reflect the hydroxyl groups, such as purine-2,6,8-triol or 2,6,8- trioxypurine for uric acid.

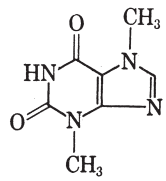
Table 26-16. Xanthine Alkaloids



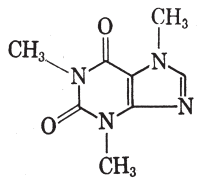
Xanthine
(3,7-Dihydro-1*H*-purine-2,6-dione)



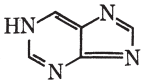
Theophylline
(1,3-Dimethylxanthine)



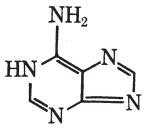
Theobromine
(3,7-Dimethylxanthine)



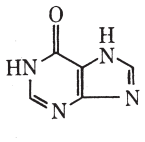
Caffeine
(1,3,7-Trimethylxanthine)



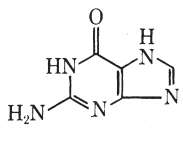
1*H*-Purine



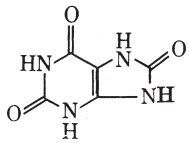
Adenine
(1*H*-Purin-6-amine)



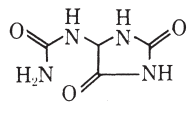
Hypoxanthine
(1,7-Dihydro-6*H*-purine-6-one)



Guanine
(2-Amino-1,7-dihydro-6*H*-purine-6-one)

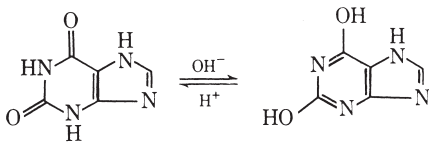


Uric Acid
(7,9-Dihydro-1*H*-purine-2,6,8(3*H*)-trione)



Allantoin
(2,5-Dioxo-4-imidazolidinyl)urea

The xanthines are very weak bases having a pK_b of approximately 13 to 14. They form readily hydrolysable salts with the stronger acids. By tautomeric shift of hydrogen from nitrogen to keto oxygen (enolization), a weakly acidic H (pK_a of about 9) is formed on the resulting OH group. Thus xanthine, along with various other oxopurines and their derivatives, forms salts with the stronger bases. Having no NH group to participate in enolization, caffeine is an exception.



keto structure **enol structure**

The xanthines are characterized by the murexide reaction, which involves evaporating a nitric acid solution of the test sample to dryness and treating the residue with ammonia, whereupon a purplish-red color develops. The color is due to the formation of murexide, an ammonium salt of purpuric acid. Uric acid and various other purine derivatives also respond to this test.

Xanthine alkaloids are present in numerous plants including tea leaves obtained from *Thea sinensis* (Ternstroemiaceae), cocoa seeds/beans obtained from *Theobroma cacao* (Sterculiaceae), and coffee seeds/beans obtained from *Coffea arabica* and other *Coffea* species (Rubiaceae). A significant quantity of caffeine is present in tea and coffee and is responsible for their CNS stimulatory and diuretic effects. Theobromine has less CNS stimulatory and diuretic effects than caffeine. Theophylline is similar to caffeine except that is has a shorter and stronger diuretic effect and more significantly relaxes involuntary muscles.

The **imidazole alkaloid**, pilocarpine, is derived from various species of *Pilocarpus* (Rutaceae). It may be biosynthesized from histidine or threonine. It is an ophthalmic cholinergic drug used to contract the pupil and act as an antagonist to atropine. It also increases irrigation and decreases ocular pressure in the treatment of glaucoma.

PHENOLS

Phenols are very widespread in nature and are probably the largest group of secondary plant metabolites. They range from simple structures having a single aromatic ring to highly complex polymeric structures and often exist in glycosidic forms. Phenols are biosynthesized through the shikimic acid pathway and may have aromatic rings derived through acetate condensation. They are frequently used as coloring agents, flavorings, aromatizers, and antioxidants. Phenols may be divided into several classes. Those of pharmaceutical importance are the simple phenolic compounds, tannins, anthraquinones, and flavonoids.

Simple phenolic compounds consist of a single phenolic ring and often possess alcholic, aldehydic, and carboxylic acid groups. Examples include vanillin, a phenolic aldehyde, and salicylic acid, a phenolic acid. Vanillin is found in the unripe fruits of varius species of *Vanilla* (Orchidaceae). It exists as the glycoside, glucovanillin, which yields vanillian and glucose upon hydrolysis. It has been used widely in both the food and perfume industries. Capsaicin (the vanillyl amide of isodecenoic acid) is found in the dried ripe fruit of different species of *Capsicum* (Solanaceae). It has been used internally for atonic dyspepsia and flatulence. Externally, it is frequently used as a counterirritant.

Tannins are more complex phenol compounds. They generally have molecular weights ranging from 1000 to 5000 and typically consist of a substantial number of phenolic groups (~1.5 per 100 MW), which are associated with an *o*-dihydroxy and *o*-trihydroxy orientation. Tannins having lower molecular weights are considered as pseudotannins. "True" tannins may be classified as hydrolysable, condensed, or complex. Hydrolysable tannins exist as glycosides with a glucose molecule and may be hydrolysed by acids or enzymes such as tannase. Their solutions turn blue with iron salts. Condensed tannins or proanthocyanidins have polymeric flavan-3-ol like structures. They are not associated with a sugar molecule, and therefore, are not readily hydrolyzed by acids or enzymes. Instead, they are usually precipitated as red insoluble compounds known as phlobaphenes. Complex tannins are formed from the joining of a hydrolysable and a condensed tannin.

Tannins are soluble in water, dilute bases, alcohol, glycerol, and acetone but generally sparingly soluble in other organic solvents. They occur widely in plants and are found in greatest quantity in dead or dying cells. Their inhibitory effects upon enzymes may contribute to the protective effects of bark. Tannins are also used commercially by the leather industry and have been used for dying and manufacturing ink. They have also been used therapeutically as a hemostatic agent and as antidiarrheals. Their ability to precipitate heavy metals, alkaloids, and glycosides has resulted in their use as antidotes in such poisonings. However, their use has recently been limited to topical astringents due to the discovery that tannic acid may cause severe necrosis of the liver.

Anthraquinones may exist in the free state or as glycosides with the sugar attached in various locations. The derivatives of anthraquinones may be di-, tri- (emodin), or tetrahydroxy (carminic acid) phenols. There may also be additional groups present such as methyl, hydroxymethyl (aloe-emodin), and carboxyl (carminic acid). Anthraquinones derivatives are often orange-red in color and soluble in hot water or dilute alcohol. This class also includes reduced derivatives of anthraquinones, the anthranols and anthrones, which are isomers and may exist in either form in solution. Anthrone is pale yellow, nonfluorescent, and insoluble in basic solutions; whereas, anthranol is brownish-yellow and strongly fluorescent in basic solutions. Anthranol derivatives are commonly found in aloes. Oxanthrones are intermediate products between anthraquinones and anthranols and may be converted to anthraquinones upon oxidation. They are found in cascara bark. Dianthrones are compounds formed by the combination of two like or unlike anthrone molecules resulting from mild oxidation. Two chiral centers are found in dianthrones, and therefore, a dianthrone consisting of two identical anthrone molecules may exist in two forms in addition to a *meso* form. Dianthrones are found in species of *Cassia, Rheum,* and *Rhamnus* with the sennidins (aglycones of sennosides) being the best-known examples. Anthraquinones and their derivatives generally have dyeing and purgative properties. The laxative action occurs only in the large intestine, and therefore, their therapeutic effect may take up to 6 hr to occur.

A variety of anthraquinone and anthrone derivatives have been isolated from senna pods, which consist of the dried, ripe fruits of *Cassia senna* and *Cassia angustifolia* (Leguminosae). Senna has been used for its purgative effects and remains to be a very important pharmaceutical laxative. Cascara bark is the dried bark of *Rhamnus purshianus* (Rhamnaceae) and contains a variety of anthracene derivatives present as both *O*- and *C*-glycosides. The primary glycosides are more active than the aloins whereas the free anthraquinones and dimers have less purgative activity. The cascarosides have a sweet and more pleasant taste than the aloins. Cascara is available as a liquid extract, elixir, or tablets and has a purgative active very similar to senna. Various types of anthraquinones and anthrones are found in the dried, underground parts of rhubarb, particularly *Rheum palmatum* and *R. officinale* (Polygonaceae), and are responsible for the purgative effects of these plants. Barbalion, the 10-glucopyranosyl glycosidic derivative of aloe-emodin-anthrone, is found in all commercial varieties of aloes, which are the solid residue obtained by evaporating the liquid that drains from the cut leaves of various species of *Aloe* (Liliaceae). This resin of aloes has been used for its purgative effects and should not be confused with "aloe vera," which is a mucilage found in the parenchymatous cells of the *Aloe vera* leaf. The red, dianthrone pigment, hypericin, is found in the dried, flowering, aerial parts of *Hypericum perforatum* (Guttiferae) or St. John's Wort. It has sedative and antiseptic properties. It also acts as a photosensitizer in mammals. Carminic acid is a *C*-glycoside anthraquinone derivative found in cochineal, which is a colorant derived from the dried female insects of *Dactylopius coccus*.

Flavonoids constitute the largest group of naturally occurring phenols and have been receiving much attention recently.[26] Flavonoids may exist in both the free and glycosidic state (typically the *O*-glycosoide form). They are formed from three acetate units and a phenylpropane unit and are distinguished by the state of oxygenation of the C3 unit. The dimeric forms, biflavonyls, are also well known. Flavonoids may be grouped into a number of classes such as flavones, flavonols, flavonones, xanthones, and isoflavones. Specific examples include hesperidin (the rhamnoglucoside of hesperetin or methyl eriodictyol) and rutin (the rhamnoglucoside of quercetin). The glycoside forms are typically soluble in water and alcohol but insoluble in organic solvents. Flavonoids dissolve in basic solutions resulting in a yellow color, which increases with pH and the number of hydroxyl groups but disappears to a colorless solution upon the addition of acid. The flavones are most commonly found in the cell sap and young tissue of higher plants (particularly Polygonaceae, Rutaceae, Leguminosae, Unbelliferae, and Compositae) but are widely distributed in nature. Their therapeutic activity may result from their effect upon arachidonic acid metabolism.[27] They posses anti-inflammatory, anti-allergic, antithrombitic, and vasoprotective (decreased capillary fragility) effects. They also prevent tumor promotion and protect the gastric mucosa. Some flavonoids also have antibacterial and antifungal activity and flavonoligans such as silybin (a 1,4-dioxan produced from the oxidative combination of taxifolin and coniferyl alcohol and found in one of the milk-thistles, *Carduus marianus* (Compositae)) have anti-hepatoxic properties.

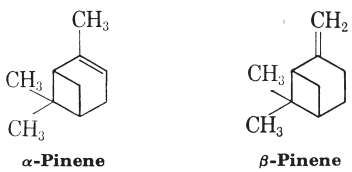
VOLATILE OILS, RESINS, AND MISCELLANEOUS ISOPRENOIDS

Composition and Structure

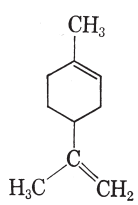
Volatile, or essential, oils differ from the other classes previously discussed in that they are complex mixtures of a variety of hydrocarbons and oxygenated compounds. In some countries they are called *olea aetherea.* In some instances they are called *essences,* a name that conflicts with our ordinary use of the word to designate an alcoholic solution of a volatile oil. The following groups of compounds occur in the volatile oils: hydrocarbons, alcohols, acids, esters, aldehydes, ketones, phenols and phenol ethers, lactones, and various nitrogen and sulfur organic compounds. In some cases, such as mustard oil and bitter almond oil, they are derived from glycosides. The hydrocarbons of chief importance are the *terpenes* ($C_{10}H_{16}$) and the *sesquiterpenes* ($C_{15}H_{24}$; literally, *one and one-half terpenes*). The terpenes have the formula C_nH_{2n-4} and typically occur in the following configurations:

- Three double bonds and no ring, such as *myrcene* (found in Myrcia Oil) and *ocimene* (found in the volatile oil from the leaves of *Ocimum gratissimum*)
- Two double bonds and one ring, such as *limonene* (widespread occurrence but especially in the citrus oils)
- One double bond and two rings, such as either α-*pinene* or β-*pinene* (the first of which is of very widespread occurrence; together, these two terpenes comprise at least 90% of the bulk of turpentine oil).

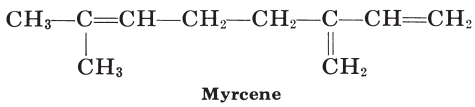
Terpenes



α-Pinene **β-Pinene**



Limonene

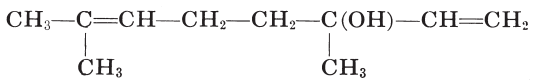


Myrcene

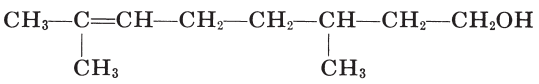
The sesquiterpenes have the formula C_nH_{2n-6}, and therefore, occur in even more varied configurations. Sesquiterpenes are biosynthesized from farnesyl pyrophosphate and may have linear, monocyclic, or bicyclic structures.[28] They are secondary metabolites with some being formed as the result of some stress or injury to the plant. Although a number of these hydrocarbons have been isolated, many of their structures are not definitely known. Among those of known structure are *zingiberene* (from Ginger oil) and *bisabolene* (from Bisabol myrrh oil).

Hydrocarbons other than the terpene types are sometimes present. An example is the saturated hydrocarbon *n*-heptane (C_7H_{16}), which occurs in the volatile oil obtained from the oleoresin of *Pinus sabiniana* and *P jeffreyi* and from the fruits of *Pittosporum resiniferum* (the so-called *petroleum nut* of a tree growing in the Philippines). However, many of the essential oils owe their character and their value to constituents other than hydrocarbons. Among these are organic *acids* such as acetic, benzoic, cinnamic, and phenylacetic; *alcohols* such as benzyl alcohol, borneol, cinnamyl alcohol, citronellol, geraniol, linalool, menthol, phenylethyl alcohol, and terpineol; *aldehydes* such as anisaldehyde, cinnamaldehyde, benzaldehyde, citral, piperonal or heliotropin, salicylaldehyde, and vanillin; *ketones* such as carvone, camphor, thujone, and pulegone; *esters* such as bornyl acetate, methyl salicylate, benzyl benzoate, geranyl acetate, and linalyl acetate; *phenols* such as thymol, carvacrol, and chavicol; *phenol ethers* such as anethol, eugenol, and safrol; and many other more complex compounds such as coumarin and indole.

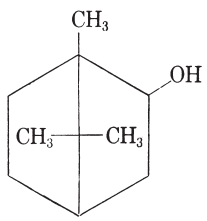
Alcohols



Linalool

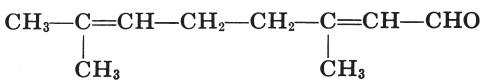


Citronellol

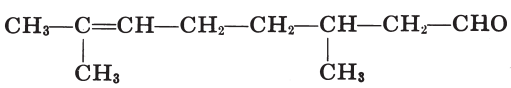


Borneol

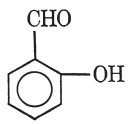
Aldehydes



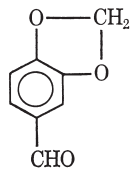
Citral
(*cis*-Neral)
(*trans*-Geranial)



Citronellal

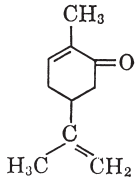


Salicylaldehyde

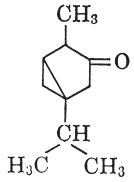


Heliotropin (Piperonal)

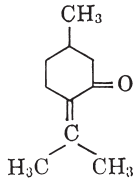
Ketones



Carvone

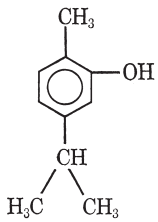


Thujone

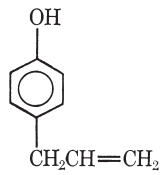


Pulegone

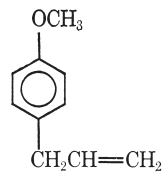
Phenols and Phenol Ethers



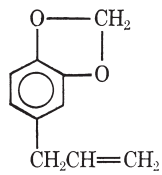
Carvacrol



Chavicol



***O*-Methylchavicol**



Safrol

Physical and Chemical Properties

The properties of volatile oils differ greatly from those of fixed oils. Most of the volatile oils are colorless when pure and fresh or can be made colorless by redistillation. Upon exposure to the air, they acquire various colors, becoming green, as in oil of wormwood; yellow, as in oil of peppermint; red, as in oil of origanum; and brown, as in oil of cinnamon. The blue color of oil of chamomile is an inherent property of the oil even when freshly distilled and is due to the highly unsaturated hydrocarbon *chamazulene* ($C_{15}H_{18}$). Their volatility results in their aromatic properties. The odors and tastes of volatile oils are determined by their oxygenated compound content, and therefore, they are extremely variable and their most characteristic feature. The odor of an oil is modified by exposure to the air. Oil of turpentine may be rectified by redistillation in an atmosphere of carbon dioxide, or *in vacuo*, so that it will be almost odorless or have an agreeable, fragrant odor. However, a very slight exposure to the air is sufficient to restore its well-known unpleasant odor. Other terpene-containing oils are quickly oxidized and the delicacy and fineness of their flavor and odor are seriously impaired. This is especially true of orange and lemon oils. Some volatile oils are sweet; others have a mild, pungent, hot, acrid, caustic, or burning taste.

The specific gravity of official volatile oils also varies (from 0.842 to 1.172) with the majority of them being lighter than water. Optical activity is used to determine the purity of many oils. Refractive index serves as a delicate test for both the identity and purity of oils. Because most volatile oils consist of complex mixtures of many types of compounds, their boiling point is of little significance. In general, the terpenes and sesquiterpenes are practically insoluble in water but soluble in alcohol, ether, chloroform, benzene, petroleum benzin, and the fixed and volatile oils. Even though water is a poor solvent for volatile oils, it acquires a decided odor and flavor when brought in contact with the oil in a finely divided state, as in the preparation of medicated waters. Alcohol, ether, chloroform, glacial

acetic acid, petroleum ether, benzene, and many other organic solvents will dissolve volatile oils. Alcohol is a better solvent for oxygenated oils than for terpenes. Many official oils are required to meet specific solubility tests in 70%, 80%, or 95% alcohol. Volatile oils freely dissolve fixed oils, fats, resins, camphors, and usually sulfur and phosphorus.

Exposure to light and air impairs the quality and destroys the fragrance of volatile oils. Peroxides frequently develop in oils containing terpenes and, after extended exposure, the oils thicken and become resinified, or deposit crystalline compounds. The whitening of corks after insertion for a long time in bottles containing certain volatile oils is caused by the bleaching action of the peroxides that are gradually produced during the oils decomposition. This is only true for oils containing notable amounts of terpenes. Therefore, such volatile oils should be kept in well-filled, tightly stoppered, amber-colored bottles in a cool place. A suggestion has been made to replace the air in the original packages with nitrogen to prevent oxidation. Storage in metal cans causes pronounced deterioration in odor and the development of color. In some volatile oils, such as thyme, a separation into a solid and a liquid portion occurs upon standing in the cold. The solid portion is frequently known by the name *stearoptene* and the liquid portion is called *eleoptene*. Some stearoptenes are of commercial importance (eg, thymol, camphor, and menthol).

Occurrence and Uses

Volatile oils are found in various plant organs and tissues. They usually constitute the savory and odorous principles of the plants in which they exist and they either preexist in the tissues or are produced by the reaction of certain constituents when the tissues are brought into contact with water, which results in hydrolysis of their glycosides. Volatile oils are often associated with other substances such as resins and gums, and as mentioned previously, they typically resinify themselves upon exposure to air. They are generally obtained from plants by distillation with steam, distillation *per se* (or without the use of water), expression, and extraction. Volatile oils are sometimes actually formed through destructive distillation (ie, the oils of tar and amber). These are occasionally referred to as *pyrolea* or *empyreumatic oils*. Volatile oils are commonly used for flavoring and perfuming. Many volatile oils also have additional therapeutic effects. For example, camphor is used as an external rubfacient, clove and thyme have been used as antiseptics due to their high phenol content, caraway has been used as a carminative and antispasmodic, cinnamon oil has been used as a germicide, and ginger has been used as an anti-inflammatory, anti-platelet, anti-ulcer, antibacterial/fungal, and anti-emetic.

Resins

Resins are usually the oxidized terpenes of volatile oils and are more or less solid, amorphous products having a complex chemical nature. They typically consist of a mixture of acids, alcohols, esters, and phenols with inert compounds known as resenes. They should not be referred to as balsams, which contain a high amount of aromatic balsamic acids and consist primarily of fixed oils and waxes. Resins typically soften or melt upon heating and are insoluble in water but dissolve to different extents in alcohol, chloroform, and ether. As a result of their poor water solubility, they typically have little taste. Resins are typically found as normal physiological products in plant ducts and cavities but their yield increases upon injury. This further differentiates them from balsams, which are usually not formed until injury occurs making them of pathological origin. Resins are often associated with volatile oils and gums. For example, natural oleoresins, such as turpentine, consist of a mixture of volatile oils and resins, and gum resins are natural mixtures of gums and resins.

Podophyllum resin is derived from the dried rhizome and roots of *Podophyllum peltatum* (Berberidaceae) also know as May-apple or Wild Mandrake. Its chief active constituents are lignans, which are C18 compounds biosynthesized from the dimerization of two C6-C3 units, such as coniferyl alcohol, at the β-carbon of the side chains. The most important lignans present in this resin are β-peltatin and α-peltatin.[29] The resin also contains smaller amounts of the closely related 4′-demethylpodophyllotoxin. Podophyllum resin has cytotoxic activities and is used in the treatment of soft warts. Etoposide (4′-demethylepipodophyllotoxin ethylideneglucoside) is a lignan derivative obtained semisynthetically from podophyllotoxin and has been used in the treatment of small-cell lung cancer, testicular cancer, lymphomas, and leukemias.

Miscellaneous Isoprenoids

In addition to the isoprenoids mentioned previously, several others are of pharmaceutical importance. Valeranone is a sesquiterpene component of the volatile oil from valerian, which consists of the rhizome, stolons, and roots of *Valeriana officinalis* (Valerianaceae) and is responsible for the herbs sedative properties.[30] The sesquiterpene lactones, parthenolide and 3β-hydroxyparthenolide, are used to standardize feverfew, which is derived from various species of *Parthenium* (Compositae) and has been used for the treatment of fever, arthritis, migraine, and other disorders.[31] The leaves of *Ginkgo biloba* (Ginkgoaceae) contain several diterpene lactones (ginkgolides A, B, C, J, and M) that are platelet-activating factor antagonists. They have been characterized to consist of a tertiary butyl group and six 5-member rings. Carotenes are C_{40} tetraterpenoids often associated with chlorophyll and participate in photosynthesis. They may also be found in other plants organs. Carotenes are yellow or orange-red in color. For example, the carotenoids, lycopene and citraurin, are responsible for the color of red tomatoes and oranges, respectively. As a result, carotenes have been used extensively as colorants. They also possess vitamin A activity, which is a diterpenoid produced in animal livers by enzymatic hydrolysis of β-carotene. The taxane diterpenoid derivative, taxol, is derived from the bark of the pacific yew, *Taxus brevifolia,* (Taxaceae). Taxol consists of a four-membered oxetane ring and a complex ester side-chain. These structures provide taxol with its anti-cancer activity.

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CHAPTER 27

Drug Nomenclature—United States Adopted Names

Pardeep K Gupta, PhD

Advances in the scientific disciplines continue to occur at such an accelerated rate that the processing of information has become a separate and distinct discipline in its own right. Precise and current terminology is an important tool of science, and nowhere is it more important than in medicine and pharmacy. Drug nomenclature, particularly, would become confusing, meaningless, and incomprehensible without a well-developed system of rules.

It is not unusual for each drug entity to be known by several chemical names, more than one code number, several trivial designations, a formally selected nonproprietary name, and one or more trademarks. Therefore, it is essential that a logical, well-defined nonproprietary nomenclature system is available to facilitate the exchange of drug information.

This chapter describes the mechanisms for creating nonproprietary drug names that are used in the US. It includes history, scope, function, and operation of the nomenclature system devised by the United States Adopted Names (USAN) Council. A brief introduction of the policies of the World Health Organization (WHO) International Nonproprietary Name (INN) program and its relationship to the USAN Council have been added.

DRUG NAME TYPES

The term *drug nomenclature* implies that drugs may have several types of names, each having its own function, and indeed this is the case. Although some names are scientifically precise, others may be ambiguous or misleading.

The first type of name, usually applied to compounds of known composition, is the *chemical name.* Among the several conventions that exist for creating chemical names, the most widely established is the American Chemical Society's Chemical Abstracts Services (CAS) Index naming system. Use of this system results in the creation of systematic (CAS Index) names for chemical entities that serve as a key to the chemical literature of the world. The CAS system is used by the USAN program.

For substances of plant or animal origin that cannot be classified as pure chemical compounds, scientific identification is given in terms of precise *biochemical, botanical, or zoological names.* Such designations are also scientifically exact, but like their chemical counterparts, they tend to be complex, unwieldy, and generally not useful to the physician, pharmacist, or other users of drug nomenclature.

Most developing drug materials while being investigated acquire a *code designation* as a convenient means of referring to the compound before it has been assigned either a nonproprietary name or a trademark. Such codes are generally a letter and number combination, eg, SC-40230 (bidisomide, *Searle*), Ro 4-3780 (isotretinoin, *Roche*), or RP 56976 (docetaxel, *Rhone-Poulenc Rorer*). The letter(s) generally represent an abbreviation of the research laboratory name; the numbers are assigned by the firm in an arbitrary manner or following some internally created convention. Codes may be acronyms or letter combinations derived from portions of the chemical or common name (eg, AZT for azidothymidine or TPA for tissue plasminogen activator).

Code designations usually are considered as convenient "shop labels" and are meant to be discarded when a more appropriate name is selected. However, many of these codes appear in early scientific literature dealing with investigative work prior to the selection of a nonproprietary name. Frequently they are used in clinical studies in the absence of a nonproprietary name to identify the chemical entity. Code designations, therefore, must be considered a part of drug nomenclature, but they are not acceptable for general use. In themselves, these codes give no information about the compound they represent.

The use of acronyms instead of the proper nonproprietary names may also be dangerous because many contractions are extremely similar, such as DDI (didanosine) and DDC (zalcitabine). Similarly, AZT, is commonly used for the antiviral zidovudine (derived from *azidothymidine,* its shortened chemical name). However, AZT can just as readily represent the immunosuppressant azathioprine. Medication errors due to use of acronyms have been reported both by the Institute for Safe Medication Practices and the USP Medication Errors Reporting Program.

Trivial names occasionally are assigned to a new compound, usually by the researchers working on it. Nomenclature agencies strongly discourage the use of trivial names as generally they are coined haphazardly and are usually not suited for adoption as official nonproprietary names. Too frequently trivial names are confusingly similar to existing names, which may lead to confusing them with established nonproprietary names.

When a new drug has successfully survived the successive research stages and testing to the point where it appears it may become a marketable product, a *trademark* is developed by the manufacturer. Properly registered trademarks become the legal property of their owners and cannot be used freely in the public domain. Selected for their brevity and ease of recall, trademarks usually give little or no scientific information about the drug.

Each type of name described thus far aims to serve its specific purpose; however, none fulfill the need for a single, simple, informative designation available for unrestricted public use. The *nonproprietary name* is the only name intended to function in this capacity. The nonproprietary name often is referred to as the *generic name,* but this practice is inaccurate, as each nonproprietary name is specific for a given compound, even though it may possess a stem that is common to a related group of drugs.

Throughout this chapter, the term *nonproprietary name* applies to those names that have been selected by the formal process of negotiation between the drug manufacturer and the USAN Council.

THE USAN COUNCIL

The agency responsible for the selection of nonproprietary names for single-entity drugs marketed in the US is the United States Adopted Names (USAN) Council. This expert committee on drug nomenclature is jointly sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention Inc (USPC), and the American Pharmaceutical Association (APhA). All three agencies were involved in the selection of drug names for many years prior to the establishment of the USAN Council in the 1960s. The aim of USAN is the global standardization and unification of drug nomenclature and related rules to ensure that drug information is communicated accurately and unambiguously. The Council conducts its negotiation activity by correspondence. Twice a year, the Council convenes to discuss nomenclature policy, liaison activity, and new nomenclature strategies.

The USA Council Secretariat is located at the AMA headquarters in Chicago, Illinois. The agency works closely with the World Health Organization (WHO) International Nonproprietary Name (INN) Committee, and various national nomenclature groups. In addition, USAN program has liaison organizations all over the world. As of 2003, these organizations include the following:

The *United States Pharmacopeia* (USP) has been supplying standards for pharmaceutical preparations since the first edition appeared in 1820. Because there was a need for titles for monographs included in the USP that described the drugs for which standards were being prepared, the USP was one of the first publications to recognize the necessity for a standardized system of drug nomenclature and the first to take action to establish such a system.

The American Pharmaceutical Association began publication of a second compendium, the *National Formulary* (NF) in 1888 and established quality standards for drugs included in the NF. The editor of the NF quickly became involved with providing nonproprietary names for the monographs published in the NF.

In 1906, the US government legally recognized the significance of the work being done by the USP and the NF by declaring both publications *official* compendia. Since that time, monograph titles have had the status of official nonproprietary names.

As new pharmaceutical products increased in number, other organizations recognized the need for formally approved names while the drug entity was still in its investigational stages. The AMA Council on Pharmacy and Chemistry (CPC), later known as the Council on Drugs, was created in 1905 as an advisory body to the Board of Trustees to encourage rational drug use by physicians. In conjunction with screening and evaluating new remedies, the CPC initiated a nomenclature program to provide nonproprietary names for individual drugs available commercially under more than one trademark. This activity continued until the early 1940s when the Council on Drugs began to re-

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2540 Olentangy River Road
PO Box 3012
Columbus, OH 43210-0012
Attn: Sabine P. Kuhn, PhD **WHO INN Committee Secretariat**
World Health Organization
1211 Avenue Appia
Geneva 27-Switzerland
Attn: Raffaella Balocco-Mattavelli, PhD

CHINA
The Deputy Chief
Drug Standard Division II Pharmacopeia Commission
Ministry of Health
Temple of Heaven
Beijing 100050
People's Republic of China

ITALY
DCE Commission - Denominazione
Communi Italiane
Director-General
Pharmaceutical Division
Ministero della Sanità
Viale della Civiltà Romana 7
1-00144 Roma

RUSSIA
Director
Pharmedinfo
Ministry of Health
PO Box 195
Moscow 103051, Russian Federation

UNITED KINGDOM
BAN - British Approved Names
The Secretary
British Pharmacopoeia Commission
Market Towers
1 Nine Elms Lane
London SW8 5NQ

BELGIUM
L'Inspecteur en chef-Directeur
Ministère de la Santé Publique et de l'EnvironementInspection générale de la Pharmacie
Pharmacie Cité administrative de l'Etat
Cité administrative de l'Etat Quartier Vésale 333 B1010
Bruxelles

FRANCE
DCF Denominations
Communes Francaises Agence du Medicament
Agence du MedicamentDirection des Laboratoires et des Controles
Unite Pharmacopee

JAPAN
JAN–Japanese Accepted Names
Japanese Ministry of Health and Welfare
New Drugs Division
Pharmaceuticals Affairs Bureau
1-2-2, Kasumigaseki, Chiyoda-ku
Tokyo 100

SPAIN
Ministerio de Sanidad Y Consumo
Direccion General de Farmacia
Centro Instit de Info de Medicamentos,
CINIME–Paseo del PrDO 18-20, Planta 15
28014 Madrid

quire a nonproprietary name for every active compound listed in all AMA publications.

The 1938 Food, Drug and Cosmetic (FD&C) Act stipulated that the *common or usual name* should be used as part of drug labeling to identify the drug entity. In the absence of such a name (or until a name attained such status), a chemical name was to be used.

The Drug Amendments of 1962 replaced the "common or usual" terminology with the more meaningful requirement that nonproprietary names must be "simple and useful." Also, for the first time, the Commissioner of the Food and Drug Administration (FDA) was given the authority to designate the official name if he determined that such action was necessary or desirable.

Despite the nomenclature activities of the AMA, USP, and APhA, large numbers of drug products did not become the subject of either the NF, the USP, or the Council on Drugs monographs and continued to be identified by their chemical names, trivial names, or trademarks selected by the manufacturers. As medicine and pharmacy advanced and drugs became more specific in their actions and structurally more complex, other nomenclature-related needs were recognized that made it apparent that each new drug needed a nonproprietary name selected early in its development. A systematic approach to assure drug name appropriateness and acceptability to AMA, USP, NF, and the drug manufacturer now became more obvious. Each new drug also needed a *global name*—one name used and accepted worldwide.

A significant step toward supplying this need was taken in June 1961, with the formation of the AMA-USP Nomenclature Committee. The names adopted by this committee were deemed acceptable as potential compendia monograph titles, and the acronym *USAN* (United States Adopted Name) was coined to designate names formally processed and approved by the Committee. The APhA participated in the program from its inception but did not become a full and official sponsor until January 1964, at which time the name of the committee was changed to the USAN Council.

The FDA and the USAN Council conducted an unofficial liaison until early 1967 when it was determined that a formal cooperative effort in the development of nonproprietary names would be more beneficial to both. In June 1967 an official agreement was signed between the sponsors of the USAN Council and the FDA that required the FDA to appoint annually one voting member to the Council. This contract stipulated that the FDA would accept as the "official or established" name any drug name the USAN Council adopted. In this agreement, the Commissioner of the FDA reserved the right to select the official name in those instances in which the USAN Council could not reach consensus. It should be noted that the designation of a name as an *official* or *established name* by the FDA did not follow automatically, but rather was accomplished by publication, subject to public comment, in the *Federal Register*. All parties upheld this agreement until it was modified 17 years later.

On November 26, 1984, the Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* an amendment to the FD&C Act that stated in part that

> "the Food and Drug Administration agrees with 'Guiding Principles for Coining US Adopted Names for Drugs', published in USAN and the USP Dictionary of Drug Names. . . [, and that] the established name . . . will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common or usual name of the drug. Interested persons, in the absence of the designation of an official name, may rely on the USAN listed in USAN and the USP Dictionary of Drug Names as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act."

Today, the USAN Council is comprised of five members: one member is appointed by each of the three sponsoring organizations, one is a liaison member from the FDA, and one is a member-at-large who must be approved by the three sponsoring organizations. Council members are nominated by their sponsoring organization annually. Every year their nomination must be approved by the boards of trustees of the other sponsoring organizations, who also approve the nominees for the FDA liaison and the member-at-large positions. Council members may serve for up to 10 consecutive years. The council members for 2003 are:

Daniel L Boring, PhD (FDA)
Everett Flanigan, PhD (USP)
William M Heller, PhD (Member-at-Large)
John E Kasik, MD, PhD (AMA)
Anthony Palmieri, III, PhD, (APhA)

At an early stage in the development of the USAN Council, it was anticipated that occasional disagreements might arise between the Council and a manufacturer over the selection of a particular nonproprietary name. In the majority of such cases, the Council and the firm can, in time, work out an acceptable compromise; however, in rare instances, an impasse may develop that needs adjudication by someone not directly involved with the USAN Council or the drug manufacturer. The USAN Review Board was established as the final arbitrator of nomenclature disputes when normal procedures have failed. Each sponsoring organization nominates two members to the Review Board annually; nominations must be approved annually by the Boards of Trustees of the other sponsoring organizations. No term limits have been placed on member's participation on the Review Board. Members of the Review Board for 2003 are

Donald R. Bennett, MD, PhD (AMA), (*Chair*)
Jordan Cohen, PhD (USP)
Stuart Feldman, PhD (APhA)
Alice Jean Matuszak, PhD (APhA)
Lauren A. Woods, MD, PhD (AMA)
Gary L. Yingling, JD (USP)
Joseph G. Valentino, JD, USP, *serves as the Review Board Secretary*

The USAN Review Board secretariat is supported by the USP. Joseph G Valentino, JD, serves the Board as Secretary. At the time of any appeal to the Board, representatives of the drug firm involved in the specific case can participate in the deliberations, but they have no voting privileges. The Secretary of the USAN Council becomes the spokesperson for the Council. The determination of the USAN Review Board is final and not subject to appeal.

PROCEDURE FOR OBTAINING A USAN

The negotiation of a USAN originates with a drug manufacturer, a licensee of that firm, or its legal representative. On rare occasions, a formal request for a nonproprietary name will be initiated by an individual who has developed a substance of potential therapeutic usefulness to the point where there is a distinct possibility of the compound being marketed in the US. Occasionally, the initiative for the development of a USAN is assumed by the FDA or the USP. The criteria set by the Council for initiating the negotiation process states that the drug must have progressed in its development to the point where clinical studies have been started. At that time an Investigational New Drug (IND) application must have been approved by the FDA.

The USAN application form was standardized in the early 1970s. Currently, each nomenclature request must be submitted on this form and accompanied by detailed chemical, pharmacological, and manufacturing information and reprints of clinical studies or other published information. Use of this form facilitates handling data and ensures that pertinent items have not been omitted. Requests for USAN are expected to conform to the established Guiding Principles for the Selection of Nonproprietary Names for Drugs and to be reasonably free from conflicts with other names, including both trademarks and

nonproprietary names. Forms can be obtained by writing to USAN Secretariat at the AMA Headquarters, 515 N State Street, Chicago, IL 60610, or by photocopying the forms appearing in the current edition of the *USAN Handbook*.

A description of how a proposed name eventually becomes an adopted USAN will illustrate the process. Assume that a submission for a new single-entity drug has been received by the USAN Secretariat. Under ideal circumstances, inspection of the submitted material indicates that timing of the negotiation is correct relative to clinical investigation, information supplied is properly entered on the USAN submission form, and adequately substantiated by CAS information and scientific data, and that the suggested names include the proper stem for the class of compounds being considered. The negotiator assigned to the USAN application will begin processing the submission without delay. Obviously, if information is missing or incomplete, valuable time will be lost contacting the applicant for the needed data.

The initial step undertaken by the USAN staff coordinator is a review of the chemical information including the chemical name, structural and molecular formulas, and the molecular weight listed on the application. The coordinator verifies the accuracy of the CA Index name and Registry number against the CAS Registry File database. The chemical information then is forwarded to the USAN Council's chemical consultant for assignment of the IUPAC name and an expert review of the structural and molecular formulas as listed by the firm.

The main work on the submission involves a detailed check of the suggested names for conflicts with other names; verification of the assignment of the proper stem based on a study of the new compound relative to similar compounds, pharmacological action, therapeutic indication, formal ballot polling of the Council for an informed opinion on the suitability of the suggested names; publication of the names under consideration on the USAN Web site (www.ama-assn.org/go/usan), and the *USP Pharmacopeial Forum* to allow other manufacturers the opportunity to examine all suggested names for possible conflict; and communication with the submitting firm to obtain its approval of a tentatively adopted name or the reaction to counterproposals from the Council. Verifying chemical structure and support for therapeutic indication/method of action requires utilization of the CAS Registry File, Prouse Trilogy, STN database, Medlines, MedScape and other pertinent databases. In addition, the USAN and USP Dictionary of Names, the WHO INN list, Merck Index, and Martindale may be used to verify that the proposed name is not in conflict with an existing nonproprietary or trade name.

Selecting even a tentatively adopted USAN often requires considerable negotiation between the Council and the applicant. The Council conducts its negotiation activities by correspondence. *It is important to note that generally a name will not achieve the first level of tentative adoption until it has been found unanimously acceptable to all members of the USAN Council and to the submitting firm.*

Once a tentatively adopted USAN has been selected, the USAN Secretariat forwards this name and appropriate background information to the WHO INN Committee Secretariat located in Geneva, Switzerland. Names under review by the USAN Council are forwarded to nomenclature agencies of several countries. Input from other countries helps avoid selection of a USAN that has an unacceptable and unintended negative or pejorative connotation in another language. The INN Committee undertakes an evaluative procedure not unlike that conducted by the USAN Council, and this process takes approximately five months, but may extend longer. A formal negotiation is initiated to accept the tentative USAN or to consider an INN counterproposal if there is a problem with use of the original name in other countries. *Only when it becomes apparent that the tentative name is acceptable to the USAN Council, the submitting manufacturer, and, in most cases, the INN Committee will it be formally adopted as a USAN*. Therefore, a USAN will be assigned in the shortest possible time if the principals involved can reach agreement with minimal negotiations.

USAN adoptions are scheduled for the last Wednesday of each month. A Letter of Adoption and a Nomenclature Statement formally notifies the applicant that the negotiation process has been completed and that a USAN has been issued for the compound.

After the applicant has reviewed the Nomenclature Statement, the USAN is submitted for publication in the journal *Clinical Pharmacology and Therapeutics* (New Names column), and the *Pharmacopeial Forum* (Nomenclature Column), and posted in the "What's New" section of the USAN Web site. Reprints of "New Names" column are distributed to the drug manufacturers, libraries, and pharmaceutical press representatives.

USAN Nomenclature Statements are published for each definable chemical substance and is identified by two chemical names: the first name is the Chemical Abstracts (CA) Index name; the second is a systematic name developed in accordance with rules devised by the International Union of Pure and Applied Chemistry (IUPAC). Occasionally, a third chemical name may be added, one that has become firmly established through extensive use. In conjunction with use of CA nomenclature, a CAS Registry number is included in the published entry. Structural and molecular formulas and the molecular weight are listed where applicable. The manufacturer supplies the intended therapeutic classification. The name of the manufacturer, brand name, manufacturer code designation, and trivial name formerly used are included to further identify the new USAN. Reprints of the monthly "New Names" column are available on request from the USAN Council Secretariat.

After reviewing the complex USAN negotiation process, one can appreciate that the time required to approve a USAN varies considerably depending on a number of factors. The time between submission of an application and adoption of a USAN averages about 8 months and ranges from 4 to 26 months. A significant portion of this time, about five months or longer, may be required for processing by WHO. The time required may be appreciably shorter when adopting a USAN for a compound that already has INN status (ie, a compound already marketed outside the United States) or when the name does not have to be considered by the INN Committee (EG, contact lens plastics, surgical sutures). The negotiation time is shortest when the name being suggested is for a new salt or ester of a compound that already has an adopted USAN (ie, for a USAN modified). Such names are routinely processed by the USAN Secretariat and adopted following completion of review of chemical information. Such negotiations may take only 3 to 4 months.

The process chart for the process of approval can be found in Chart 27-1.

LIAISON RELATIONSHIP WITH THE US FOOD AND DRUG ADMINISTRATION

The FDA and the USAN Council conducted an unofficial liaison until early 1967 when it was determined that a formal cooperative effort in the development of nonproprietary names would be more beneficial to both. In June 1967, an official agreement was signed between the sponsors of the USAN Council and the FDA to appoint annually one voting member to the Council. This contract stipulated that the FDA would accept as the "official or established" name any drug name the USAN Council adopted. In this agreement, the Commissioner of the FDA reserved the right to select the official name in those instances in which the USAN Council could not reach consensus. It should be noted that the designation of a name as an "official or established" name by the FDA did not follow automatically but was accomplished by publication, subject to public comment, in the *Federal Register*. All parties upheld this agreement until it was modified 17 years later.

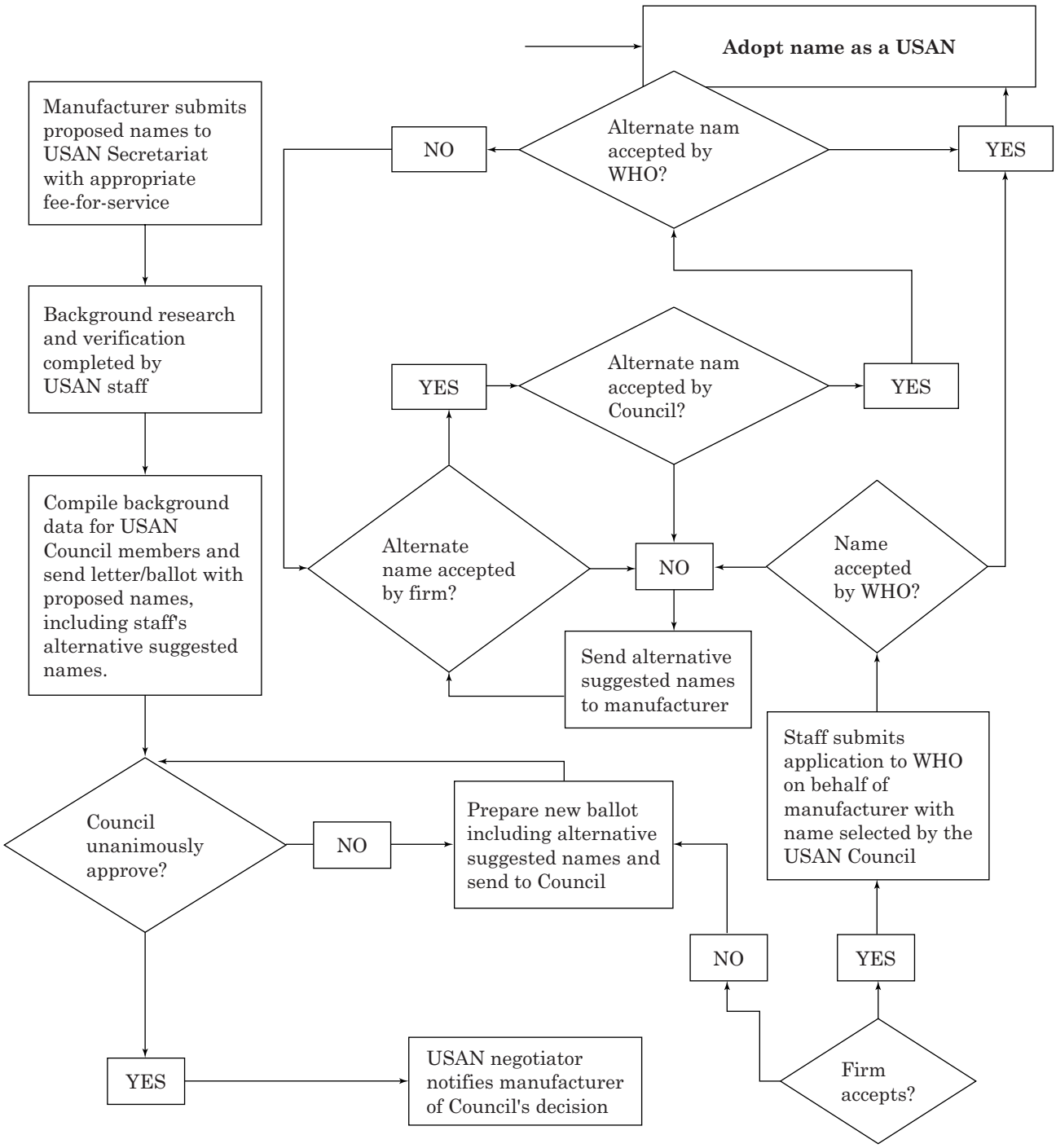

Chart 27-1. Process Chart for Approval Process.

On November 26, 1984, the Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* an amendment to the FD&C Act that stated in part that " . . . the Food and Drug Administration agrees with *"Guiding Principles for Coining US Adopted Names for Drugs,"* published in *USAN and the USP Dictionary of Drug Names* . . . "and that . . . the established name . . . will ordinarily be either the compendia name of the drug or, if there is no compendia name, the common or usual name of the drug. Interested persons, in the absence of the designation of an official name, may rely on the USAN listed in *USAN and the USP Dictionary of Drug Names* as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act."

The FDA also plays a role when a manufacturer seeks to register a trademark (proprietary name) for a drug entity that has been assigned a USAN. Within the Center for Drug Evaluation and Research (CDER) of the FDA, the Labeling and Nomenclature Committee (LNC) provides recommendations on the acceptability of proposed proprietary names. One of the criteria for rejection is use of USAN syllables or stems in the proposed trademark.

INTERNATIONAL NONPROPRIETARY NAMES

The USAN Council functions primarily to serve the health professions in the US. However, at a time when drug manufacturers market their products in many countries and medical and pharmaceutical literature is widely translated around the world, the need for cooperation in nomenclature activities among the major drug-producing countries clearly is evident.

In addition to the USAN Council, nomenclature agencies exist in Great Britain, France, Italy, Japan, Spain, the Nordic countries, and Switzerland. These agencies function at varying levels of authority and work with their pharmaceutical industries to select appropriate nonproprietary names for drugs marketed within their borders. These agencies maintain liaisons with each other and coordinate the approval of identical nomenclature rules and the selection of identical nonproprietary names.

To prevent the confusion that arises when several nonproprietary names used for a single drug, either in the same country or in different countries, the WHO has assumed the responsibility for coordinating drug nomenclature at the international level. Through its Committee on Nonproprietary Names, whose members are drawn from representatives of the national nomenclature agencies, WHO has developed procedures and formulated guiding principles for the selection of International Nonproprietary Names (INN). National nomenclature agencies usually act as agents for the drug manufacturers by referring mutually selected designations (usually *prior* to national adoption) to the WHO with a request that these names be selected as INN.

A drug manufacturer located in a country without a nomenclature agency is permitted to make a direct submission for a nonproprietary name to the INN Committee or, alternatively, to an established nomenclature agency in another country, preferably a country in which the pharmaceutical preparation is likely to be marketed.

INN are selected for substances that can be characterized unequivocally by a chemical name or formula, and exceptions to this rule are rare. The INN is designated for the active part of the molecule only. The INN program does not select names for mixtures or herbal substances.

THE WHO NOMENCLATURE PROGRAM

In 1915 the International Pharmaceutical Federation established a Committee on International Nomenclature and assigned it the responsibility for identifying each pharmaceutical substance by a globally available and unique nonproprietary name. The WHO Constitution in 1946 relegated the duty of drug nomenclature to the WHO. By 1953, the WHO initiated the selection and publication of International Nonproprietary Names (INN) for pharmaceutical substances. The present INN program is administered by the Secretariat (Dr. Raffaella Balocco-Matavelli) located in Geneva, Switzerland. Nonproprietary names are selected biannually by members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, Nomenclature Section. This advisory panel is comprised of representatives from national nomenclature groups (ie, the USAN Council Secretary, the British Approved Names (BAN) Committee Secretary, the French, Japanese, and Spanish nomenclature Secretariats, and representatives from Nigeria, Tunisia, and Poland. The process of INN selection is similar to that utilized to select a USAN. After the manufacturer submits an application, review and objections periods are followed by selection of the INN. Details of the process are explained below.

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Members States. The WHO INN Committee initially publishes in *WHO Drug Information* the selected names as "proposed International Nonproprietary Names (pINN)." From the date of publication, 4 months are allowed for member states or other interested parties to submit comments or objections to any proposal. An objection generally reflects a belief that the proposal is confusingly close to (ie, conflicts with) a name already in use. If no objection is received, the proposed INN will attain the status of recommended INN. Subsequently, WHO will publish the name as a "recommended International Nonproprietary Name (rINN)." The WHO publishes lists of rINN on a biannual basis. Many member states then recognize the rINN as the sole or preferred nonproprietary name for use in their respective countries.

A cumulative list of INN and the guidelines for coining an INN (*INN for Pharmaceutical Substances*) can be obtained from the World Health Organization in Geneva, Switzerland. The INN Cumulative List now contains more than 7000 names for drug entities. The INN Committee adds 120 to 150 new designations each year.

Guidelines on the Use of International Nonproprietary Names (INN) for Pharmaceutical Substances is available, on CD-ROM, for public distribution.

PHILOSOPHY OF THE USAN PROGRAM

A closer examination of nonproprietary names for drugs will likely result in an inaccurate understanding of present nomenclature practices. Many drug names for products on the market were coined prior to the creation of systematized nomenclature procedures, principles, and drug classifications. Indeed, many of the older names demonstrate the obvious need for selection of useful, simple, and appropriate nonproprietary names for drugs. Existing names, therefore, reflect a mixture of old and new nomenclature practices and philosophies. In many instances, poor naming of drugs was due to the now discarded practice of condensing the full chemical name into a chemically oriented nonproprietary name, eg, (1) amphetamine was assigned to the parent central stimulant, and methamphetamine to its methyl analog; and (2) the large perazine antipsychotic series—butaperazine, prochlorperazine [Compazine], trifluoperazine [Stelazine]—have very close names, represented by chlorpromazine [Thorazine] and triflupromazine [Vesprin]. Names for each new member in the perazine or promazine series were devised by adding a structure-based prefix, such as *but-* (butyl group), *prochlor-* (*propyl-* and *chloro-*), *trifluo-* (*trifluoro-*) to the base name *-perazine*. At the time this practice came into being, the chemistry of most drugs was not too complex, nor were there that many drugs on the market. The nomenclature confusion was lessened because each of these agents was marketed under a short, memorable trademark. With advancing chemical complexity of drug entities, however, nonproprietary names so derived became increasingly long and difficult to spell, pronounce, or remember. Using the above presented *perazine* series as an example, one can see that it becomes increasingly more difficult to distinguish one *perazine* from the others.

In addition to the problems caused by the complexity of the word itself, chemically derived names have been criticized because they fail to provide useful information to anyone but a scientist involved in drug development.

Nonproprietary nomenclature is intended primarily for physicians, pharmacists, and those in related health professions. A physician is not concerned with the sometimes subtle structural manipulation of molecules that produce a potential new drug. His or her primary concern is to understand the drug's pharmacological and therapeutic properties. Therefore, it must be emphasized again that nonproprietary names should be coined in such a way as to be most useful to the health professionals who are their primary users.

A well-coined nonproprietary name should be distinctive. How many hundreds of drug names begin with the familiar letters *di-*, *tri-*, *meth-*, *chlor-*, *oxy-*, or *phen-*? Repetitious use of chemical prefixes leads to similar, look-alike, and sound-alike

names, so this practice has now been discarded. By abandoning strict adherence to chemical antecedents, names can be made not only simpler but also unique.

To assign meaningful nonproprietary names to new drug compounds, it is necessary to indicate through the name any relationship that exists between the new entity and established drugs. Conversely, inappropriate names suggesting nonexistent relationships are misleading and must be avoided. The USAN Council has used standardized prefixes, infixes, or suffixes in nonproprietary names to classify and relate new chemical entities to existing drug families. These standardized syllables collectively are called *stems*, and they can emphasize a special chemical nucleus, a pharmacological property, or a combination of both these attributes.

Chemically derived stems
cef- (cephalosporins)
*cef*otetan, *cef*metazole, *cef*ixime
-nab- (can*nab*inols)
*dronab*inol, ti*nab*inol
-conazoles (antifungal imidazoles)
keto*conazole*, flu*conazole*, cis*conazole*
Pharmacologically derived stems
-stat- (enzyme inhibitors)
alres*stat*in, lova*stat*in
-vir- (antivirals)
acicl*ovir*, riba*vir*in, *vir*oxime
-astine (antihistaminics)
acriv*astine*, temel*astine*, zep*astine*
Combination Stems
-olol (propranolol-type beta-blockers)
tim*olol*, aten*olol*
-profen (ibuprofen-type anti-inflammatory/analgesic agents)
ibu*profen*, flurbi*profen*
-tecan (camptothecine antineoplastics)
topo*tecan*, irino*tecan*

The USAN recommended list of stems (see Appendix A) is revised and updated regularly to keep pace with the changing chemical and pharmacological nature of new drugs.

Again, a random survey of names for drugs currently in use will show a mixture of "old" and "new" nomenclature practices. In fact, such a survey, presented below, should illustrate effectively the principles behind the newer nomenclature approach.

Figure 27-1 presents a pair of compounds named many years ago, meprobamate and carisoprodol, that are related both chemically and pharmacologically; despite these similarities, the drugs have dissimilar names.

The opposite situation is illustrated in Figure 27-2; the relationship between fluorometholone and oxymetholone is limited to the classification of both agents as steroids: fluorometholone is an anti-inflammatory corticosteroid, and oxymetholone is an anabolic 17α-alkylated testosterone derivative used as an erythropoietic. This class of compounds, however, is so large and so diverse that the common ring nucleus alone is hardly sufficient to warrant the use of a common stem (*-metholone*).

The steroids are, in fact, typical of several large groups of compounds that (within each group) exhibit somewhat similar chemical and pharmacological properties. Because of diversity within the group, however, it is desirable to establish subseries of names based on the nature of the substituent groups and on the placement of such substituents. In recent years the USAN

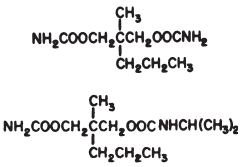

Figure 27-1. Meprobamate (*top*) and carisoprodol (*bottom*) are closely related chemically and pharmacologically; the assigned names, however, do not indicate this relationship.

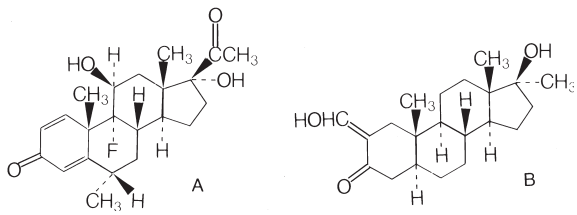

Figure 27-2. Illustrative of poor practice in nomenclature are the compounds fluorometholone (A) and oxymetholone (B). The compounds are not as closely related as the names suggest.

Council increasingly has developed this principle, which is typified by the examples in Figure 27-3.

Figure 27-3 depicts a basic glucocorticoid structure (glucocorticoids, in themselves, being a division of the broader category of steroids) in which the R groups indicate the positions at which the principal differences in the subseries occur. There is no common suffix for the entire glucocorticoid series, but the suffixes *-olone, -sone,* and *-onide* are indicative of this series and are used in the stems of the various subseries.

A more recent example of stem subdivision is represented by the various subgroups formed based on the stem *vir*: the *vir* stem represents drugs exhibiting antiviral properties, which was further subdivided to form the subclassification *-amivir* for antivirals capable of inhibiting the enzyme neuraminidase, *-ciclovir* for acyclovir-type antivirals, *-virsen* for antisense antivirals, *-navir* for antiviral HIV protease inhibitors, plus other lesser known subclasses of antivirals.

The use of common stems to indicate particular classes of drugs is reexamined constantly by the USAN Council. The development of nomenclature for the tetracycline series of drugs (Fig 27-4) demonstrates the review and revision processes by which the Council's principles are assessed to ensure their validity in the light of current nomenclature requirements. The first drugs in this series were chlortetracycline and oxytetracycline, both of which can be converted chemically to the parent compound, tetracycline. Further research led to still another variant, demethylchlortetracycline, which, in keeping with the standard practice of the time, was named in strict accordance

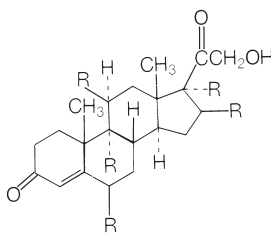

Figure 27-3. The R groups indicate the position on the glucocorticoid nucleus where the principal modifications occur. Such changes give rise to various structurally defined subseries differentiated by means of the following stems:

-olone		
	-cinolone	triamcinolone fluocinolone
	-cortolone	fluocortolone clocortolone
-sone		
	-sone	cloticasone ticabesone
	-met(h)asone	dexamethasone mometasone
-onide (16,17-acetal)		
	-cinonide	amcinonide fluocinonide

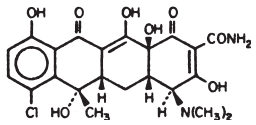

Figure 27-4. Chlortetracycline. Other names in this series include rolitetracycline, meclocycline, and amicycline.

with its chemical derivation to represent the desmethyl variant of chlortetracycline. The next member of this series to require a nonproprietary name was characterized by a distinctive pyrrolidine group and, following traditional patterns, the name might have become pyrrolidinotetracycline. Instead, the first step was taken toward simplifying names in this series by shortening the prefix, and the resulting name became rolitetracycline. The logical next step taken by the USAN Council members was to drop the syllables *tetra* from the suffixes of newer nonproprietary names for drugs in this group, thus yielding simpler and more useful designations. Examples of such designations are amicycline, sancycline, and doxycycline; the series stem became *-cycline*.

Although it is a very difficult thing to do for several valid reasons, occasionally the need and the opportunity arise to go back and change the poorly coined name of a well-established drug. Such was the case with demethylchlortetracycline. The name of this compound, which is commercially available as the hydrochloride salt, was changed to demeclocycline hydrochloride.

Captopril and the subsequently named angiotensin-converting enzyme inhibitors (enalapril, spirapril, quinapril, etc) were assigned names using the *pril* stem derived from *proline,* a common structural feature present in members of this series (Fig 27-5). The second member, enalapril, a tripeptide derivative, is a substituted alanylethyl ester. Later, when the di-acid form of enalapril was made available, the *pril* stem was modified to *prilat* (eg, enalaprilat) to accommodate this structural change from the ethyl ester to the acid.

The *stat* stem has been used to identify various enzyme inhibitors. As the series developed, it became apparent that subdivision was needed to group chemically related agents inhibiting a specific enzyme. Two very prominent subgroups in this series are (1) *-vastatin* HMG-CoA reductase inhibitors (mevastatin, lovastatin, simvastatin, pravastatin), and (2) *-restat-* for the aldose-reductase inhibitors (alrestatin, tolrestat) as seen in Figure 27-6.

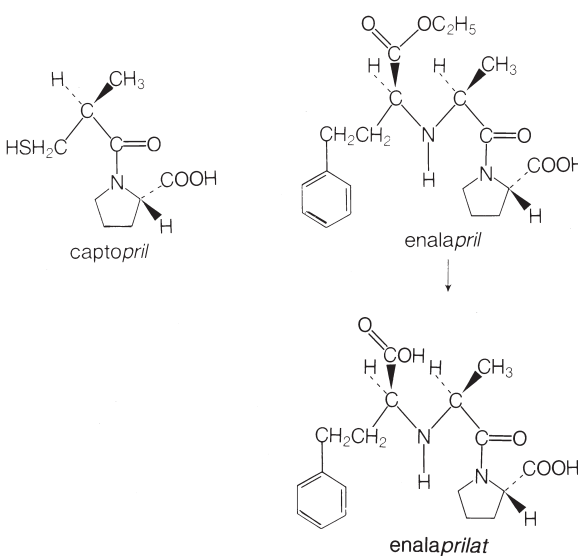

Figure 27-5. The *pril* series of related angiotensin-converting enzyme inhibitors. Hydrolysis of the ethyl ester of enalapril produced the modification from *pril* to *prilat*.

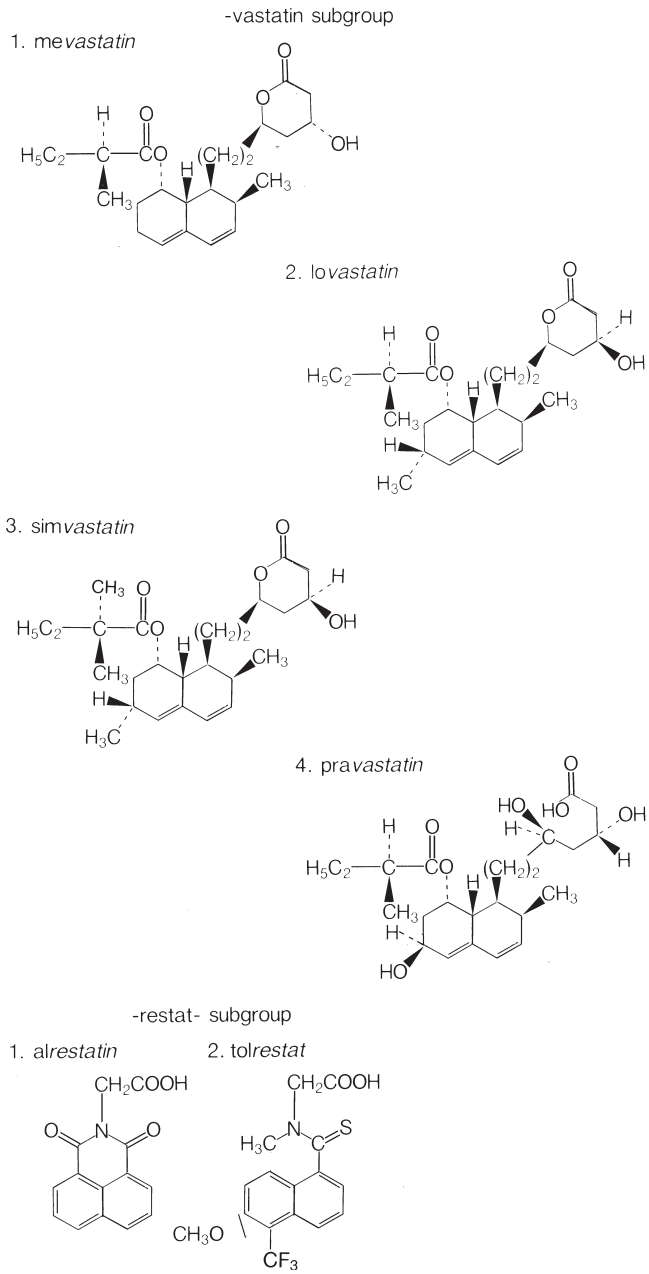

Figure 27-6. The *-vastatin* and *-restat* subgroups within the large stat (enzyme inhibitors) series.

These examples illustrate the USAN Council's developed policy of coining meaningful nonproprietary names. Its aim is to select short, unique names that are informative and useful to the primary health providers, the medical and related health professionals. These examples also illustrate the Council's policy of establishing classifications of stems based on chemical and/or pharmacological similarities and of subdividing stem classifications by the addition of, usually, structurally based infixes to create a taxonomy of drug nomenclature useful to the intended primary target of this nomenclature system, the various health practitioners.

PROTECTION OF USAN AND INN

After adoption of a USAN, the entry is submitted for publication in the "New Names" column in the journal of *Clinical Pharmacology and Therapeutics* and is transmitted to the USP for

publication in the annually released *USP Dictionary of USAN and International Drug Names*. The 35th edition of the USP dictionary contained 8713 nonproprietary drug name entries, with more than 4115 trademarks.

With the growing number of USAN/INN and brand names, the possibility of conflicts between nonproprietary names, between trademarks, and between trademarks and nonproprietary names has increased significantly. A frequent source of conflict in the latter category is the practice of *piggybacking* on the USAN/INN or the incorporation of a nomenclature stem in the trademark. If trademark registration is obtained for names containing an officially reserved stem, this may diminish the freedom of the USAN and the INN programs in the selection of further nonproprietary names in the same series of substances.

To inhibit this practice at the WHO INN level, the issue of piggybacking and incorporation of the official stems into trademarks was taken up in a resolution of the World Health Assembly WHA46.19. Based on recommendations made by the WHO Expert Committee on the use of Essential Drugs, resolution WHA46.19 on Nonproprietary Names for pharmaceutical substances was adopted in May 1993, during the 46th World Health Assembly.

WHA resolution WAH46.19 was discussed by the USAN Council, and on January 22, 1996, the USAN Council approved the following statement as part of its nomenclature policy.

Co-Existence of Nonproprietary Names and Trademarks

In devising the Guiding Principles for coining USAN for drugs, the program originators included a rule stating that a USAN "should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor misleading." Through its various name-screening procedures, the Council Staff attempts to comply with this requirement. Unfortunately, the same kind of protection is not afforded to nonproprietary names by many drug manufacturers. The USAN Council, WHO INN Committee, and other nomenclature committees have actively discouraged the undesirable practices of devising trademarks from the nonproprietary names or incorporating into trademarks the *stems* used by the nomenclature committees to create new nonproprietary names.

USAN Statement on WHA Resolution 46.19

As the designated drug nomenclature agency of the US, the USAN Council is responsible for the selection of simple and useful nonproprietary names for drugs and such related substances as pharmaceutic aids, contact lens plastics, surgical materials, diagnostic agents, carriers, and excipients. The USAN Council cooperates and works with the WHO in devising nonproprietary names for drugs, in standardizing drug nomenclature, and in establishing rules governing the classification of new substances.

In 1993, the WHO Executive Board placed Resolution WHA46.19 before the World Health Assembly (WHA) seeking to encourage the WHO member states to intensify their efforts to discourage manufacturers from devising trademarks derived from recommended International Nonproprietary Names (rINN) and from including INN stems in trademarks. Resolution WHA46.19 was adopted by the 46th WHA on May 12, 1993. Resolution WHA46.19 was discussed by the USAN Council on January 28, 1994. The USAN Council agreed in principle with the resolution statements and supported the premises stated in the resolution.

The expression of general support for WHA Resolution 46.19, although in keeping with the historical support by the USAN Council for harmonization of global drug nomenclature policies, has led to a misapprehension of USAN Council views in some US-based and multinational pharmaceutical corporations and associations. A statement of the USAN Council's views is provided below.

WHO Resolution WHA46.19: Nonproprietary Names for Pharmaceutical Substances

The Forty-sixth World Health Assembly Requests Member States:

> ". . . to enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic names) used in labeling and advertising of pharmaceutical products are always displayed prominently."

The principle that the USAN should be prominently displayed is not an issue in the US, as this has been required by the FD&C Act for more than three decades. Section 502(E) requires, for labeling, that

> "[t]he established name . . . is printed prominently and in type at least half as large as that used thereon for any proprietary name or designation for such drug . . . to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on trademarks, to promote and market multisource products introduced after patent expiration."

The USAN Council also recognizes that trademarks constitute intellectual property for their holders. USAN Council encourages manufacturers of multisource prescription drug products, other than those who obtained the original NDA approvals, to rely on the USAN and their corporate names in marketing such products instead of creating additional trademarks. Nevertheless, USAN Council recognizes that the use of trademarks is common and valuable in marketing over-the-counter drug products and is often useful in special cases with prescription drug products. Such special cases may arise when, for example, (1) there are differences in bioavailability between a drug product marketed by an innovator firm and a later version introduced by the same or another firm, and (2) drug products, containing the same drug substance but with different uses, are introduced "to develop policy guidelines on the use and protection of international nonproprietary names, and to discourage the use of names derived from INNs, and particularly names including established INN stems as trade-marks." The USAN Council discourages the use in trademarks of substantial portions of USAN and established USAN stems. This practice is an infringement on USAN and an impediment to the work of USAN Council in establishing new USAN in a class of drugs. It should be noted that USAN Council attempts to avoid establishing USAN that are in conflict with US and foreign trademarks as well as other nonproprietary names of drugs. Furthermore, the USAN Council is cognizant of the US FD&C Act, Section 508(A), which states, in part, "[I]n no event . . . shall the secretary establish an official name so as to infringe a valid trademark."

Conclusion

The USAN Council was established to serve the health professions in the US by

1. Selecting simple, informative, and unique nonproprietary names for drugs.
2. Establishing a logical nomenclature classification based on pharmacological and/or chemical relationships.
3. Formulating nomenclature rules for selecting appropriate nonproprietary names for drugs.

The USAN Council, other national nomenclature groups, and the WHO Nomenclature Committee aim for global standardization and unification of drug nomenclature and related rules to ensure that drug information is communicated accurately and unambiguously.

GUIDING PRINCIPLES FOR COINING UNITED STATES ADOPTED NAMES FOR DRUGS

By definition, nonproprietary names are not subject to proprietary trademark rights, but exist entirely in the public domain. This feature distinguishes them from the trademarked names that have been registered for private use. A USAN is a nonproprietary name selected by the USAN Council according to principles developed to ensure safety, consistency, and logic in the choice of names. These principles take into account practical considerations, such as the existence of trademarks and the fact that the intended uses of substances for which names are being selected may change. These guidelines are and must be sufficiently flexible to be revised if this is considered to be desirable and/or necessary.

General Rules

1. A nonproprietary name should be useful primarily to health practitioners, especially physicians, dentists, pharmacists, nurses, educators, and veterinarians.
   a. The primary criterion for judging usefulness is suitability, including safety for use in the routine processes of prescribing, ordering, dispensing, and administering drugs throughout the United States.
   b. The second criterion is suitability for use in educational programs for students in medically oriented professions and for use in scientific and lay publications.
   c. The third criterion is suitability for use internationally for drug identification, for the exchange of information and translation into different languages.

2. Attributes that contribute to usefulness are simplicity (brevity and ease of pronunciation), euphony, and ready recognition and recall.
   a. The name for the active moiety of a drug should be a single word, preferably with no more than four syllables.
   b. The name for the active moiety may be modified by a single term, preferably with no more than four syllables, to show a chemical modification, such as salt or ester formation (eg, cortisone acetate from cortisone, cefamandole sodium from cefamandole, erythromycin acistrate from erythromycin).
   c. Only under compelling circumstances is a name with more than one modifying term acceptable (eg, pharmaceuticals containing radioactive isotopes, the different classes of interferons).
   d. Acronyms, initials, and condensed words may be acceptable in otherwise appropriate terminology.
3. A name should reflect characteristics and relationships that will be of practical value to the users.
   a. A common, simple word element (a "stem") should be incorporated in the names of all members of a group of related drugs when pertinent, common characteristics can be identified (eg, similarity of pharmacological action). When pharmacological similarity is found in drugs of distinctly different chemical nature, stems should differ (eg, the antipsychotics, promazine and haloperidol; the nonsteroidal anti-inflammatory agents [NSAID], ibuprofen, etodolac, and isoxicam).
   b. Distinctive terminology should be used for specific drugs or groups (eg, insulin I 131, dextran 40, interferon alfa-2a and interferon alfa-n1; licryfilcon A and licryfilcon B; epoetin alfa and epoetin beta).
4. A name should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor misleading.
   a. Prefixes that imply "better," "newer," or "more effective," or evoke the name of the manufacturer, dosage form, duration of action or rate of drug release should not be used.
   b. Prefixes that refer to an anatomical connotation or medical condition are not acceptable.
   c. Prefixes that indicate a chemical element or compound (Ca, Ni, and Stannous) are not acceptable.
5. Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks.
6. Identical negotiations submitted by two or more manufacturers will be conducted in accordance with the Council's practice of maintaining confidentiality. The applicants involved will not be notified of the multiple sources of the submission. However, the name selected by the USAN Council will need to be accepted by each manufacturer involved in the negotiation process.
7. A request for a USAN should be made after the drug manufacturer or sponsor has submitted an Investigational New Drug (IND) application to the Food and Drug Administration (FDA) to obtain permission to initiate studies on humans.
8. Deferred Negotiations:
   a. The USAN Council Secretariat will defer an ongoing negotiation for 6 months plus one additional 3-month extension upon receipt of a written request from the manufacturer. If the USAN Council has selected a name candidate and recommended this name to the manufacturer, the maximum deferral is one 6-month period.
   b. The negotiation will be canceled after the maximum 9-month deferral has lapsed.
   c. If the negotiation is to be reopened at a later time, it will receive a new USAN file number and will be treated as a new application. The manufacturer will be expected to submit a new USAN negotiation form, update the background information, and submit the appropriate user's fee.

Specific Rules

1. Because of the international exchange of drug information, specific guidelines have been formulated to ensure appropriate translation of nonproprietary names into other languages. The following rules of preferred spelling should be used when coining USAN designations:
   a. the letter "f" should be used instead of "ph"
   b. the letter "t" should be used instead of "th"
   c. the letter "e" should be used instead of "ae" or "oe"
   d. the letter "i" should be used instead of "y"
   e. the letter "h" should be avoided
   f. the letter "k" should be avoided.
   g. the letter "j" should be avoided.
   h. the letter "w" should be avoided.
   i. "ar", "rac", "lev", "dex", or "es" are reserved for stereochemical configurations
2. Additionally, these letter combinations are restricted until further notice. Please avoid the following prefixes:
   a. the beginning letter "z"
   b. the beginning letter combination of "me"
   c. the beginning letter combination of "str"
   d. chemical connotations such as, "ben", "bu", "cat", "cel", "fen", "flu", "piro"
   e. Chemical symbols unless present in the compound, "al", "ba", "ca", "li", "ni"

In order to facilitate the development of names that will be accepted on an international level please note:

A. The following letter combinations pose pronunciation problems in several languages:

   -ch-
   -rs-
   -xn-

B. The letter sequence "-m" and "-n" followed by consonants may be regarded as difficult.
   1) "m" before a consonant other than "p", "n", or "b"
   2) -nb-, and -np- should be avoided
C. The letter sequence "-vr" should be avoided.
D. In addition, it should be kept in mind that there is, in some languages, no distinction between:

   "b" and "v" or "p"
   "l" and "r"
   before "e" and "i": "z" and "g"

3. Isolated letters, numbers, or hyphenations are restricted to those groups of substances for which such usage fulfills a clearly demonstrable purpose (eg, interferon alfa-2b, paflufocon A, technetium Tc 99m siboroxime).
4. Group relationships in a name preferably should be indicated by use of syllables or stems; conversely, use of the stem for other than the appropriate group should be avoided. When multiple stems are available, the stem conveying the most information should be used.
5. Esters, salts, chelates, and complexes ordinarily require a two-word name to indicate the inactive as well as the active portion.
6. The preferred order for the name of an inorganic salt is cation-anion (eg, sodium bromide). The same order is preferred for well-known salts of simple organic acids (eg, sodium lactate, magnesium citrate, potassium acetate). However, for more complex organic compounds, the pharmacologically active portion should be identified first (eg, oxacillin sodium, ibuprofen piconol, dexibuprofen lysine).
7. A name for a salt or ester generally should be derived from the name of the pharmacologically active moiety or corresponding acid (eg, sodium acetate or ethyl acetate, derived from acetic acid). When a nonacid suffix is used, as in the penicillin series, a salt should be named without modification of the parent acid name (eg, oxacillin sodium, derived from oxacillin). Names for different salts or esters of the same active moiety should differ only in the name of the inactive portion; exceptions are permissible when the salt and ester forms possess pharmacologic activity.
8. A name for the salt form of the pharmacologically active moiety is specific to the number of molecules used to react with the active moiety (eg, balsalazide *di*sodium, gusperimus *tri*hydrochloride). If only one molecule is used to react with the active moiety, the designation for the salt name is used without reference to the mono- prefix (eg, besipirdine hydrochloride, afovirsen hydrochloride). [This rule was formulated and approved in January 1993; different requirements were applied prior to this date.]
9. A name for a quaternary ammonium substance should designate the cation and anion separately (eg, octonium bromide, not octonine methylbromide). The name assigned to the cation must contain the *-ium* suffix stem.
10. A name for a complex of two or more components should list the name of the principal active ingredient followed by a coined designation for the second component ending with an "-ex\'\' " suffix to indicate "complex\'\' " (eg, bisacodyl tann*ex*, doxycycline fosfat*ex*). Complexes formed from sulfonated diethenylbenzene-ethenylbenzene copolymers and an active ingredient should list the name of the principal active ingredient followed by "polistirex\'\' " (eg, chlorpheniramine *polistirex*, codeine *polistirex*).
11. A name for a drug containing a radioactive atom should list, in the order given: (1) the name of the drug containing the radioactive atom, (2) the element symbol, (3) the isotope number, and (4) the name of the carrier agent, if any (eg, rose bengal sodium I 131, cyanocobalamin Co 60, potassium bromide Br 82, technetium Tc

99m butilfenin, technetium Tc 99m medronate, indium In 111 oxyquinoline, indium In 111 satumomab pendetide).

12. A name for a substance generally should not indicate the state of hydration, the morphology, or the mode of preparation. Reference to the water of hydration is retained in the chemical information (chemical names, formulas, weight) but is excluded from the nonproprietary name. The degree of hydration becomes a part of the chemical entity identified by the USAN.
13. Under the terms of the Orphan Drug Act of 1983, the development and marketing of drug products that are of limited commercial application but that are potentially useful in relatively rare disease conditions are encouraged. The selection of a name for an orphan drug may be based on special considerations. Therefore, when the name for an orphan drug appears to follow a more chemically oriented terminology style than is customary for drug nomenclature generally, this is not to be regarded as a basis or a precedent for a future selection of a USAN.
14. A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula. A USAN can, therefore, identify the racemic mixture (eg, carnitine, ibuprofen, tetramisole), the levo isomer (eg, remoxipride, quadazocine), or the dextro form (eg, butopamine). Subsequently, if a name is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing name:
    a. For the racemate, the rac-/race- prefix is used (eg, racemethionine, racepinephrine, ractopamine).
    b. For the levorotatory form, the "(S)" isomer, the lev-/levo- prefix is used (eg, levocarnitine, levamisole, levcromakalim, levdobutamine).
    c. For the levo rotatory form but for the "(R)" isomer, ["R(-)"-isomer], the "ar-" prefix is added to the base name.
    d. For the dextrorotatory form, the "(R)" isomer, the dex-/dextro- prefix is used (eg, dexamisole, dexibuprofen, dextroamphetamine, dexverapamil, dexrazoxane, dexfosfoserine, dexniguldipine).
    e. For the dextro rotatory form but for the "(S)" isomer ["S(+)"- isomer], the "es-" prefix is added to the base name.
15. Official names have been selected for a number of radicals and adducts used to form salts or esters of the pharmacologically active moiety. In a majority of cases, these names represent contractions of the chemical name assigned to the radical or adduct. In four specific cases, the official name identifies a multicomponent adduct:
    - *acistrate* identifies the 2′-acetate (ester) and octadecanoate (salt) (eg, erythromycin acistrate).
    - *probutate* identifies the double ester 1-oxobutoxy and 1-oxopropoxy (eg, hydrocortisone probutate).
    - *estolate* identifies the double salt propanoate and dodecyl sulfate (eg, erythromycin estolate).
    - *hyclate* identifies the monohydrochloride salt, hemiethanolate, hemihydrate combination (eg, doxyclin hyclate).

The complete list of official names for radicals is presented under Appendix B.

Specific Nomenclature Rules for Contact-Lens Materials

The USAN Council began its involvement in the area of polymer nomenclature in 1971 and formulated the first nomenclature rules for assigning nonproprietary names to contact lens materials in 1972. Based on then-available polymer technology and input from the Food and Drug Administration, lens polymers were divided into the *filcon* (hydrophilic) and the *focon* (hydrophobic) series.

The following nomenclature rules, approved by the USAN Council in 1994, represent several expansions and revisions of the initial guidelines:

General Rules

For nomenclature purposes, contact lens materials are divided into hydrophilic and hydrophobic groups, depending on their water content. The hydrophilic lens materials with water content equal to or more than 10% by weight at ambient temperature are assigned "filcon" names. "Focon" names are assigned to hydrophobic lens materials with water content less than 10%.

In addition to water content, nomenclature for contact lens materials depends primarily on the polymeric composition, ie, the repeating monomer units comprising the lens material. These repeating units include linear monomers, and crosslinking entrapped color additives or ultraviolet absorbers are excluded in establishing the polymeric composition of the contact lens material for nomenclature purposes.

The first member of a series is assigned a unique nonproprietary name containing the proper *-filcon* or *-focon* suffix stem. A separate capital letter "A" is added after each parent designation. Subsequent designations for polymers consisting of identical monomers receive the same parent name but a different appended letter (B, C, D, etc). These letters are needed to differentiate between polymers of identical monomeric units but with different ratios of units that have different physiochemical properties, as determined by water content, oxygen permeability [Dk] value, specific gravity, refractive index, surface charge, wetting angle, elasticity, and toughness of the lens.

A contact lens material having the same repeating monomeric units as a named substance but made by a different manufacturing process (eg, lathe-cut versus cast-molded) is not required to obtain a new USAN if the lens material has the same water content and oxygen permeability as the initially named polymer.

The addition of a surface treatment to an existing lens material that has been assigned a USAN does not require a new USAN.

a. A new USAN will not be assigned to contact lens materials containing chemically bound or physically entrapped color additives. The USAN Council defers to FDA labeling rules to identify color additives used to make tinted lenses.
b. A new USAN will not be assigned to contact lens materials containing either chemically bound or physically entrapped ultraviolet absorbers. The USAN Council defers to the Food and Drug Administration labeling rules to identify UV absorber used to make these lenses.

A revision of the guiding principles regarding the publication timeframe of USAN for contact lens materials, was approved by the USAN Council at their February, 10, 2003, meeting. Therefore, information on USAN for contact lens materials, will not be published until the manufacturer files a Premarket Approval Application (PMA) with the FDA's Center for Devices.

Contact lens materials are not assigned nonproprietary names by the World Health Organization International Nonproprietary Names Committee. Names for contact lens polymers have USAN status only.

Specific Nomenclature Rules for Biological Products

The USAN Council has been involved in coining names for various biological products: the insulins, interferons, interleukins, growth hormones, colony-stimulating factors, cytokines, and monoclonal antibodies. With increasing development of highly purified biological extracts and recombinant materials, the Council expects to have an increasingly greater role in developing nomenclature rules for these agents.

Listed below are specific guidelines created by the USAN Council, in conjunction with the FDA, the US FDA Center for Biologics Evaluation and Research (CBER), and the WHO INN Committee.

Interferons—The following multi-tiered style for creating nonproprietary names for new interferons was adopted by the USAN Council:

1. The word *interferon* is the first element in the name. Interferon is defined as the class name for a family of species-specific proteins (or glycoproteins) that are produced according to information encoded by species of interferon genes, and exert complex antineoplastic, antiviral, and immunomodulating effects. The three main forms of interferon used in therapy are interferon alfa (formerly leukocyte or lymphoblastoid interferon), interferon beta (formerly fibroblast interferon), and interferon gamma (formerly immune interferon).
2. The appropriate Greek letter (spelled out) is the second word of the name: alfa, beta, gamma.
3. An appropriate Arabic numeral and letter are appended to the Greek letter by a hyphen (no space) to delineate subcategories. The numbers conform to the recommendation of the Interferon Nomenclature Committee. The lowercase letter is assigned by the drug nomenclature agencies to differentiate one manufacturer's interferon from another's. Examples of pure interferon substances are

    interferon alfa-2a
    interferon alfa-2b
    interferon beta-1a
    interferon beta-1b
    interferon gamma-1a

4. For mixtures of naturally occurring interferons, the lowercase letter *n* precedes the number. Examples of names of mixtures of interferons obtained from a natural source, whether the exact percentage of a mixture is known or not, are

    interferon alfa-n1
    interferon alfa-n2

Interleukins—The suffix *-leukin* is used in naming interleukin 2 (IL-2) type substances, eg,

aldesleukin
celmoleukin
teceleukin

Somatotropins—The following guidelines have been developed for somatotropin analogs:

1. The *som-* prefix is used for growth hormone derivative, eg,

   somatropin for human growth hormone
   somatrem for methionyl human growth hormone

2. The *som-* prefix and the *-bove* suffix are required for bovine somatotropin derivatives, eg,

   somidobove
   sometribove
   somagrebove

3. The *som-* prefix and the *-por* suffix are required for porcine somatotropin derivatives, eg,

   somalapor
   somenopor
   sometripor
   somfasepor

Colony-Stimulating Factors—The following guidelines have been selected for recombinant colony-stimulating factors:

1. The suffix *-grastim* is used for granulocyte colony-stimulating factors (G-CSF), eg,

   lenograstim
   filgrastim

2. The suffix *-gramostim* is used for granulocyte macrophage colony-stimulating factors (GM-CSF), eg,

   molgramostim
   regramostim
   sargramostim

3. The suffix *-mostim* is used for macrophage colony-stimulating factors (M-CSF), eg,

   mirimostim

4. The suffix *-plestim* is used for interleukin 3 (IL-3) factors classified as pleiotropic colony-stimulating factors, eg,

   muplestim
   daniplestim

Erythropoietins—The word *epoetin* is used for recombinant human erythropoietin, followed by the appropriate Greek letter (spelled out). The word *epoetin* describes erythropoietin preparations that have an amino acid sequence identical to the endogenous cytokine; the words *alfa, beta, gamma* are added to designate the preparations that differ in the composition and the nature of the carbohydrate moieties. Erythropoietins assigned USAN are

epoetin alfa
epoetin beta
epoetin gamma

Monoclonal Antibodies—The following guidelines have been devised for monoclonal antibodies:

1. The suffix *-mab* is used for monoclonal antibodies and fragments.
2. Identification of the animal source of the product is an important safety factor based on the number of products that may cause source-specific antibodies to develop in patients. The following letters were approved as product source identifiers: *u* = human, *e* = hamster, *o* = mouse, *i* = primate, *a* = rat, *xi* = chimera, and *zu* = humanized. These identifiers are used as infixes preceding the *-mab* suffix stem, eg,

   -umab (human)
   -omab (mouse)
   -ximab (chimera)
   -zumab (humanized)

3. The general disease state subclass must be incorporated into the name by use of a code syllable. The following disease state subclasses were approved based on products currently before the Council. Additional subclasses will be added as necessary.

Disease or Target Class	
Viral	*-vir-*
Bacterial	*-bac-*
Immune (immunomodulator)	*-lim-*
Tumors	
colon	*-col-*
melanoma	*-mel-*
mammary	*-mar-*
gonad	
testis	*-got-*
ovary	*-gov-*
prostate	*-pr(o)-*
miscellaneous	*-tum-*
Cardiovascular	*-cir-*

4. In order to create a unique name, a distinct, compatible syllable should be selected as the starting prefix.
5. Sequence of stems—the order for the key elements is as follows:
   a. Infix representing the target disease state, the source of the product.
   b. The monoclonal root *-mab* used as a suffix (eg, bi*ciromab*, sa*tumomab*, ne*bacumab*, se*virumab*, and tu*virumab*).
   c. When combining a target or disease infix stem with the source stem for chimeric (*xi*) or humanized (*zu*) monoclonal antibody, the last consonant of the target/disease specific syllable is dropped, eg,

targe	source	*-mab* stem	USAN
-cir-	*-xi-*	*-mab*	abcixi*mab*
-lim-	*-zu-*	*-mab*	daclizu*mab*

   These modifications were deemed necessary to facilitate pronunciation of the resultant designation.

6. If the product is radiolabeled or conjugated to another chemical such as a toxin, identification of this conjugate is accomplished by use of a separate, second word or other acceptable chemical designation. For monoclonals conjugated to a toxin, the *-tox* stem must be included as part of the name selected for the toxin (eg, in zolimomab aritox, the designation aritox was selected for ricin A-chain). For radiolabeled products, the word order is: name of the isotope, element symbol, isotope number, and name of the monoclonal antibody, eg, technetium Tc 99m biciromab, indium In 111 altumomab pentetate.
7. A separate, distinct name must be assigned to any linker/chelator used to conjugate the monoclonal antibody to a toxin, isotope, or for pegylated monoclonal antibodies, eg, telimomab aritox, indium In 111 satumomab, pendetide, and enlimomab pegol. For the USAN Council to initiate the selection of a name for a monoclonal antibody or fragment, the nomenclature application must provide the following relevant information:
   1. The immunoglobulin class and subclass and the type of associated light chain. Identity of the fragment of the immunoglobulin used (if applicable).
   2. Identity of the fragment of the immunoglobulin used (if applicable).
   3. Species source from which the coding region for the immunoglobulin originated and specific, complete origin of all parts of chimeric, humanized, or semi-synthetic immunoglobulins.
   4. The antigen specificity of the immunoglobulin, including its source.
   5. The clone designation (specify if vector or vector-cell combination).
   6. For conjugated monoclonal antibodies, the identity of any linkers, chelators, toxins, and/or isotopes present in the product.
   7. Identity of other modifications to the antibody, eg, reduction of disulfide bonds, glycosylation or deglycosylation, amino acid modification, or substitution.

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Appendix A Stems Used by the USAN Council

STEM	DEFINITION	EXAMPLES
-abine	(see -arabine, -citabine)	
-ac	anti-inflammatory agents (acetic acid derivatives)	bromfen***ac*** dexpemedol***ac***
-acetam	(see -racetam)	
-actide	synthetic corticotropins	ser***actide***
-adol or -adol-	analgesics (mixed opiate receptor agonists/antagonists)	taz***adol***ene spir***adol***ene levonantr***adol***
-adox	antibacterials (quinoline dioxide derivatives)	carb***adox***
-afenone	antiarrhythmics (propafenone derivatives)	alpra***fenone*** *dipra****fenonex***
-afil	PDE5 inhibitors	tadal***afil***
-aj-	antiarrhythmics (ajmaline derivatives)	lor***aj***mine
-aldrate	antacid aluminum salts	mag***aldrate***
-algron	alpha$_1$-adrenoreceptor agonists	dabuz***algron***
-alol	combined alpha and beta blockers	labet***alol*** medrox***alol***
-amivir	(see -vir)	
-andr-	androgens	n***andr***olone
-anib	angiogenesis inhibitors	semax***anib***
-anserin	serotonin 5-HT$_2$ receptor antagonists	alt***anserin*** trop***anserin*** adat***anserin***
-antel	anthelmintics (undefined group)	carb***antel***
-arabine	antineoplastics (arabinofuranosyl derivatives)	faz***arabine*** flud***arabine***
aril-, -aril, -aril-	antiviral (arildone derivatives)	plecon***aril*** ***aril***done fos***aril***ate
-arit	antirheumatics (lobenzarit type)	lobenz***arit*** clobuz***arit***
-arol	anticoagulants (dicumarol type)	dicum***arol***
-arot-	arotinoids	et***arot***ene sum***arot***ene taz***arot***ene
-arotene	arotinoid derivatives	bex***arotene*** lin***arotene*** taz***arotene***
arte- -ase	antimalarials (artemisin derivatives) enzymes	***arte***flene algluc***erase*** dorn***ase*** alfa
	subgroups:	
-dismase	superoxide dismutase activity (exception: orgotein)	su***dismase***
-teplase	tissue-type plasminogen activators	al***teplase*** du***teplase*** sil***teplase***
-uplase	urokinase-type plasminogen activators	sar***uplase*** nasar***uplase***
-ast	antiasthmatics/antiallergics (not acting primarily as antihistamines; leukotriene biosynthesis inhibitors)	
subgroups:		
-lukast	leukotriene receptor antagonists	cina***lukast*** pobi***lukast***
-milast	type IV phosphodiesterase inhibitors	picla***milast***
-trodast	thromboxane A$_2$ receptor antagonists	sera***trodast***
-zolast	benzoxazole derivatives	ecla***zolast*** onta***zolast***
-(a)tadine	tircyclic histaminic-H1 receptor antagonists, loratadine derivatives	deslor***atadine*** rup***atadine*** soman***tadine***
-astine	antihistaminics (histamine-H$_1$ receptor antagonists)	eb***astine***
-atadine	tricyclic antiasthmatics	olop***atadine*** lor***atadine***
-azenil	benzodiazepine receptor agonists/antagonists	bret***azenil*** flum***azenil***
-azepam	antianxiety agents (diazepam type)	lor***azepam***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-azepide	cholecystokinin receptor antagonists	dev***azepide***
-azocine	narcotic antagonists/agonists (6,7-benzomorphan derivatives)	quad***azocine***
		ket***azocine***
-azoline	antihistamines/local vasoconstrictors (antazoline type)	ant***azoline***
-azosin	antihypertensives (prazosin type)	dox***azosin***
-bactam	beta-lactamase inhibitors	sul***bactam***
-bamate	tranquilizers/antiepileptics (propanediol and pentanediol groups)	mepro***bamate***
		fel***bamate***
-barb or	barbituric acid derivatives	pheno***barb***ital
-barb-		seco***barb***ital
		etero***barb***
-begron	beta 3 adrenoreceptor agonist	tali***begron***
-bendazole	anthelmintics (tibendazole type)	cam***bendazole***
-bersat	anticonvulsants; antimigraine (benzoylamino-benzpyran derivatives)	cara***bersat***
		tidem***bersat***
bol- or	anabolic steroids	***bol***andiol
-bol-		mi***bol***erone
-bufen	non-steroidal anti-inflammatory agents, fenbufen derivatives	indo***bufen***
-bulin	antineoplastics (mitotic inhibitors; tubulin binders)	mivo***bulin***
-butan	antiseptics (dapabutan type)	dapa***butan***
		lopo***butan***
-butazone	anti-inflammatory analgesics (phenylbutazone type)	mofe***butazone***
-caine	local anesthetics	dibu***caine***
calci- or	vitamin D analogues	***calci***potriene
-calci-		ta***calci***tol
-camra	antivirals (intracellular adhesion molecules, icam-1 derivatives***)***	trema***camra***
-camsule	camphorsulfonic acid derivatives used as UVA sunscreens	e***camsule***
-casan	caspase (interleukin–1b) converting enzyme inhibitors	pralna***casan***
-castat	(see -***stat)***	
-carbef	antibiotics (carbacephem derivatives)	lora***carbef***
-cavir	(see -vir)	
cef-	cephalosporins	***cef***azolin
-cept	receptors	al***vircept***
subgroups:		
-facept	lymphocyte function-associated with antigen 3 (LFA) receptor	ale***facept***
-farcept	interferon receptors	pi***farcept***
-lefacept	lymphocyte function-associated antigen 3	a***lefacept***
-nercept	tumor necrosis factor receptors	le***nercept***
-vircept	antiviral receptors	al***vircept***
-cet	receptors (small molecule)	
subgroup:		
-calcet	calcium	te***calcet***
-cetrapib	cholesterol ester transfer protein inhibitors	tor***cetrapib***
-cic	hepatoprotectives (timonacic type)	limazo***cic***
-ciclovir	(see vir-)	
-cidib	cyclin dependent kinase inhibitor	alvo***cidib***
-cidin	natural antibiotics (undefined group)	grami***cidin***
-ciguat	guanaline cyclase activator	ata***ciguat***,
		atri***ciguat***
-cillin	penicillins	ampi***cillin***
-citabine	antivirals (nucleosides)	gem***citabine***
		fia***citabine***
		zal***citabine***
-clidine	muscarinic agonists (various indications)	veda***clidine***
		talsa***clidine***
-clone	hypnotics/tranquilizers (zopiclone type)	pago***clone***
-cog	blood coagulation factors	
subgroups:		
-eptacog	blood coagulation factor VII	***eptacog*** alfa (activated)
-nonacog	blood coagulation factor IX	***nonacog*** alfa
-octocog	blood coagulation factor VIII	mor***octocog***-alfa
		octocog alfa
-cogin	blood coagulation cascade inhibitor	tifa***cogin***
-conazole	systemic antifungals (miconazole type)	flu***conazole***
		oxi***conazole***
-cort-	cortisone derivatives	hydro***cort***isone

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-coxib	cyclooxygenase-2 inhibitors	cele***coxib*** pare***coxib*** valde***coxib***
-cridar	(see -dar)	
-crinat	diuretics (ethacrynic acid derivatives)	bro***crinat***
-crine	acridine derivatives	amsa***crine*** quina***crine***
-cromil	antiallergics (cromoglicic acid derivatives)	nedo***cromil***
-curium (also -curonium)	neuromuscular blocking agents (quaternary ammonium compounds)	atra***curium*** al***curonium*** pipe***curonium***
-cycline	antibiotics (tetracycline derivatives)	mino***cycline***
-dan	positive inotropic agents (pimobendan type)	prinoxo***dan*** indoli***dan***
-dapsone	antimycobacterials (diaminodiphenylsulfone derivatives)	ace***dapsone***
-dar	multidrug resistance inhibitors	
subgroups:		
-cridar	acridine carboxamide derivatives	ela***cridar***
-icodar	pipecolic acid derivatives	bir***icodar***
-quidar	quinoline derivatives	lami***quidar*** zozu***quidar***
-spodar	ciclosporin D derivatives	val***spodar***
-denoson	selective A_1 adenosine receptor subtype agonists	teca***denoson***, bino***denoson***
-dermin	(see -ermin)	
dil-, -dil- or -dil	vasodilators (undefined group)	foste***dil***
-dipine	phenylpyridine vasodilators (nifedipine type)	daro***dipine*** felo***dipine***
-dismase	(see -ase)	
-distim	(see -stim)	
-ditan	antimigraine (5-HT_1 receptor agonists)	alni***ditan***
-dopa	dopamine receptor agonists	levo***dopa***
-dralazine	antihypertensives (hydrazine-phthalazines)	hy***dralazine*** en***dralazine***
-dronate	calcium metabolism regulators	eti***dronate*** tilu***dronate***
-dutant	(see -tant)	
-ectedin	ecteinascodin derivatives	mon***ectedin***
-ectin	antiparasitics (ivermectin type)	doram***ectin*** moxid***ectin***
-elestat	(see -stat)	
-elvakin	(see -kin)	
-emcinal	erythromycin derivatives lacking antibiotic activity	mit***emcinal***
-entan	endothelin receptor antagonists	bos***entan***
-eptacog	(see -cog)	
-eptakin	(see -kin)	
-erg-	ergot alkaloid derivatives	p***erg***olide
-eridine	analgesics (meperidine type)	anil***eridine***
-ermin	growth factors	
subgroups:		
-bermin	vascular endothelial growth factors	tel***bermin***
-dermin	epidermal growth factors	muro***dermin***
-fermin	fibroblast growth factors	erso***fermin***
-nermin	tumor necrosis factors	so***nermin*** taso***nermin***
-plermin	platelet derived growth factors	beca***plermin***
-sermin	insulin-like growth factors	meca***sermin***
-termin	transforming growth factors	ce***termin***
subgroup:		
-otermin	bone morphogenetic proteins	dib***otermin*** alfa
estr- or -estr-	estrogens	***estr***one fen***estr***el
-estrant	estrogen antagonists	fulv***estrant***
-etanide	diuretics (piretanide type)	bum***etanide***
-exakin	(see -kin)	
-ezolid	oxazolidinone antibacterials	eper***ezolid*** lin***ezolid***
-farnib	farnesykltransferase inhibitor	tipi***farnib***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-fenamate	"fenamic acid" ester or salt derivatives	eto***fenamate***
-fenamic acid	anti-inflammatory agents (anthranilic acid derivatives)	flu***fenamic acid***
-fenin	diagnostic aids ((phenylcarbamoyl)methyl iminodiacetic acid derivatives)	arclo***fenin***
-fenine	analgesics (fenamic acid subgroup)	flocta***fenine***
-fentanil	narcotic analgesics (fentanyl derivatives)	al***fentanil*** mir***fentanil*** bri***fentanil***
-fentrine	phosphodiesterase inhibitor	puma***fentrine***
-fermin	(see -ermin)	
-fiban	fibrinogen receptor antagonists (glycoprotein II_b/III_a receptor antagonists)	lami***fiban*** tiro***fiban***
-fibatide	(see -tide)	
-fibrate	antihyperlipidemics (clofibrate type)	beza***fibrate***
-filcon	hydrophilic contact lens materials	alpha***filcon*** A xylo***filcon*** A mipa***filcon*** A
-fingol	sphingosine derivatives	cede***fingol*** sa***fingol***
-flapon	5-lipoxygenase-activating protein (FLAP) inhibitors	qui***flapon***
-flurane	general inhalation anesthetics (halogenated alkane derivatives)	en***flurane***
-focon	hydrophobic contact lens materials	tri***focon*** A pasi***focon*** B sata***focon*** A
-formin	hypoglycemics (phenformin type)	bu***formin***
-fradil	calcium channel blockers acting as vasodilators	mibe***fradil***
-fulven	antineoplastic, acylfulven derivatives	virido***fulven***
-fungin	antifungal antibiotics (undefined group)	kala***fungin***
-fylline	theophylline derivatives	enpro***fylline*** bami***fylline*** cipam***fylline***
-gab-	gabamimetics	fen***gab***ine
gado-	gadolinium derivatives (principally for diagnostic use)	***gado***diamide ***gado***teridol ***gado***benate
-gapil	neuronal apoptosis	omi***gapil***
-gapit	neuronal apoptosis	omi***gapit***
-ganan	antimicrobial, bactericidal permeability increasing polypeptide	ise***ganan*** pexi***ganan***
-gatran	thrombin inhibitors (argatroban type)	efe***gatran***
-gest-	progestins	me***gest***rol
-giline	MAO inhibitors, type B	sele***giline***
-gillin	antibiotics (*Aspergillus* strains)	mito***gillin***
gli-	hypoglycemic agents (glipizide type)	***gli***flumide
-gliptin	antidiabetics, didpeptidyl aminopeptidase-IV inhibitors	vilda***gliptin***
-glitazar	antidiabetics, PPAR agonists (not thiazolidene derivatives)	far***glitizar***
-glitazone	antidiabetics (thiazolidene derivatives)	en***glitazone*** pio***glitazone*** tro***glitazone***
-glumide	CCK antagonists, antiulcer, anxiolytic agent	ami***glumide*** itri***glumide***
-golix	GnRH receptor antagonists (nonpeptide)	rupu***golix***
-gosivir	(see -vir)	
-gramostim	(see -stim)	
-grastim	(see -stim)	
-grel- or	platelet antiaggregants (primarily thromboxane	itazi***grel***
-grel	synthetase inhibitors)	dimeta***grel*** fure***grel***ate
guan-	antihypertensives (guanidine derivatives)	***guan***octine
-ibat	ileal bile acid transport inhibitor	barix***ibat***
-icam	anti-inflammatory agents (isoxicam type)	enol***icam*** tenox***icam***
-icodar	(see -dar)	
-ifen(e)	antiestrogens of the clomifene and tamoxifen groups	nitrom***ifene*** ralox***ifene*** drolox***ifene***
-ilide	class III antiarrhythmic agents	ibut***ilide*** risot***ilide*** dofet***ilide***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-imepodib	inosine monophosphate dehydrogenase inhibitors	mer***imepodib***
-imex	immunostimulants	forfen***imex***
		roquin***imex***
		uben***imex***
-imib-	acycloA:cholesterol acetyltransferase (ACAT) enzyme inhibitors	eldac***imib***e
		lec***imib***ide
		oct***imib***ate
-imod	immunomodulators	ivar***imod***
		pidot***imod***
subgroup:		
-mapimod	mitogen-activated protein (MAP) kinase inhibitors	dor***mapimod***
-imus	immunosuppressives	tacrol***imus***
		napir***imus***
		gusper***imus***
		sirol***imus***
io-	iodine-containing contrast media	***io***damide
-irudin	anticoagulants (hirudin type)	des***irudin***
-isant	histamine H3 receptor antagonists	cipral***isant***
-isomide	antiarrhythmics (disopyramide derivatives)	bid***isomide***
-ium (also -onium)	quaternary ammonium derivatives	clidin***ium***
		disiqu***onium***
		polixet***onium***
-kacin	antibiotics obtained from *Streptomyces kanamyceticus* (related to kanamycin)	ami***kacin***
-kalant	potassium channel antagonists	almo***kalant***
		teri***kalant***
-kalim	potassium channel agonists	croma***kalim***
		apri***kalim***
-kalner	opener of large conductance calcium-activated (map-k) K+ channels	flindo***kalner***
-kef-	enkephalin agonists (various indications)	met***keph***amide
		caso***kef***amide
-kin	interleukin type substances	
subgroups:		
-decakin	interleukin-10 analogues and derivatives	ilo***decakin***
-dodekin	interleukin-12 analogues and derivatives	edo***dekin*** alfa
-elvekin	interleukin 11 analogues and derivatives	opr***elvekin***
-eptakin	interleukin 7 analogues and derivatives	
-exakin	interleukin 6 analogues and derivatives	at***exakin*** alfa
-leukin	interleukin 2 analogues and derivatives	tece***leukin***
		aldes***leukin***
-nakin	interleukin 1 analogues and derivatives	
subgroups:		
-onakin	1-α analogues and derivatives	pit***onakin***
-benakin	1-β analogues and derivatives	mobe***nakin***
-nonakin	interleukin 9 analogues and derivatives	
-octakin	interleukin 8 analogues and derivatives	em***octakin***
-penkin	interleukin 5 analogues and derivatives	
-trakin	interleukin 4 analogues and derivatives	bine***trakin***
-kinra	interleukin receptor antagonists	
subgroups:		
-nakinra	interleukin 1 (IL-1) receptor antagonists	a***nakinra***
-kiren	renin inhibitors	dite***kiren***
		terla***kiren***
		zan***kiren***
-lazad	lipid peroxidation inhibitors	tiri***lazad***
-leptin	leptin derivatives	metre***leptin***
-leukin	(see -kin)	
-lipim	lipoprotein lipase activators	ibro***lipim***
-lubant	leukotriene receptor antagonists (treatment of inflammatory skin disorders)	tico***lubant***
-lukast	(see -ast)	
-lutamide	antiandrogens	bica***lutamide***
		f***lutamide***
-lutril	neutral endopeptidase inhibitors possessing additional endothelin	dag***lutril***
-mab	monoclonal antibodies	imciro***mab***
		abcixi***mab***
		capro***mab***
		daclixi***mab***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
		detumo***mab***
		enlimo***mab***
-mantadine or	antivirals/antiparkinsonians	ri***mantadine***
-mantine	(adamantane derivatives)	dopa***mantine***
-mastat	(see -stat)	
-meline	cholinergic agonists (arecoline derivatives used in treatment of Alzheimer's disease)	xano***meline***
-mer	polymers	cadexo***mer***
		carbeti***mer***
-mesine	sigma receptor ligands	ig***mesine***
		pana***mesine***
-mestane	antineoplastics (aromatase inhibitors)	plo***mestane***
-metacin	anti-inflammatory agents (indomethacin type)	zido***metacin***
-micin	antibiotics (*Micromonospora* strains)	madura***micin***
		genta***micin***
-monam	monobactam antibiotics	gloxi***monam***
		oxi***monam***
		tige***monam***
-morelin	(see -relin)	
-moren	non-peptidic growth hormone secretagogues	ibuta***moren***
-mostim	(see -stim)	
-motine	antivirals (quinoline derivatives)	fa***motine***
-moxin	monoamine oxidase inhibitors (hydrazine derivatives)	ben***moxin***
		do***moxin***
-mustine	antineoplastics (chloroethylamine derivatives)	car***mustine***
-mycin	antibiotics (*Streptomyces* strains)	linco***mycin***
nab- or	cannabinol derivatives	***nab***azenil
-nab-		dro***nab***inol
-nakin	(see -kin)	
nal-	narcotic agonists/antagonists (normorphine type)	***nal***mefene
-navir	(see vir-)	
-nercept	(see -cept)	
-nermin	(see -ermin)	
-nertant	neurotensin receptor antagonists	remi***nertant***
-netant	(see -tant)	
-neurin	neurotensin receptor antagonists; neurotropins	abri***neurin***
-nicline	nicotinic acetylcholine receptor agonists	alti***nicline***
-nidap	nonsteroidal anti-inflammatory agents (tenidap type)	ilo***nidap***
		te***nidap***
-nidazole	antiprotozoal substances (metronidazole type)	ti***nidazole***
nifur-	5-nitrofuran derivatives	***nifur***atel
		nifuratrone
-nixin	anti-inflammatory agents (anilinonicotinic acid derivatives)	clo***nixin***
-nonacog	(see -cog)	
-nonakin	(see -kin)	
-octacog	(see -cog)	
-octakin	(see -kin)	
-olol	beta-blockers (propranolol type)	tim***olol***
		aten***olol***
-olone	steroids (*not* prednisolone derivatives)	minax***olone***
-onide	topical steroids (acetal derivatives)	amcin***onide***
-opilone	epothilone	fil***opilone***
-orex	anorexiants	flud***orex***
-orphan	narcotic antagonists/agonists	
dextro-	(morphinan derivatives)	meth***orphan***
		dextr***orphan***
-osuran	urotensin receptor antagonists	pal***osuran***
-otermin	bone morphogenetic proteins	dib***otermin*** alfa
-otilate	hepatoprotectants, di-isopropyl-1,3-dithiol-malonate derivatives	miv***otilate***
-oxacin	antibacterials (quinolone derivatives)	difl***oxacin***
		ciprofl***oxacin***
-oxan	alpha-adrenoceptor antagonists (benzodioxane derivatives)	imil***oxan***
-oxanide	antiparasitics (salicylanilide derivatives)	brom***oxanide***
-oxef	antibiotics (oxacefalosporanic acid derivatives)	flom***oxef***
-oxetine	antidepressants (fluoxetine type)	dap***oxetine***
		sepr***oxetine***
-pafant	platelet-activating factor antagonists	a***pafant***
		daco***pafant***
		tulo***pafant***
		lexi***pafant***
-pamide	diuretics (sulfamoylbenzoic acid derivatives)	ali***pamide***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-pamil	coronary vasodilators (verapamil type)	tia***pamil***
-pamine	dopaminergics (butopamine type)	foso***pamine***
		ibo***pamine***
-panel	AMPA receptor antagonists	fana***panel***
		irum***panel***
		talam***panel***
-parcil	antithrombotics	beci***parcil***
		ili***parcil***
-parcin	glycopeptide antibiotics	avo***parcin***
-parin	heparin derivatives and low molecular weight (or depolymerized) heparins	he***parin***
		tinza***parin***
		dalte***parin***
-parinux	antithrombotyic indirect selective synthetic factor Xa inhibitors	fonda***parinux***
-paroid	antithrombotics (heparinoid type)	dana***paroid***
		sul***paroid***
peg-	PEGylated compounds	***peg***caristim
		pegnartograstim
		pegvisomant
-penem	antibacterial antibiotics (carbapenem derivatives)	imi***penem***
-penkin	(see -kin)	
perflu-	blood substitutes and/or diagnostics (perfluorochemicals)	***perflu***bron
		perflunafene
-peridol	antipsychotics (haloperidol type)	halo***peridol***
-peridone	antipsychotics (risperidone type)	ris***peridone***
		ilo***peridone***
		oca***peridone***
-perone	antianxiety agents/neuroleptics (4′-fluoro-4-piperidinobutyrophenone derivatives)	duo***perone***
-pezil	acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease	ico***pezil***
		done***pezil***
-pidem	hypnotics/sedatives (zolpidem type)	zol***pidem***
		al***pidem***
-pirdine	cognition enhancers	lino***pirdine***
		besi***pirdine***
		sibo***pirdine***
-pirox	antimycotics (pyridone derivatives)	ciclo***pirox***
-pitant	(see -tant)	
-plact	platelet factor 4 analogs and derivatives	iro***plact***
-pladib	phospholipase A2 inhibitors	eco***pladib***
		vares***pladib***
-planin	antibacterials (*Actinoplanes* strains)	mide***planin***
		ramo***planin***
		teico***planin***
-platin	antineoplastics (platinum derivatives)	cis***platin***
-plermin	(see -ermin)	
-plestim	(see -stim)	
-plon	non-benzodiazepine anxiolytics, sedatives, hypnotics	ocina***plon***
		zale***plon***
-poetin	erythropoietins	e***poetin*** alfa
		e***poetin*** beta
-porfin	benzoporphyrin derivatives	verte***porfin***
		temo***porfin***
-pramine	antidepressants (imipramine type)	lofe***pramine***
-prazan	acid pump inhibitors, not dependent on acid activation	omida***prazan***
-prazole	antiulcer agents (benzimidazole derivatives)	ome***prazole***
		disu***prazole***
subgroup: -maprazole	acid pump inhibitors	pu***maprazole***
pred-, -pred- or -pred	prednisone and prednisolone derivatives	***pred***nicarbate
		clo***pred***nol
		oxiso***pred***
-pressin	vasoconstrictors (vasopressin derivatives)	desmo***pressin***
-pride	sulpiride derivatives	remoxi***pride***
		zaco***pride***
-pril	antihypertensives (ACE inhibitors)	enala***pril***
		temoca***pril***
		spira***pril***
-prilat	antihypertensives (ACE inhibitors) (diacid analogs of the -pril entity)	enala***prilat***
		spira***prilat***
-prinim	nootropic agents, purine derivatives	lete***prinim***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-prim	antibacterials (trimethoprim type)	ormeto***prim***
-prisnil	selective progesterone receptor modulators (SPRM)	aso***prisnil***
-pristin	antibacterials, pristinamycin derivatives	quinu***pristin***
		efe***pristin***
-profen	anti-inflammatory/analgesic agents (ibuprofen type)	flurbi***profen***
-prost-	prostaglandin derivatives	rio***prost***il
or -prost		dino***prost***
-protafib	protein tyrosine phosphatase 1B inhibitors	erti***protafib***
-pultide	(see -tide)	
-punil	mitochondrial benzodiazepine receptor (MBR) selective antagonists (purine derivatives)	ema***punil***
-projet	nonsteroidal ligand for the progesterone receptor	tana***proget***
-queside	cholesterol sequestrants (glycosides)	pama***queside***
-racetam	nootropes (piracetam type)	pi***racetam***
-racil	uracil type antineoplastics	enilu***racil***
		geme***racil***
		ote***racil***
-relin	prehormones or hormone-release stimulating peptides	nafa***relin***
subgroups:		
-morelin	growth hormone-release stimulating peptides	du***morelin***
-tirelin	thyrotropin releasing hormone analogues	pro***tirelin***
-relix	hormone-release inhibiting peptides	deti***relix***
-renone	aldosterone antagonists (spironolactone type)	can***renone***
-restat	(see -stat)	
-retin- or	retinol derivatives	et***retin***ate
-retin		pel***retin***
-ribine	ribofuranil derivatives (pyrazofurin type)	loxo***ribine***
-rifa-	antibiotics (rifamycin derivatives)	***rifa***pentine
		rifampin
-rinone	cardiotonics (amrinone type)	mil***rinone***
-rozole	aromatase inhibitors (imidazole/triazole derivatives)	let***rozole***
		fad***rozole***
		vo***rozole***
-rsen	antisense oligonucleotides	alicafo***rsen***
-rubicin	antineoplastic antibiotics (daunorubicin type)	eso***rubicin***
		ida***rubicin***
sal-, -sal-	anti-inflammatory agents	me***sal***amine
o -sal	(salicylic acid derivatives)	difluni***sal***
		bal***sal***azide
-sartan	angiotensin II receptor antagonists	lo***sartan***
		epro***sartan***
-semide	diuretics (furosemide type)	azo***semide***
-sermin	(see -ermin)	
-serod	serotonin receptor antagonists	pibo***serod***
		sulam***serod***
		tega***serod***
-serpine	*Rauwolfia* alkaloid derivatives	re***serpine***
-setron	serotonin 5-HT_3 antagonists	ondan***setron***
		grani***setron***
		luro***setron***
-siban	oxytocin antagonists	baru***siban***
-sidomine	antianginals (sydnone derivatives)	pir***sidomine***
		mol***sidomine***
		lin***sidomine***
som-	growth hormone derivatives	***som***atrem
		somatropin
som- -bove	bovine somatotropin derivatives	***som***etri***bove***
som- -por	porcine somatotropin derivatives	***som***etri***por***
		somagre***por***
-sonan	5-HT_{1B} receptor antagonists	elza***sonan***
-spirone	anxiolytics (buspirone type)	zalo***spirone***
		tio***spirone***
-spodar	(see -dar)	
-sporin	immunosuppressants (cyclosporine type)	gecle***sporin***
		oxeclo***sporin***
-stat-, -stat	enzyme inhibitors	
or -stat-		
subgroups:		
-castat	dopamine β-hydrolase (DBH) inhibitors	nepi***castat***
-elestat	elastase inhibitors	siv***elestat***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-inostat	inhibitors of histon acetylase	dac***inostat***
-mastat	antineoplastics (matrix metalloproteinase inhibitors)	bati***mastat***
-(a)mostat	proteolytic enzyme inhibitors	naf***amostat***
-restat- or	aldose-reductase inhibitors	ponal***restat***
-restat		tol***restat***
-vastatin	antihyperlipidemics (HMG-CoA inhibitors)	ator***vastatin***
		lo***vastatin***
		pra***vastatin***
(other series members)	urease inhibitor	ben***urestat***
	renal dehydropeptidase inhibitor	cila***stat***in
	pepsin inhibitor	pep***stat***in
-ster-	steroids (androgens, anabolics)	testo***ster***one
-steride	testosterone reductase inhibitors	epri***steride***
		fena***steride***
-stigmine	cholinesterase inhibitors (physostigmine type)	quilo***stigmine***
		teser***stigmine***
-stim	colony-stimulating factors	
subgroups:		
-distim	conjugates of two different types of colony-stimulating factors	milo***distim***
-gramostim	granulocyte macrophage colony-stimulating factors (GM-CSF)	mol***gramostim***
		re***gramostim***
		sar***gramostim***
		eco***gramostim***
-grastim	granulocyte colony-stimulating factors (G-CSF)	fil***grastim***
		leno***grastim***
-mostim	macrophage colony-stimulating factors (M-CSF)	miri***mostim***
-plestim	interleukin 3 derivatives; pleiotropic colony-stimulating factors	dani***plestim***
-stinel	NMDA receptor antagonists (glycine recognition site)	lico***stinel***
-sulfa-	antimicrobials (sulfonamides derivatives)	***sulfa***salazine
-sulfan	antineoplastics, alkylating agents (methanesulfonate derivatives)	bu***sulfan***
-lind	pro-apoptotic cGMP phosphodiesterase inhibitors	
subgroups:		
-sulind	sulfone metabolite	racta***lind***
		dracta***lind***
-tant	tachykinin (neurokinin) receptor antagonists	
subgroups:		
-dutant	NK_2 receptor antagonists	sare***dutant***
-netant	NK_3 receptor antagonists	osa***netant***
-pitant	NK_1 receptor antagonists	da***pitant***
		zina***pitant***
		lane***pitant***
-tapide	microsomal triglyceride transfer protein (MTP) inhibitors	impli***tapide***
-tecan	antineoplastics (camptothecine derivatives)	topo***tecan***
		irino***tecan***
-tepa	antineoplastics (thiotepa derivatives)	aze***tepa***
-teplase	(see -ase)	
-termin	(see -ermin)	
-terol	bronchodilators (phenethylamine derivatives)	albu***terol***
-tesind	thymidilate synthetase inhibitors (benzindole derivatives)	me***tesind***
-texafin	tesaphyrin derivatives	mo***texafin***
-thiazide	diuretics (thiazide derivatives)	chloro***thiazide***
-tiapine	antipsychotics (dibenzothiazepine derivatives)	qui***tiapine***
-tiazem	calcium channel blockers (diltiazem type)	dil***tiazem***
		clen***tiazem***
		ipro***tiazem***
-tibant	antiasthmatics (bradykinin antagonists)	ica***tibant***
-tide	peptides and glycopeptides	octreo***tide***
subgroups:		
-fibatide	platelet aggregation inhibitors (glycoprotein IIe/IIIa receptor antagonists)	epti***fibatide***
-pultide	peptides used as pulmonary surfactants	sina***pultide***
-tidine	H_2-receptor antagonists (cimetidine type)	lupi***tidine***
		done***tidine***
		rani***tidine***
-tinib	tyrosine kinase inhibitors	caner***tinib***,
		ima***tinib,***
		mubri***tinib***

Appendix A Continued

STEM	DEFINITION	EXAMPLES
-tirelin	(see -relin)	
-tirome	antihyperlidaemic, thyromimetic derivatives	ani***tirome***
		axi***tirome***
-tocin	oxytocin derivatives	oxy***tocin***
-toin	antiepileptics (hydantoin derivatives)	albu***toin***
-tox(a)-	toxins	ur***toxa***zumab
-traposin	aP2 inhibitors	sel***traposin***
-trexate	antimetabolites (folic acid derivatives)	metho***trexate***
-trexed	antineoplastic thymidylate synthase inhibitors	peme***trexed***
		rali***trexed***
		nola***trexed***
-tricin	antibiotics (polyene derivatives)	mepar***tricin***
-triptan	antimigraine agents (5-HT_1 receptor agonists)	nara***triptan***
		oxi***triptan***
		suma***triptan***
-triptyline	antidepressants (dibenzo[*a,d*]cycloheptane derivatives)	ami***triptyline***
-troban	antithrombotics (thromboxane A_2 receptor antagonists)	dal***troban***
		sulo***troban***
-trodast	(see -ast)	
-troline	antipsychotics (dopamine D_2 antagonists)	carvo***troline***
		gevo***troline***
trop- or -trop-	atropine derivatives	benz***trop***ine
-uplase	(see -ase)	
-uracil	uracil derivatives used as thyroid antagonists and as antineoplastics	fluoro***uracil***
-uridine	antivirals; antineoplastics (uridine derivatives)	idox***uridine***
-vaptan	vasopressin receptor antagonists	coni***vaptan***
		relco***vaptan***
-vastatin	(see -stat)	
-verine	spasmolytic agents (papaverine type)	mebe***verine***
vin- or -vin-	vinca alkaloids	***vin***epidine
		apo***vin***camine
vir-, -vir- or -vir	antiviral substances (undefined group)	ganciclo***vir***
		en***vir***adine
		viroxime
		al***vir***cept
		dela***vir***dine
subgroups:		
-amivir	neuraminidase inhibitors	zan***amivir***
-cavir	carbocyclic nucleosides	lobu***cavir***
-cyclovir/ -ciclovir	antivirals (acyclovir type)	des***ciclovir***
		fam***ciclovir***
		pen***ciclovir***
-gosivir	glucosidase inhibitor	cel***gosivir***
-navir	HIV protease inhibitors (saquinavir type)	droxi***navir***
		indi***navir***
		rito***navir***
-virdine	antivirals (non-nucleoside reverse transcriptase inhibitors; pyridine derivatives)	ate***virdine***
		dele***virdine***
-virenz	antivirals (non-nucleoside reverse transcriptase inhibitors; benzoxazinone derivatives)	efa***virenz***
-virsen	antivirals (antisense)	afo***virsen***
		fomi***virsen***
		treco***virsen***
-vircept	(see -cept)	
-virdine	(see vir)	
-virenz	(see vir)	
-vudine	antineoplastics; antivirals (zidovudine group) (exception: edoxudine)	sta***vudine***
		lami***vudine***
		alo***vudine***
-xaban	antithrombotic; factor X inhibitor	tami***xaban***
-xanox	antiallergic respiratory tract drugs (xanoxic acid derivatives)	ti***xanox***
-(x)antrone	antineoplastics, mitoxantrone derivatives aza-anthracenedione class of antitumor agents	pi***xantrone***
-zolamide	carbonic anhydrase inhibitors	brin***zolamide***
		dor***zolamide***
		se***zolamide***
-zolast	(see -ast)	
-zomib	proteozome inhibitors	borte***zomib***

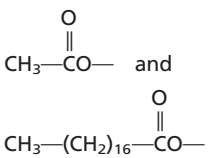
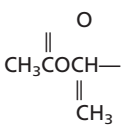
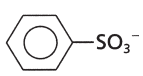
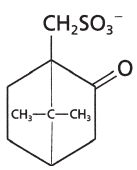
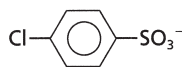
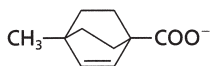
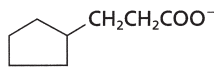
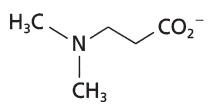
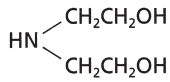
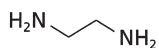
Appendix A Continued

The following USAN stems have received official approval by the USAN Council at the July 14, 2003 USAN Council meeting:

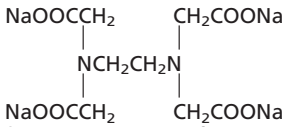
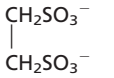
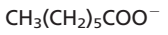
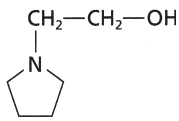
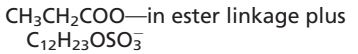
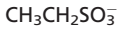
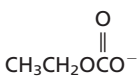
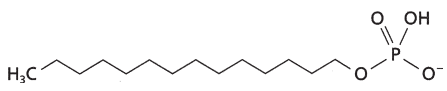
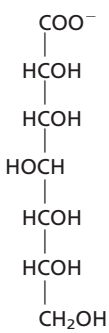
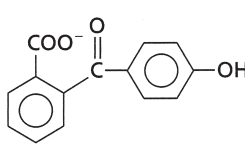
STEM	DEFINITION	EXAMPLES
-algron	alpha$_1$-adrenoreceptor agonists	dabuz***algron***
-casan	caspase (interleukin-1b) converting enzyme inhibitors	pralna***casan***
-gliptin	didpeptidyl aminopeptidase-IV inhibitors	vilda***gliptin***
-lutril	neutral endopeptidase inhibitors possessing additional endothelin	dag***lutril***
-imod	mitogen-activated protein (MAP) kinase inhibitors	dor***mapimod***
-mapimod		
-nertant	neurotensin receptor antagonists	remi***nertant***
-pladib	phospholipase A2 inhibitors	eco***pladib***
-punil	motochondrial benzodiazepine receptor (MBR) selective antagonists (purine derivatives)	ema***punil***
-proget	nonsteroidal ligand for the progesterone receptor	tana***proget***
-osuran	urotensin receptor antagonists	pal***osuran***
-otermin	bone morphogenetic proteins	dib***otermin*** alfa
-tinib	tyrosine kinase inhibitors	caner***tinib***, imat***inib***, mubri***tinib***

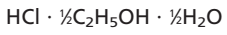
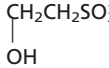
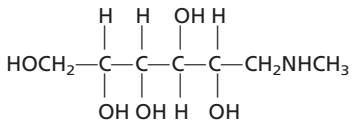
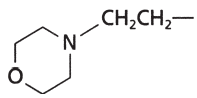
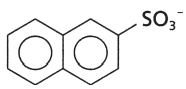
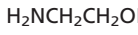
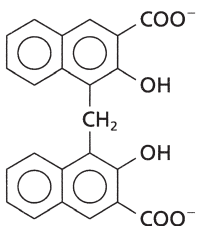
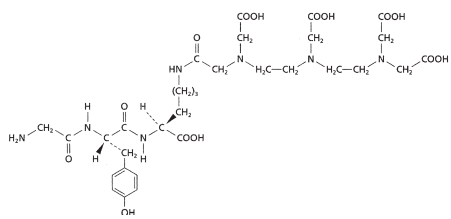
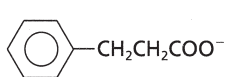
This list represents common stems for which chemical and/or pharmacologic parameters have been established. These stems and their definitions have been approved by the USAN Council and are recommended for use in coining new nonproprietary names for drugs that belong to an established series of related agents. The list is not exhaustive in that it does not include all stems used by the Council and other national or international nomenclature groups. It is the nature of the nomenclature process that new, potential stems are constantly being created and that definitions of older stems may need to be modified as new information becomes available.

Appendix B Contractions for Radicals and Adducts

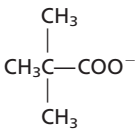
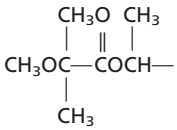
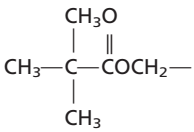
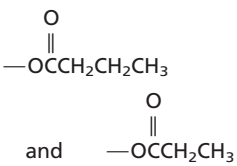
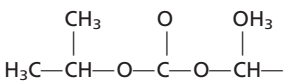
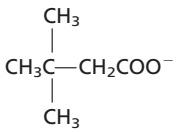
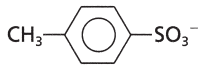
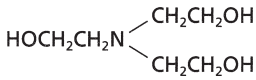
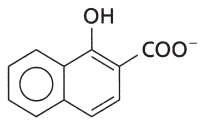
CONTRACTION	CHEMICAL NAME AND GRAPHIC FORMULA
aceturate	*N*-acetylglycinate $CH_3CONHCH_2COO^-$
acistrate	2′-acetate (ester) and octadecanoate (salt) 
axetil	1-acetoxyethyl 
besylate	benzenesulfonate 
camsylate	camphorsulfonate 
caproate	hexanoate $CH_3(CH_2)_4COO^-$
closylate	*p*-chlorobenzenesulfonate 
cyclotate	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate 
cypionate	cyclopentanepropionate 
dapropate	*N,N*-dimethyl-β-alanine 
diolamine	diethanolamine 
edamine	ethylenediamine 

Appendix B Continued

CONTRACTION	CHEMICAL NAME AND GRAPHIC FORMULA
edetate*	ethylenediaminetetraacetate  (All anions derived from edetic acid; edetate sodium is portrayed here.)
edisylate	1,2-ethanedisulfonate 
enanthate	heptanoate 
epolamine	1-pyrrolidineethanol 
erbumine	2-methyl-2-propanamine 
estolate	propanoate and dodecyl sulfate (salt) 
esylate	ethanesulfonate 
etabonate	(ethoxycarbonyl)oxy 
fostedate	tetradecyl hydrogen phosphate 
gluceptate	glucoheptonate 
hybenzate	*o*-(4-hydroxybenzoyl)benzoate 

CONTRACTION	CHEMICAL NAME AND GRAPHIC FORMULA
hyclate	monohydrochloride, hemiethanolate hemihydrate 
isethionate	2-hydroxyethanesulfonate 
meglumine	*N*-methylglucamine 
mesylate	methanesulfonate 
mofetil	2-(4-morpholinyl)ethyl 
napsylate	2-naphthalenesulfonate 
olamine	ethanolamine 
pamoate	4,4′-methylenebis[3-hydroxy-2-naphthoate] 
pendetide	N^6-[*N*-[2-[[2-[bis(carboxymethyl)-amino]ethyl](carboxymethyl)amino]-ethyl]-*N*-(carboxymethyl)glycyl]-N^2-(*N*-glycyl-L-tyrosyl-L-lysine-tyrosyl) 
phenpropionate	3-phenylpropionate 

Appendix B Continued

CONTRACTION	CHEMICAL NAME AND GRAPHIC FORMULA
pivalate	trimethylacetate 
pivoxetil	1-(2-methoxy-2-methyl-1-oxopropoxy)ethyl 
pivoxil	(2,2-dimethyl-1-oxopropoxy)methyl 
probutate	(1-oxobutoxy) (ester) and (1-oxopropoxy) (ester) 
proxetil	1-[(isopropoxycarbonyl)oxy]ethyl 
tebutate	*tertiary* butyl acetate 
tosylate	*p*-toluenesulfonate 
triflutate	trifluoroacetate 
trolamine	triethanolamine 
xinafoate	1-hydroxy-2-naphthalenecarboxylate 

CHAPTER 28

Structure–Activity Relationship and Drug Design

Randy J Zauhar

For centuries humans have observed not only that natural substances could be used for their nutritional value and for treatment of diseases, but they could also bring about toxic or lethal effects. The Chinese Emperor Sheng Nang in 2735 BCE compiled a book of herbs and employed *Chang Shan* in the treatment of malaria. Although the majority of the drugs used from antiquity to the 19th century came from natural sources, in the past century a new era was brought about by treatment of diseases with synthetic drugs. Also, the modification of natural products, through various synthetic processes, has provided useful semisynthetic drugs.

The field of medicinal chemistry has evolved from an emphasis on the synthesis, isolation, and characterization of drugs to an increased awareness of the biochemistry of disease states and the design of drugs for the prevention of diseases. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and biological activity. An increased consideration in recent years has been to correlate the chemical structure with chemical reactivity or physical properties and these correlations can, in turn, be related to their therapeutic actions.

Although there has been a great deal of success in understanding the relationship between chemical structure and biological activity in a number of areas, especially for antibacterial drugs, there are still many human afflictions that require new and improved drugs. Cancer, viral infections, cardiovascular disease, and mental disease need new agents and approaches for treating and preventing these maladies. As more information is gained as to causative factors of different diseases, the move will be from the empirical approach to the rational design of new drugs. General principles of drug design have been and are continuing to be developed in medicinal chemistry.

In developing drugs with specific activities, several approaches are used. The effects of natural products or synthetic drugs are determined on various biological systems (or screens) to identify lead compounds with specific biological activities. Once the effect of the drug is known, the medicinal chemist and pharmacologist work together to improve the activity of a known active molecule or "lead molecule." This process normally goes through a synthesis—biological test—synthesis—biological test cycle until a drug with the desired activity is obtained. Today, the structure of receptors and function of enzymes, which may be involved in the pathogenesis of a disease, are understood better. These molecules, in turn, are used as targets for the design of drugs that act as agonists or antagonists of receptors or inhibitors of the enzymes. Thus, this information adds a new phase to the cycle, which is now drug design—synthesis—biological activity—drug design, and so on.

ANALOG APPROACH

The most frequent approach to obtaining drugs to treat a particular disease is to synthesize analogs of drugs that are known to be effective in the treatment of the disease. The *pharmacophore* is a chemical segment of a molecule that is responsible for biological action. Normally, it is found that the specific type of biological activity of a molecule depends on more than just one functional group. Consequently, the addition of a single functional group to an inert organic substance ordinarily does not imbue a molecule with a specific biological activity because more than one functional group normally is required for potent activity, and in addition these must usually be arranged with a specific geometry.

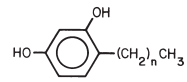
Drug activity depends on the size, shape, and degree of ionization of the drug molecule. These parameters are studied by making analogs or molecular modifications of a parent molecule. In those instances where a molecule has a known biological action, this substance serves as a prototype or lead molecule for the synthesis of analogs for further biological testing. In the past this process has produced a greater number of active analogs than just preparing and testing molecules obtained through a random process. In addition, structure–activity relationship studies often are used to determine the pharmacophore and also to obtain drugs with increased potency, greater selectivity, increased or decreased duration of action, low toxicity, and increased stability.

Finally, economics may be a prime reason for the search for analogs if a natural product is too difficult to obtain or if a synthetic molecule is too expensive to prepare in quantities needed for the manufacturing process.

Homologs

A *homologous series* refers to a series of analogs that differ in structure by a simple increment in the molecular formula. For example, these may be produced by sequential chemical change that includes increasing or decreasing the length of a carbon chain. A series of homologs of this type is used to provide insight into the relationship of biological activity and chemical changes that involve only the number of methylene groups. This type of determination has provided valuable information as to the importance of the partition coefficient and biological action. Often, the compounds with short, alkyl chains are low in activity; as the chain length is increased, the biological activity increases to an optimum point, and as more methylene groups are added, activity decreases. An interesting example of this phenomenon is

the activity of the *n*-alkylresorcinols in which the optimum biological activity, as measured by phenol coefficients against *B typhosus*, is hexylresorcinol (**1**)

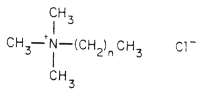


hexylresorcinol (n = 5)

1

with six carbon atoms ($n = 5$) in the side chain. If the alkyl chain is lengthened or decreased, a decrease in activity is observed relative to hexylresorcinol.

There are times in which changing the number of methylene groups may lead to a change in the type of biological activity rather than its intensity. For example, it is known that alkyltrimethylammonium analogs (**2**)

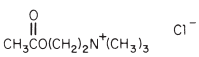


alkyltrimethylammonium

2

possess different types of activity depending on the length of the alkyl group.

If the alkyl group is up to six carbons ($n = 5$), as in 2, the compounds are muscarinic agonists. Thus, these compounds have activity similar to acetylcholine (**3**)



acetylcholine chloride

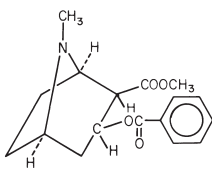
3

on muscarinic receptors. With seven carbons ($n = 6$) to eight ($n = 7$) carbons, these compounds are partial agonists; when the length is greater than nine carbons ($n = 8$), these compounds are muscarinic antagonists.

Molecular Fragmentation

The synthesis and biological evaluation of molecular fragments of a *lead* compound often is used in structure–activity studies. This process also may be called *molecular simplification, molecular dissociation,* or *disjunction.* Often, this process is used when the structure of a natural product is elucidated and the molecule has an important and possibly new biological action. When the natural product may be too difficult or expensive to obtain for drug use, the process of trial and error is used to determine which portion of the molecule is required for a desired biological activity. Several illustrations of the molecular fragmentation approach will be given in which the starting point is a natural product.

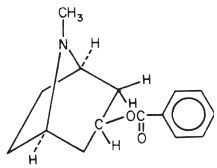
Cocaine (**4**),



cocaine

4

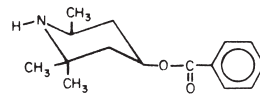
an alkaloid obtained from *Erythroxylon coca*, has served as the prototype molecule for the development of a number of local anesthetics. The carbomethoxy group of cocaine is not required for local anesthetic action, as can be seen with tropacocaine, which lacks this group (**5**).



tropacocaine

5

The synthesis of β-eucaine (**6**)

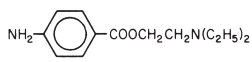


β-eucaine

6

and subsequent biological testing showed that a tropane ring system also was not a prerequisite for local anesthetic activity.

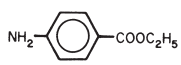
The synthesis of procaine (**7**)



procaine

7

demonstrated that the critical part of the molecule required for activity was the hydrophilic amine segment attached to an intermediate chain, which in turn was attached to a lipophilic ester function. Many analogs of procaine have potent local anesthetic activity. The amine section of procaine can be removed to give benzocaine (**8**),

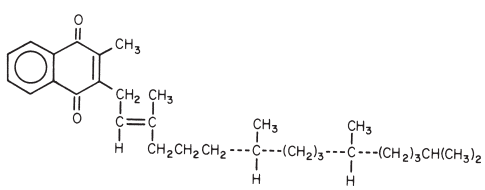


benzocaine

8

a substance known to possess local anesthetic activity. However, the mechanism of action of benzocaine in the production of local anesthesia is different from that of procaine. Therefore, one must be cautious in relating chemical changes to activity, particularly because the drug may retain activity but the mechanism by which the activity is produced may change.

Vitamin K_1 (**9**)

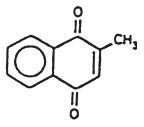


vitamin K_1

9

is a natural product (phytonadione) composed of a naphthoquinone bearing a 2-methyl group and a side-chain phytyl group at the 3 position. It is known that vitamin K is useful in preventing hemorrhage and attempts have been made to prepare drugs that were less complex but maintained vitamin K activity.

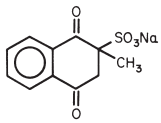
Menadione (**10**)



menadione

10

is a highly active, vitamin K–like drug that can be prepared by the oxidation of 1-methylnaphthalene with chromic acid. It is an analog of vitamin K that lacks the phytyl side chain at the 3 position. A bisulfite-addition product, menadione sodium bisulfite (**11**),



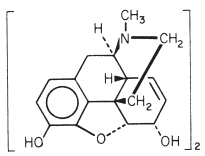
menadione sodium bisulfite

11

is available as a water-soluble anticoagulant. The substance is known to decompose under appropriate conditions to liberate menadione, the free quinone (10).

Another area in which molecular fragmentation has led to the development of a number of useful drugs is with the analgesics related to morphine. The structure of morphine was determined in 1925; subsequently, many analogs were prepared and examined for analgesic activity. In most instances new analogs were prepared with the goal of possibly separating the analgesic effects from the undesirable effects of dependence liability, nausea, constipation, and respiratory depression.

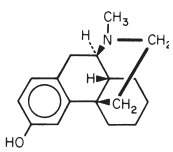
It can be seen that, through molecular fragmentation, one can reduce the number of ring systems from the pentacyclic, morphine (**12**)



morphine

12

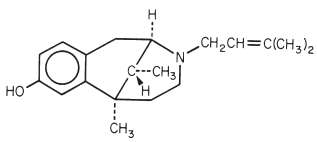
to a tetracyclic, levorphanol (**13**),



levorphanol

13

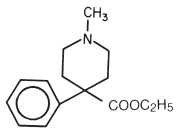
and a tricyclic, pentazocine (**14**),



pentazocine

14

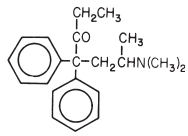
a bicyclic, meperidine (**15**);



meperidine

15

and to (**16**), methadone,



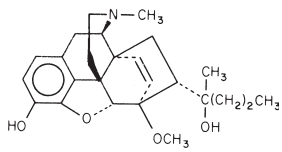
methadone

16

which has only the A ring of morphine remaining, but still retains potent analgesic activity. Certainly, the amine and aromatic ring play an important role in the production of analgesic activity. The intermediate carbon atoms between the amine and the phenyl ring do not have to be in a specific configuration for the molecule to possess analgesic activity.

Addition of Functional Groups

Another approach often used in structure–activity relationships is to add functional groups to a molecule with known biological activity. This approach was used by Bently and Hardy[1] to see if a molecule more complex than morphine could be synthesized that would interact with the analgesic receptor but, because of its complex structure, would not interact with the receptors that produced side effects. One of the analogs, etorphine (**17**),

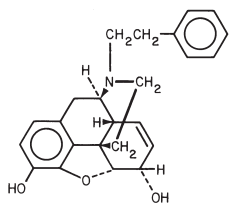


etorphine

17

is some 1000 times more potent than morphine and is used primarily in veterinary medicine to immobilize large animals. Of major importance is the fact that etorphine and related agents have enhanced potency, suggesting that etorphine may bind to an additional site that dramatically enhances the analgesic activity of morphine.

It also is known that replacement of the *N*-methyl group with the larger *N*-phenethyl group to give *N*-phenethylnormorphine (**18**)

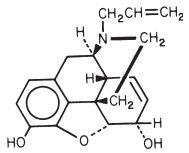


N-phenethylnormorphine

18

produces a compound six times as potent as morphine. An important observation is that not only may a quantitative change be brought about by modifying the *N*-methyl group of morphine but also a qualitative change in activity is observed if it is

changed to an *N*-allyl group as shown in **19,**

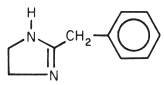


nalorphine

19

to produce *N*-allylnormorphine (nalorphine), a morphine antagonist. This finding has stimulated a great deal of study of structure–activity relationships with the *N*-substituents to find potent agonists, antagonists, and mixed agonist-antagonists of opioid receptors.

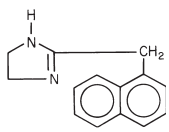
In other drug categories, it has been shown that tolazoline (**20**)



tolazoline

20

is an antagonist of α-adrenergic receptors, while the addition of another phenyl ring produces naphazoline (**21**),



naphazoline

21

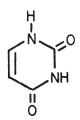
which is an α-adrenergic agonist. This is a rather unusual transformation of an antagonist into an agonist by the addition of a functional group.

Isosteric Replacements

The concept of *isosterism* or *bioisosterism* has been used for a number of years in the search for new drugs. This has been an extremely important approach in the design of antimetabolites. In 1919, Langmuir[2,3] first defined *isosteres* as those molecules or groups of atoms that have the same number and types of electrons. For example, N_2 and CO or N_3^- and NCO^- are examples of isosteres. These substances have similar physical properties. Later, Friedman[4] introduced the concept of *bioisosteres,* compounds that fit the broadest definitions for isosteres and have a similar type of biological activity. This concept included drugs with agonist or antagonist activity. When a substance is found that does possess promising therapeutic activity, the medicinal chemists will attempt to prepare closely related compounds with improved properties such as greater potency or fewer side effects. In the past, a considerable amount of intuition had been used by medicinal chemists in selecting bioisosteric replacements. The standard isosteric replacements are divided into five classes, as illustrated in Table 28-1.

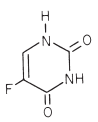
A variety of nonclassic bioisosteric replacements also are known and include paired examples such as H and F, —CO_2H and —SO_3H and —CO— and —SO_2—.

Some of the examples of isosteric replacement that have provided useful drugs are a fluorine replacement of the hydrogen in uracil (**22**)



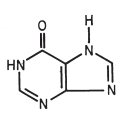
uracil

22



5-fluorouracil

23



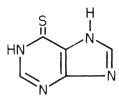
hypoxanthine

24

Table 28-1. Isosteric Replacements

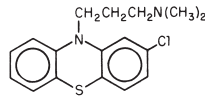
CLASS 1 (MONOVALENT)	2 (DIVALENT)	3 (TRIVALENT)	4 (TETRAVALENT)	5 (RINGS)
F, Cl, Br, I	—O—	—N═	═C═	—CH═CH—
OH, SH	—S—	—P═	═Si═	—S—
NH_2, PH_2	—Se—	—As═	═N^+═	—O—
CH_3	—Tc—	—Sb═	═P═	—NH—
		—CH═	═As═	
			═Sb^+═	

to give 5-fluorouracil (**23**), a very useful anticancer drug; and the replacement of the carbonyl oxygen in hypoxanthine (**24**) to give 6- mercaptopurine (**25**),



6-mercaptopurine

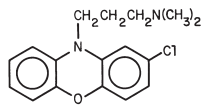
25



chlorpromazine

26

a potent antitumor antimetabolite. The replacement of oxygen by sulfur in chlorpromazine (**26**) to give the oxygen isostere (**27**)

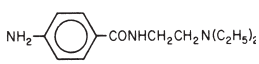


oxygen isostere of chlorpromazine

27

produced a compound with 1/10 the tranquilizing activity of the parent molecule.

The replacement of the ester function of procaine (**7**), a local anesthetic, with an amide function produced procainamide (**28**),

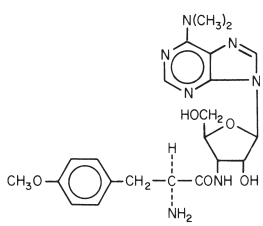


procainamide

28

which has found an important role in the treatment of cardiac arrhythmias. An important difference between the two drugs is that the amide function, which allows for similar biological activity, is more stable chemically, can be given orally, and is not affected by the esterases that catalyze the hydrolysis of procaine.

The antibiotic puromycin (**29**),

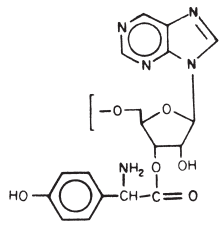


puromycin

29

which has antibacterial, antitumor, and antitrypanosomidal activity, inhibits protein synthesis by interfering with the utilization of transfer-RNA. Puromycin is the isosteric analog of

the aminoacyl-*t*-RNA (**30**);

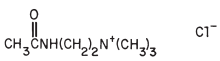


terminus of tyrosinyl-*t*-RNA

30

after puromycin is taken up, it blocks the subsequent protein synthesis.

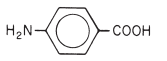
The isosteric replacement of ester groups does not always produce compounds with significant biological activity, as the modification of acetylcholine ester (**3**) with an amide function resulted in the amide analog (**31**)



amide analog of acetylcholine

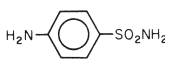
31

that does not show significant agonist or antagonist activity. One of the oldest nonclassic isosteric replacements that provided an important class of antibacterial agents was the replacement of carboxylic acid group of *p*-aminobenzoic acid (PABA, **32**)



p-aminobenzoic acid

32

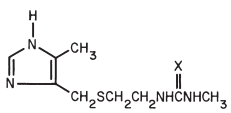


sulfanilamide

33

with a sulfonamide group to give sulfanilamide (**33**).

A final illustration of bioisosteric replacement in drug design is the replacement of the thiourea functional group of metiamide (**34**),



X = S, metiamide

34

X = NCN, cimetidine

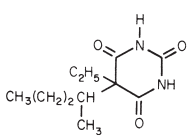
35

a histamine H_2-blocker, with the cyanoguanidine group to produce the popular antiulcer drug cimetidine (**35**). This bioisosteric replacement overcame the granulocytopenia toxicity that had been observed with metiamide.

Stereochemistry

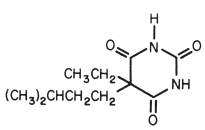
An important consideration in drug–receptor interactions is the stereochemistry of the drug and the proper positioning of functional groups so that they will interact optimally with an enzyme or receptor. Four types of isomeric drugs will be considered: positional isomers, geometrical isomers, optical isomers, and diastereomers.

With *positional*, or *constitutional*, *isomers* the compounds have the same empirical formula but the atoms of the molecule are rearranged in a different order. To illustrate positional isomers, one can consider the relationship of pentobarbital (**36**)



pentobarbital

36

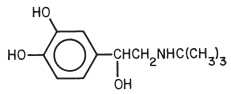


amobarbital

37

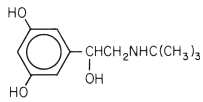
and amobarbital (**37**), both of which belong to the barbiturate family. These positional isomers differ only in the makeup of the 5-carbon side chain attached to the barbiturate ring system. The former compound has a short duration of action while the latter has an intermediate duration of action.

Another example of positional isomers is *N*-(*tert*-butyl)-norepinephrine (**38**)



N-tertiary-butyl norepinephrine

38

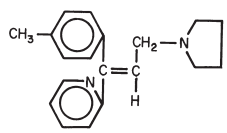


terbutaline

39

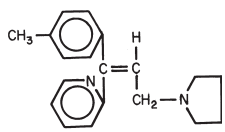
and terbutaline (**39**). The resorcinol portion of 39 has served as a biologically effective replacement of the catechol group in 38. The resorcinol analog (39), in contrast to the catechol (38), is not a substrate for catechol-*O*-methyltransferase (COMT), an important metabolic enzyme; therefore, it has a longer duration of action. Terbutaline is a useful selective β_2-adrenergic stimulant for the treatment of bronchial asthma and related conditions, and it can be administered orally.

Geometrical isomers are another important set of molecules in which a possible difference in biological activity between isomers may exist. The *trans*, or *E*, isomer of triprolidine (**40**)



(*trans* or *E*-isomer)
triprolidine

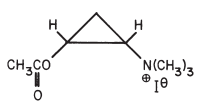
40



(*cis* or *Z*-isomer)
triprolidine

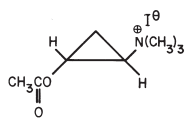
41

is over 1000 times as potent as the *cis*, or *Z*, isomer (**41**) as a H_1-histamine antagonist. Another example of a set of geometrical isomers is the *cis* and *trans*-2-acetoxycyclopropyltrimethyl ammonium iodides (**42** and **43**),



(*cis*-isomer) (*Z*)
cis-2-acetoxycyclopropyltrimethyl ammonium iodide

42



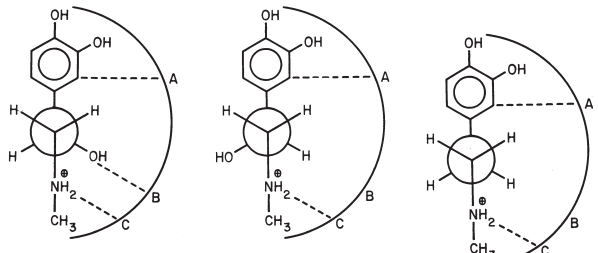
(*trans*-isomer) (*E*)
trans-2-acetoxycyclopropyltrimethyl ammonium iodide

43

respectively. The *trans* isomer is much more potent as a muscarinic agonist than the *cis* isomer and also is a good substrate for the enzyme acetylcholinesterase.

The term *absolute configuration* refers to the arrangement of atoms in space of a chiral compound. In a number of instances there is a distinct difference in biological activity of the *optical isomers* (enantiomers). For example, the *R*(−)

isomer of epinephrine (**44**)

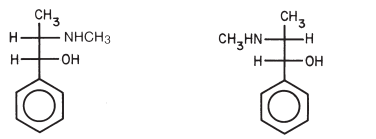


R (−) isomer epinephrine **44** | *S* (+) isomer epinephrine **45** | epinine **46**

is more potent on both α- and β-adrenergic receptors than the *S*(+) isomer (**45**). The binding of the isomers of epinephrine and epinine (**46**) (the desoxy analog of epinephrine) is illustrated. The three points of binding on the receptor are the catechol binding site (*A*), hydroxy binding site (*B*), and anionic binding site (*C*).

According to the Easson–Stedman theory,[5] the relative order of activity of the isomers on adrenergic receptors are $R > S \sim$ deoxy. Only the *R* isomer can bind to all three sites, whereas both the *S* isomer and the deoxy isomer, which show similar activity, can bind only to two of the sites. Refer to Chapter 13 for a discussion of isomerism.

Although enantiomers have the same chemical and physical properties, except for the direction of rotation of polarized light, diastereomers have different physical properties. *Diastereomers* are compounds with two or more chiral centers. While 1*R*,2*S*(−)-ephedrine (**47**)

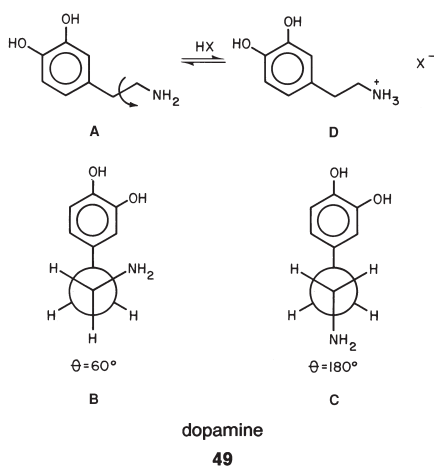


1*R*,2*S* (−)-ephedrine **47** | 1*R*,2*R* (−)-ψ-ephedrine **48**

has direct activity on both α- and β-adrenergic receptors, the 1*R*,2*R* (−)-Ψ-ephedrine (**48**) shows α-adrenergic blocking activity. Both diastereomers show indirect adrenergic activity.

An important strategy often used in drug design is to take a conformationally flexible molecule and to convert it into a conformationally rigid molecule in order to find the optimum conformation for binding to a drug receptor. This approach may be used to introduce selectivity for receptors, eliminate undesired side effects, and learn about the spatial relationships of functional groups for receptors.

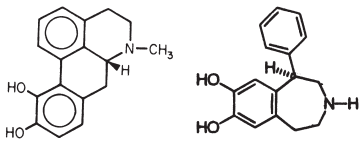
Dopamine (**49A**)



dopamine **49**

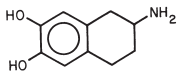
can exist in an infinite number of conformations about the side-chain carbon–carbon bond. Two such conformations are illustrated [θ = 60° *gauche* and θ = 180° *trans* conformation (49B and C)].

Apomorphine (**50**)



apomorphine **50** | **51**

and 6,7-dihydroxy-2-aminotetralin (ADTN) (**52**)



6,7-dihydroxy-2-aminotetralin (ADTN) **52**

are two potent dopamine D_1 and D_2 agonists that exist in the *trans* conformation, whereas the selective D_1 agonist SKF 38393 (**51**) does not exist in a similar conformation. Apomorphine, a conformationally rigid molecule, can bind to both D_1 and D_2 dopamine receptors.

In other instances, a drug molecule may need conformational flexibility for proper binding to the receptor to produce biological activity in an induced-fit receptor model. Thus, conformational flexibility may in some instances be a prerequisite for drug agonist activity.

Ionization

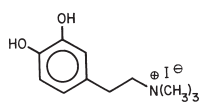
Many of the substances used as drugs are weak acids or weak bases. Therefore, an important question is whether the charged or uncharged form of the drug binds to the receptor. Also of importance is the degree of ionization and the effect ionization may have upon absorption and distribution. In general, the ionization can be demonstrated as

$$\text{[Weak Acids]}\quad \underset{\text{(nonionized drug)}}{\text{AH}} \rightleftharpoons \underset{\text{(ionized drug)}}{\text{A}^- + \text{H}^+}$$

$$\text{[Weak Bases]}\quad \underset{\text{(ionized drug)}}{\text{BH}^+} \rightleftharpoons \underset{\text{(nonionized drug)}}{\text{B} + \text{H}^+}$$

It is very difficult to know which molecular form of the drug is active if the charged and uncharged forms are in equilibrium in physiological solution; for example, with dopamine the pK_a of the amine is ~10. Thus, although most of the drug in solution is in the ionized form (49D), the un-ionized form of the drug molecule still may be the active form.

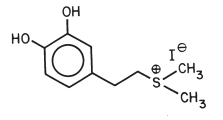
The quaternary salt of dopamine (**53**)



quaternary salt of dopamine **53**

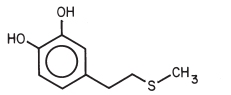
has been prepared and exhibits agonist activity on D_2-receptors, indicating that the ionized form of the drug is an active molecular species. However, it is almost impossible to determine if a primary, secondary, or tertiary amine is active as the un-ionized form of the drug because these amines are always in equilibrium under physiological conditions.

It has been shown that the permanently charged dimethylsulfonium analog (**54**)



dimethylsulfonium analog

54

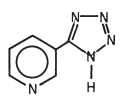


permanently uncharged sulfide

55

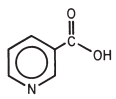
is active as a D_2-dopamine agonist, whereas the permanently uncharged sulfide (**55**) is inactive as a D_2-dopamine agonist.[6] This suggests that the uncharged form of a dopamine agonist is unlikely to produce D_2-dopamine activity. It also has been found using this approach that both charged agonists and antagonists are responsible for binding to and activating dopamine D_2-receptors. This work, along with observations made using agents that interact with carboxyl groups that block dopaminergic receptors, indicates an ionic attraction between dopamine D_2-agonists and D_2-antagonists and their target receptor.

In order to improve on the pharmacological activity of a drug or to enhance metabolic stability, various replacements of acid and basic groups have been attempted. One of the bioisosteric replacements of an acid functional group often employed is that of the tetrazole group, which has a $pK_a \sim 4.9$. It was found that the tetrazole analog (**56**)



tetrazole analog of nicotinic acid

56



nicotinic acid

57

of nicotinic acid (**57**) was more active as an antihyperlipidemic than the parent molecule, nicotinic acid.

Drug Disposition

It should be recognized that a number of factors can affect the interaction of a drug with a receptor, including interatomic distances, shape, size, absolute configuration, rigidity, flexibility, and charge distribution. Some or all of these factors play a part in the consideration of drug design. Normally, by starting the drug-design process at the level of receptors or enzymes, the variables such as absorption, transportation, metabolism, and excretion are set aside temporarily in order to optimize affinity and potency. Regardless of how the medicinal chemist chooses to modify the structure, the process of developing a drug is very complex and the additional factors that must be considered in obtaining a useful drug will be discussed below.

ABSORPTION—Most drugs are administered orally and pass through the stomach, small intestine, and colon; they may be absorbed at any location. During their passage through the gastrointestinal (GI) tract, drugs will experience a range of pH changes starting at about 1.5 in the stomach and reaching as high as pH 8 in the colon. Additionally, drugs are subjected to a variety of enzymes and complexing agents, all of which tend to reduce the effective concentration of the compound.

For a drug to be absorbed (through lipid membranes), it must be present in the fat-soluble un-ionized form. The pK_a of the drug and the pH of the absorption site determine the ease of absorption. Acidic drugs (eg, aspirin) are absorbed best from the stomach, whereas basic compounds (eg, ephedrine) are absorbed preferentially in the small intestine. Permanently ionized molecules (eg, quaternary ammonium salts) lack lipid solubility and usually are absorbed poorly from any region of the GI tract.

TRANSPORT—The blood is the primary carrier of drugs throughout the body. Independent of the method of administration, the drug must pass through several membranes on its way to the active site. Solubility, degree of ionization, and other colligative properties all affect the transport process. Other factors that complicate the transport process include complexation or protein-binding. Most drugs move through a membrane by a simple diffusion mechanism (passive transport); a few compounds that resemble normal body substrates may bind to transport molecules and are carried via an *active-transport* process in which drugs can move against a concentration gradient—that is, they can be transported from a compartment of low concentration to one of higher concentration.

METABOLISM—As soon as a drug enters the body, it becomes susceptible to a variety of metabolic processes that usually *detoxify* the foreign substance. In addition, through oxidation, reduction, hydrolysis, esterification, or conjugation the drug usually is made more water soluble, to enhance its excretion from the body. However, there are instances when a drug metabolite actually may be the active compound, having activity similar to the original compound. Usually, after several biotransformations, the modified form is excreted.

The liver is the primary site of detoxification, but enzyme processes also may occur in the stomach, intestine, and other areas in the body. The metabolic reactions occurring in the liver traditionally are separated into two categories.

1. The drug undergoes what might be termed *functional-group changes,* such as ring or side-chain hydroxylation, nitrogroup reduction, aldehyde oxidation, dealkylation, or deamination.
2. The drug undergoes what is called *conjugation*, in which the metabolized compound combines with solubilizing groups such as glucuronic acid or glycine to form excretable conjugates.

Because drugs can undergo such a wide variety of chemical changes in the body, the specifics of which are unpredictable, the medicinal chemist must at least be aware of these metabolic processes. At some point in the development of a new drug, the molecular structure of the drug may have to be altered in order to change the way in which it is metabolized.

INTERACTION WITH ACTIVE SITES—Ehrlich[7] first introduced the concept that a drug must first combine with a *receptor* (active site) to produce an effect. A receptor is considered to be a cellular substance on which a drug acts to produce its effects. A receptor may be composed of protein, RNA, or DNA. Proteins are an important set of receptors, and drug action may be a consequence of the influence of a drug on an enzyme. Often, the drugs reserved for cancer and viral diseases interact with DNA.

An *enzyme system* is composed of a *coenzyme,* usually nonprotein in nature; an *apoenzyme* (the protein portion), which also may enjoin a nonprotein prosthetic group; and *cofactors,* often inorganic metallic ions and the substrate, which is acted upon by the enzyme. The *active site* on the enzyme may consist of an anionic, cationic, acidic, basic, and/or neutral sites. In addition, the physical shape of the site is such that the contour of the molecule that interacts with the receptor must have a proper shape to insure a *fit* on the receptor.

BINDING AND STORAGE—It is known that other substances, including mucins and proteins, bind drugs. If the binding force is strong, the drug may combine quickly with the macromolecules and thus be removed from the transport system, metabolized, and excreted. Besides complexation to macromolecules, storage also can occur by partitioning in the body lipids or chelation by bony tissue. In any case, the location and degree of storage is a factor influencing the potency, toxicity, and duration of action of a drug. For example, the short-acting barbiturates are thought to be bound very rapidly by body tissues, and thus the active species is removed quickly from the transport system and its action ceases. Yet suramin sodium has an extremely long biological half-life, with noticeable concentrations evident months after cessation of dosing with the drug.

EXCRETION—The excretion process is coupled closely to metabolism and results in the removal of the drug from the body. Elimination may occur via the kidney, liver, skin, lungs, or GI tract. The route of excretion used is determined largely by

the drug; the volatile compounds (ether, alcohol) excrete via the lungs, poorly absorbed or insoluble substances through the GI tract with the feces, and very few through the skin. The main route of elimination is through the kidney. The biochemical aspects relating to the complexity of the biosystem that the drug must survive are intricate and little understood.

QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIPS

A long-standing goal of workers in the area of quantitative structure–activity relationships (QSAR) has been the development of quantitative methods of determining the activities of a series of compounds. One of the earliest hypotheses that attempted to relate activity to a physicochemical parameter was the Meyer–Overton narcosis theory.[8] In 1901, both men working independently observed that, for general anesthetics, activity was related to the lipid/water partition coefficient; cyclopropane with a value of 65 was far more effective than nitrous oxide with a coefficient of 2.2.

In the field of theoretical chemistry, Hammett[9] was the first to demonstrate that the pK_a values of substituted benzoic acids could be predicted as a function of the various substituents attached to the ring and their abilities to either donate or withdraw electrons from the carboxyl group. These results then were extended to other reactions and other series of compounds using the same substituent constants derived from the benzoic acid series. In the Hammet equation,

$$\log k/k_0 = p\sigma \qquad (1)$$

where k is the rate constant for the reaction of a substituted aromatic compound, k_0 is the rate constant for the unsubstituted aromatic compound, p is the reaction constant, and σ is the substituent constant. Later work led to substituent constants in which the electronic effect is separated into inductive and resonance terms; in the Taft equation, a term E_s is defined as a measure of the steric requirements of a substituent.

In more recent times there have been numerous mathematical attempts to correlate molecular structure with drug activity. Many of these attempts were destined to fail because they grossly oversimplified what is now known as a very complex problem, even more so than *simple* chemical reactivity. Moderate success has been achieved within narrow limits of drug type, but a universal equation has yet to find expression.

One of the most successful investigators in this field is Hansch,[10] who derived a general equation based on linear free-energy considerations. Inherent in this equation is the ability to incorporate parameters that encompass the full range of known biological requirements for drug activity. Among these are terms for biological transport, drug/enzyme binding energies, substituent effects (both electronic and steric), and electron densities of possible active sites on the drug molecule.

The most general form of the Hansch equation usually is written

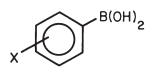
$$\log 1/C = -a(\log P)^2 + b \log P + p\sigma + c \qquad (2)$$

Activity is expressed as $1/C$, where C is the concentration of a drug required to elicit a given response and P is the octanol/water partition coefficient, a measure of the hydrophobic bonding power of the drug. Its magnitude is indicative of the constant, p, which is characteristic of a given molecular type; and σ is the Hammett substituent constant, which is a measure of the electronic effect on the rate of reaction.

The equation also is expressed as

$$\log 1/C = -a\pi^2 + b\pi + p\sigma + c \qquad (3)$$

where $\pi = \log P_x - \log P_H$. P_x is the partition coefficient of the substituted molecule, and P_H is the partition coefficient of the parent unsubstituted molecule. The particular benefit of the π term is the observation by Hansch that π values are additive and thus numerous partition coefficients can be calculated without the necessity of synthesizing and measuring P_x of the actual compound. An example was the calculation of P_x values for a series of substituted benzeneboronic acids. The values of π were taken from the known series of substituted benzoic acids and, when added to the log P_H value for benzeneboronic acid, gave values of log P_x for the substituted boronic acids (**58**).



substituted boronic acid

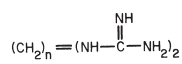
58

When these values were used in a Hansch equation to predict drug penetration into brain tissue, excellent correlation with experimental values was obtained.

Another feature of Hansch's work is the use of the technique of regression analysis. In seeking structure–activity correlation it often is not necessary to include all of the defined parameters in the equation to obtain good results. In effect, what has been done is to fit the data to several forms of the equation using the method of least squares, to determine which equation is statistically the best. Thus, if good correlation can be obtained by including only π values, it is probable that the electronic effect of the substituent is not critical for drug activity in that series.

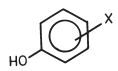
Postulates as to specific drug mechanisms thus can be made when activity dependence, or lack thereof, is found for a given parameter. Further expansions of the equation also permit mechanistic considerations to be formulated. The $p\sigma$ term (actually a log k term) can be expanded to include a steric parameter (E_s) or electron-density parameters for various parts of a molecule. Thus, if inclusion of a steric substituent constant leads to improved correlation, the steric requirements of the drug/enzyme interaction can be better understood. Several examples are given below for derived equations in which excellent correlation with experimental results is found when one or more parameters are omitted.

For the antibacterial effects on gram-negative bacteria of a series of diguanidines, the structures of which are shown in **59**,



diguanidines

59



substituted phenols

60

the equation

$$\log 1/C = -0.081\,\pi^2 + 1.483\pi - 1.578 \qquad (4)$$

predicts quantitative activity very accurately. Substituent effects are neglected here because molecular modification involves only a change in the number of methylene groups.

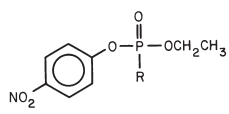
For the antibacterial activity of substituted phenols of the structure indicated by 60, the equation

$$\log 1/C = 0.684 \log P - 0.921\sigma + 0.268 \qquad (5)$$

fits the data best.

It would seem that substituents that donate electrons ($-\sigma$ values) would have the highest activity, but in the series studied, these compounds have relatively small values of log P, and this offsets much of the substituent effect. Thus, the most active compounds were those that had the best balance between partition coefficient and electronic effect.

For a series of phosphonate esters known cholinesterase inhibitors (**61**),



phosphonate esters

61

the equation that gave the best correlation was

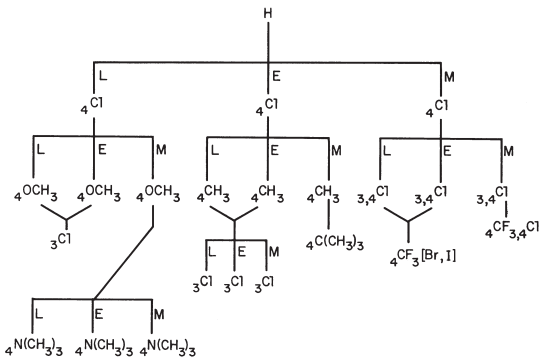
$$\log K = -0.152\pi - 1.68\sigma + 4.053\,E_s + 7.212 \qquad (6)$$

where K is the inhibition constant, σ is the substituent constant for aliphatic systems, and E_s is the Taft steric constant. Here is a series in which the steric effect of the substituents plays an important role. The bulkier groups cause a decrease in cholinesterase inhibition.

These are just a few of the many structure–activity correlations that Hansch has been able to formulate. A study of those equations of best-fit also can give an indication of how to modify a structure to affect biological activity. In a study of thyroxine derivatives, it was predicted (and substantiated) that the replacement of iodine by a *t*-butyl group should lead to a more active molecule. To date, the Hansch equation is one of the most ambitious attempts to explain drug activity in terms of structural variations.

To obtain a good statistical correlation in fitting data to an equation that should lead to the prediction of the most active compound in a series, the more compounds that are prepared, the better the results. At least five compounds should be prepared for each variable on the right side of the equation; and the greater the number of compounds synthesized, the more likely an optimum compound will be found.

Topliss[11] devised an operational scheme (**62**),



Topliss decision tree appraoch

62

which shows the beginning steps in this decision-tree approach) for the optimization of compounds using the substituent constants π and σ values used in the Hansch method. However, this approach avoids the mathematical and statistical requirements of the Hansch equation. For optimum aromatic substitution a *p*-chloro analog is prepared; if this is more (*M*) active than the parent, unsubstituted compound (*H*), a positive π and σ value is thought to be important, and the next type of substitution would be a 3,4-dichloro analog. If the *p*-chloro analog is less active (*L*), a 4-methoxy substituent would be the next compound to be prepared and tested; if equally (*E*) active, a 4-methyl substituent would be tried. Using this selection-grid approach, the optimum compound normally can be found with a fewer number of synthesized compounds than with the Hansch approach. A similar type of scheme has been devised by Topliss for side-chain substitutions.

In recent years, advances in computing power have made possible QSAR studies that do not rely solely on experimentally-derived parameters that describe substituent effects, but instead compute various descriptors (HOMO and LUMO energies, partial atomic charges, molecular dipole moment, polarizability) directly from the molecular wavefunction using both *ab initio* and semiempirical methods. For example, Olivero-Verbel and Pacheco-Londono[12] successfully modeled the cytotoxic and anti-HIV activity of 29 flavonoids using regression models based on descriptors such as atomic partial charges and total dipole moment computed using the Gaussian quantum-chemical package; Yao et al[13] constructed predictive models of the anti-cancer activity of a series of indane nucleosides based on molecular surface area and the energy of the LUMO (lowest unoccupied molecular orbital); Clare and Supuran[14] built successful QSAR models for the activities of a series of 36 carbonic anhydrase inhibitors using as descriptors various quantities derived from *ab initio* quantum calculations, including partial atomic charges, components of molecular dipole moment projected along key chemical bonds, and molecular surface area.

Perhaps the most ambitious technique for directly correlating molecular structure with activity is CoMFA (Comparative Molecular Field Analysis). In this approach a three-dimensional grid is superimposed on a set of aligned molecules (usually a congeneric series, but not necessarily so), and electrostatic and steric potentials for the molecules are computed at each vertex of the grid. A multiple regression model is then constructed to relate experimental activities with the variations in the fields measured on the grid. The method can be used to create predictive models which have the added benefit of highlighting portions of the grid associated with large variations in activity (for example, regions where high positive electrostatic potential is correlated with high activity). It is possible to generate color-coded graphical displays that can serve as a guide in modifying molecules so as to realize increased activity. CoMFA has been successfully applied to a wide range of molecular targets, including HIV protease inhibitors,[15,16] androgenic compounds,[17] and opioids.[18]

MECHANISM-BASED DRUG DESIGN

Theories of drug design have evolved from the concept of drug-receptor interactions. In a viable biosystem, a variety of substrates are known to be metabolized through the intervention of enzyme systems. A large proportion of drugs are believed to act by altering the ability of the substrate to interact with the enzyme or receptor. Without attempting to be comprehensive, extensions of the drug-receptor concept that have some experimental verification will be discussed.

The theory of *metabolite antagonism,* or *antimetabolites,* is one that has gained credence. An antimetabolite can, through structural or functional group similarity, compete with a metabolite by blocking a site on an enzyme at which the metabolite ordinarily acts. This latter mechanism, *enzyme inhibition,* probably has been studied more than any other single mechanism. In its most recent version the theory postulates that there are sites of particular conformation on the surface of the enzyme. Spacing and chemical affinity are such that only a molecule having a shape that is the mirror image of the enzyme surface and has the correct chemical groups can interact with the enzyme.

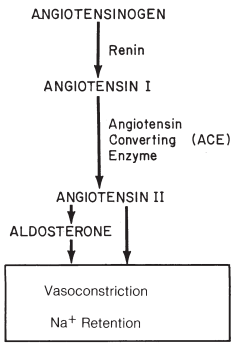
The classic example of metabolite antagonism by a drug is sulfanilamide (**33**) and its derivatives. In work carried out by Woods,[19] sulfanilamide was shown to be antagonistic to *p*-aminobenzoic acid (PABA), a biological precursor of dihydrofolic acid. A fascinating feature of these studies was the demonstration that PABA would reverse the effect of sulfanilamide on a bacterial culture, an example of metabolite antagonism in reverse. Because the two compounds are isosteres, it is easy to see why they are mutually antagonistic.

Either the metabolite or its antagonist can attach itself to the critical area of the dihydrofolate synthetic enzyme surface. If the former occurs, PABA begins its transformation into dihydrofolic acid, but if the latter happens, the metabolic process ceases and, in the case of bacteria, multiplication is inhibited. The degree of inhibition depends on the relative concentrations of the substrate and the inhibitor. Selective toxicity is shown for bacteria because mammals do not need to synthesize dihydrofolic acid, but obtain it in their diets.

Another mode of drug action involves enzyme deactivation without actual competition. Here, the drug can react with the enzyme or even the enzyme-substrate complex and, in some manner, prevent the metabolism of the substrate. The nitrogen

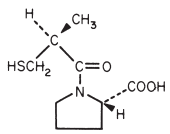
mustards, and other alkylating agents used for cancer chemotherapy, act in this fashion. These drugs are relatively nonspecific inhibitors that act by forming irreversible bonds with enzyme and nucleic acid molecules. In doing so they may not block necessarily a particular site, but rather many active sites; in this way, they inactivate enzymes and react with base residues of DNA, to form cross-links. Nitrogen mustards can prevent replication, and thus arrest cell division.

One of the recent advances in the treatment of hypertension came about through a better understanding of the mechanism of *angiotension*. The renin–angiotensin system (RAS) (**63**),



renin-angiotensin system

63



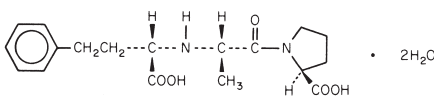
captopril

64

plays a key role in the maintenance of sodium and fluid volume, resulting in the regulation of blood pressure. The system is composed of two important enzymes: renin and angiotensin-converting enzyme (ACE). Renin converts angiotensinogen to the decapeptide angiotensin I; ACE acts upon angiotensin I to give the octapeptide angiotensin II, which is responsible for the peripheral effects leading to an elevation of blood pressure.

Although ACE was identified in the mid-1950s, it wasn't until 1977 that Cushman and Ondetti[20] reported a new drug, captopril (**64**), that competitively could inhibit ACE. This provided a major advance in the treatment of hypertension.

Based on the concepts learned from a knowledge of the binding points of captopril—that the mercapto group binds to Zn ion, the amide carbonyl to a hydrogen-bonding site, and the carboxylate to a positive center on the enzyme—new inhibitors have been synthesized. One of the most successful of these new analogs is enalaprilat (**65**),



enalaprilat

65

which has the advantage of oral activity and lacks central effects. Modern approaches at preparing new drugs that will affect the RAS include inhibitors of renin and the preparation of angiotensin receptor antagonists.

Besides substrate analogs, the design of transition-state inhibitors also is an important approach to drug design. Transition-state analogs are intended to resemble the substrate in transition from substrate to products, and they should be stable substances. In designing this inhibitor, a very good understanding of the specific enzyme mechanism and the chemical nature of the transition state is needed. Another approach that is being used is to prepare k_{cat} or suicide-substrate inhibitors. In designing these types of inhibitors, the mechanism of the enzyme should be known; it is important to generate a reactive intermediate that, in turn, undergoes an irreversible reaction with the enzyme.

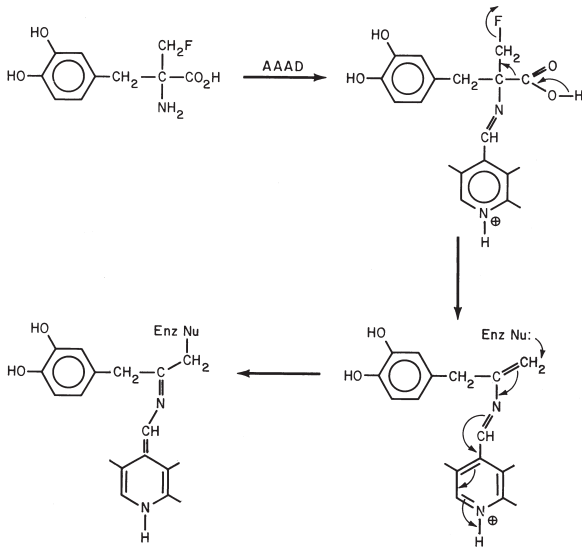


Figure 28-1.

Enzymes using pyridoxal phosphate have been used a great deal with this approach. An example is monofluoromethyl dihydroxyphenylalanine (Fig 28-1), which inhibits the enzyme aromatic amino acid decarboxylase (AAAD). The inhibition of the enzyme is shown with the cofactor in Figure 28-1. There are many examples of k_{cat} inhibitors, but at this time one of the most-used classes of drugs therapeutically are the propargylamine derivatives, which inhibit monoamine oxidase (MAO). The inhibitors form a covalent bond with the flavine portion of MAO.

COMPUTER USE IN DRUG DESIGN

One of the early uses of computer-assisted drug design (CADD)[21] was in the QSAR approaches of Hansch, as previously discussed. Other uses of the computer have been to apply computational chemistry to learn about the shape of molecules. In conformational studies, molecular mechanics and quantum mechanics calculations are carried out to provide insight as to the preferred conformations of a molecule. A variety of approaches are used to carry out such computations. Molecular mechanics calculations are fast, but require extensive lists of atom types and detailed sets of parameters, and will fail when confronted with novel chemical structures. On the other hand, high-level quantum calculations provide high accuracy and can be applied to any chemical structure, but are time-consuming and limited to relatively small compounds. Fast semiempirical quantum methods ranging from CNDO to PM3 fill an important gap, being applicable to a wide range of compounds and fast enough to be used with relatively large molecules. Although a preferred-conformation, low-energy form of a drug may be calculated using these concepts, this may not be the conformation required to produce drug activity.

Molecular modeling and molecular graphics have shown dramatic growth and are becoming an integral part of the drug-discovery process. *Molecular modeling* is the generation, manipulation, and representation of the three-dimensional form of molecules; *molecular graphics* refers to the use of computer graphics to represent the molecular structure. In the past, synthetic chemists have used molecular models, but computer modeling has enhanced the detailed display of molecular structures.

An important use of CADD is in the design of hypothetical drugs. For example, when the structure of an enzyme or receptor obtained through x-ray studies is known, one can begin to design hypothetical drugs that actually can be shown to interact with the active site. Computer programs such as GOLD[22] and UCSF DOCK[23] allow the positions, orientations, and conformations of putative drug molecules to be automatically optimized inside a receptor site, and their relative affinities to be predicted on the basis of binding energetics. A number of graphical rendering techniques can be used to highlight important interactions and features of interest, including the use of color and representations of molecular surfaces and volumes. This type of work, in combination with experimental methods such as x-ray, nuclear magnetic resonance (NMR), and infrared spectroscopy, should provide a powerful tool for the future design of drugs.

COMBINATORIAL CHEMISTRYAND DRUG DISCOVERY

The drug-discovery environment underwent a major evolution in the 1990s. These revolutionary changes are evident to those close to the drug-discovery process. The need for a more efficient and effective means of finding new drug molecules is one of a number of factors driving this new approach. Combinatorial chemistry has shown itself to be both effective and efficient in both drug-lead generation and the optimization of a new drug-lead molecule. An important part of this process is the introduction of new computing and chemical automation processes, along with the merging of the combinatorial chemistry with biology via high-throughput screening.

Two basic combinatorial processes are currently used.[24]

Parallel Synthesis This process was invented in the 1980s by H Mario Geysen. He used this approach initially to find the small segment of a protein that bound to antibodies. In parallel synthesis, reactions are carried out separately but simultaneously using different starting materials and reactants with such reactions yielding a single product. Thus, using an 8×12 array of reaction vessels and 20 different starting materials, one can obtain a library of 96 different compounds. Advances in robotics have allowed full automation of the routine chemistry involved. Pharmaceutical companies are expanding upon this process and are currently are generating thousands of new compounds every day.

Split and Mix Synthesis This method[24] was used in the late 1980s by Arpad Furka. The parallel synthesis affords a single product per reaction vessel, but a split and mix synthesis produces a mixture of compounds in each reaction vessel. This reduces the number of vessels needed per number of compounds, making it possible to prepare millions of compounds for a library. Split and mix synthesis has several complications compared to parallel synthesis; for example, it is difficult to keep track of the compounds in a given vessel. Furthermore, deconvolution of the mixture to identify the active component(s) of a mixture is also difficult and time-consuming.

The rate of discovery of new drugs has been accelerated greatly, almost beyond belief, by these new chemical technologies. Thus, combinatorial chemistry should increase cross-disciplinary research and already has started an exciting era in the discovery of new drugs.

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CHAPTER 29

Fundamentals of Medical Radionuclides

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For years the alchemist sought the secret of *transmutation* without success. Today, this nuclear process—converting one element into another—is commonplace, but the knowledge of nuclear processes is of recent origin. It was not until 1896 that Becquerel observed the fogging of his photographic plates by a uranium salt. His observation aroused the curiosity of the Curies concerning the uranium ore, pitchblende, from which they isolated the elements polonium and radium. Research over the next few years by the Curies, Becquerel, Schmidt, Debierne, and others soon resulted in the discovery and isolation of still other new elements from uranium and thorium ores. These elements, too, were found to fog photographic plates.

It was known that the fogging of photographic plates was caused by some sort of radiation. By 1899 Rutherford concluded that this radiation was of two types, which he called *alpha* and *beta*. The next year Pierre Curie and Villard observed a third, very penetrating, type of radiation, which they called *gamma*.

The *theory of radioactive disintegration* was proposed by Rutherford and Soddy in 1903. They suggested that atoms of radioactive elements undergo spontaneous emission of alpha and beta particles with the formation of atoms of a new element. These deductions were amazing when one considers the status of atomic knowledge of that day.

The *electron*, later found to be physically identical with the beta particle, had been discovered by Thomson in 1897. In 1909 Rutherford and Royds identified the alpha particle as a helium nucleus; in 1911, data on alpha particle scattering provided the evidence needed for Rutherford to propose the *nuclear theory* of the atom, that the positive charge of an atom is concentrated in a centrally located *nucleus* rather than being interspersed with the negatively charged electrons.

Two years later, Bohr published his theory of atomic structure, based upon Rutherford's nuclear theory and the quantum theory of Planck. The same year (1913) Soddy proposed the name *isotope* (from the Greek, for "same place"). Aston had just separated two isotopes of neon by fractional diffusion in confirmation of Thomson's discovery of these two forms of neon in 1912.

Rutherford was the foremost nuclear scientist of his time. In 1919 it was he who first observed and identified *transmutation* of one element into another. It was achieved by bombarding nitrogen with alpha particles. In the process, the nitrogen was converted into an isotope of oxygen with a mass of 17. Rutherford died in 1937 believing that nuclear power would never be achieved. This was achieved only 5 years later when Fermi built the first nuclear reactor in Chicago.

Constructive research on the nucleus of the atom has resulted not only in the means to harness this tremendous power for the production of electricity and other forms of useful energy, but also has provided scientists with more than 2500 different species of atoms. These find innumerable applications in industry, medicine, pharmacy, agriculture, and other disciplines where the atom is used for the benefit of humanity.

The purpose of this chapter is to review some fundamental properties of radionuclides, including their nature and source, and methods for their detection and measurement. This basic information should facilitate a better understanding of how and when they can be applied to the disciplines of medicine and pharmacy.

APPLICATIONS OF RADIONUCLIDES IN MEDICINE AND PHARMACY

Radium has the distinction of being the first radionuclide used in medicine, employed as early as 1901. This nuclide was the most important medical radionuclide in use up to about 1946 when artificially produced radionuclides became available in quantity. Since that date, growth in the medical applications of radionuclides has been very rapid as their usefulness has become more and more apparent in medical diagnosis, therapy, and research and as greater numbers of physicians and other scientific personnel have been trained in their use. Current medical procedures employ more than 50 radionuclides in a wide variety of chemical and physical forms.

Other than for basic research, radionuclides are used in medicine and pharmacy in two different ways: as (1) sealed radiation sources or (2) radiopharmaceuticals.

As sealed radiation sources, their principal roles are in (1) therapy and (2) calibration of radiation detection instrumentation. For therapy, the choice of the radionuclide for a given application is governed largely by the properties of the radiation required for treatment; the type and energy of the radiation and range in tissues are prime considerations. For therapeutic applications, the radiation sources are either (1) externally beamed into cancerous tissue (teletherapy) or (2) implanted in the form of seeds, wires, or ribbons (or other physical forms) within, or in proximity to, cancerous tissue for specified periods of time (brachytherapy). For these purposes the chemical properties or chemical form of the radionuclide are relatively unimportant. Likewise, for calibration purposes, the nature of the radiation emitted is usually pertinent whereas the chemical properties are not.

A *radiopharmaceutical* is a preparation, intended for in vivo use, that contains a radionuclide in the form of a simple salt or a complex. It may exist as a solid, liquid, gas, or pseudogas. The chemical and physical identity and form of a radiopharmaceutical is very important because in each case, once administered, the radiopharmaceutical is intended to target certain tissues, binding sites, and/or biochemical pathways. Depending on its specific physicochemical and radiation properties, a radiopharmaceutical can be used for either diag-

nostic or therapeutic purposes, and in a few cases for both. For diagnostic applications, a radiopharmaceutical should not be pharmacologically active in that it should not produce a physiologic effect. It is administered in extremely small (tracer) quantities so that it does not alter the physiologic or pathophysiologic process which is being measured. The nature of the radiation emitted by a diagnostic radiopharmaceutical is important primarily for its ease of detection (ie, to obtain an image or other diagnostic data). On the other hand, for a therapeutic radiopharmaceutical, the type and energy of the radiation as well as its range in tissues are very important considerations, as was the case with sealed sources used for therapy. A radiopharmaceutical preparation designed for therapeutic purposes must contain enough radioactivity to produce the intended tissue effects.

The development, evaluation, preparation, testing, and clinical use of radiopharmaceuticals have led to the introduction of the specialty disciplines known as *nuclear medicine* and *nuclear pharmacy*. In the US alone, practitioners in these specialties are responsible for the care of approximately 40,000 to 50,000 patients each day on average.

RADIOACTIVITY AND RADIATION

Radioactivity is defined as the phenomenon by which one nuclide is spontaneously transformed into another nuclide with the emission of energy in the form of radiation. Therefore, a nuclide that undergoes a spontaneous nuclear reaction is said to be *radioactive*. Such elements are radioactive because the configuration of protons and neutrons in the nucleus produces an unstable structure. During the process of spontaneous transformation (*decay*) the ratio of neutrons to protons changes. After one or more decay processes, a stable nucleus is formed. Because of its special importance in nuclear pharmacy and nuclear medicine, radioactive decay is discussed in detail in a subsequent section. There are several types of radiation that may be emitted from radionuclides, each of which has found usefulness in some medical application.

RADIATION FROM RADIOACTIVE NUCLEI

Three types of radiation are emitted most frequently from radioactive nuclei: alpha, beta, and gamma.

Alpha particles, which constitute alpha radiation, are compound particles consisting of two protons and two neutrons. The alpha particle is identical with the helium nucleus—that is, a helium atom, less two orbital electrons. As an alpha particle loses energy, its velocity decreases. It then attracts electrons to its *K-shell* and becomes an ordinary helium atom. The range of alpha particles in air is about 5 cm; the range in tissue is less than 100 μm in tissue.

Beta radiation exists as two types because there are two kinds of electrons, the *negative electron* (or *negatron*), and the *positive electron* (or *positron*). The positron is identical with the negatron in all respects except for its charge of +1 instead of −1. The positron also is known as the *antiparticle* of the electron. When these electrons are emitted from radioactive nuclei, they are called *beta particles*. That is, the two particles β− and β+ are the same as e− and e+, respectively, except for their origin. Beta particles may have a range of over 3 m in air and up to about 1 mm in tissue (or more), depending on the specific energy of the beta particle.

Because alpha and beta particles release large amounts of energy over a short distance (*path*), they are locally destructive to tissue. As a result, radionuclides that emit these particles are useful as therapeutic agents if deposited internally or placed strategically in proximity to lesions (eg, therapeutic radiopharmaceuticals or sources for brachytherapy). To date, beta-emitting radionuclides have been used more commonly than alpha-emitters in medicine, although several radiopharmaceuticals containing the latter are currently under investigation.

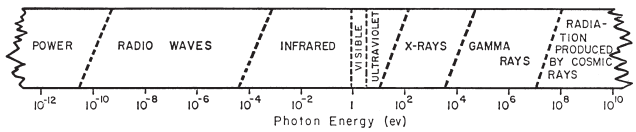

Figure 29-1. Electromagnetic spectrum.

Gamma radiation is different from alpha and beta radiation. Gamma radiation is electromagnetic, whereas alpha and beta radiation are particulate. Gamma rays are radiated as photons or quanta of energy at a velocity c of 3.0×10^{12} m/sec. They are often emitted as a result of *nuclear deexcitation,* which is required when nuclei produced in nuclear reactions are in an *excited state* rather than in the *ground state*. When excited, nucleons occupy high-energy quantum levels. They tend to lose excess energy, returning to the ground quantum state by *gamma ray emission.* Gamma radiation differs from X-rays, ultraviolet rays, and visible light only in wavelength (or frequency), as illustrated in Figure 29-1.

Gamma rays are the most penetrating of all types of radiation emitted by radionuclides (except neutrinos) and can pass easily through more than 25 cm of tissue or several centimeters of lead, again depending on the specific energy of the gamma ray. Radiotracers typically contain radionuclides that emit gamma rays. Gamma-emitting radionuclides are particularly useful for diagnostic radiopharmaceuticals; once the radiopharmaceutical has distributed within the body, the photons can penetrate the tissues and be detected externally using specially designed imaging equipment.

EXTRANUCLEAR RADIATION

There is a certain probability that, instead of emitting a gamma ray during nuclear deexcitation, the excited nucleus may transfer its excitation energy to an electron in an electron shell of its own atom. In this case, the electron is ejected from its shell provided that the excitation energy exceeds the electron binding energy. The ejected electron is called a *conversion* electron, and this entire process is referred to as *internal conversion*. When an electron is emitted from its electron shell, the vacancy will be filled with an electron from a more distant orbital shell. The energy difference between the two shells will be emitted as an x-ray. Because this process may result in multiple electron shell vacancies, a cascade effect may induce the emission of multiple x-rays.

Atomic deexcitation is a process that of necessity must follow any change in the identity of a nucleus. The daughter produced in a radioactive decay process is a different element. Orbital electrons find themselves in excited states and proceed to lose energy, either as *fluorescence* radiation or as *Auger electrons*, until a stable configuration is achieved.

Conversion electrons and Auger electrons are particulate radiation and thus are useful for therapeutic applications; x-rays are electromagnetic radiation, and hence are more applicable to radiotracer methodologies.

THE ATOM

To better understand the concepts of radioactivity and radiation, it is helpful to review selected properties of the atom.

ATOMIC STRUCTURE

A neutral atom consists of a positively charged nucleus (composed of protons and neutrons) with which orbital electrons are associated. The number of orbital electrons is equal to the number of protons in the nucleus, and the number of protons in the nucleus defines the *atomic number*, Z. The *neutron number*, N,

is the number of neutrons in the nucleus, and the *mass number*, A, is equal to the sum of the protons and neutrons. Thus, $A = Z + N$.

The radius of an atom is approximately 10^{-10} m or 1 Å. The nucleus is roughly 1/100,000 the size of the atom. For example, the radius of the oxygen nucleus is about 3×10^{-15} m and that of the lead nucleus is about 7×10^{-15} m. To gain some appreciation of the smallness of the nucleus, let us suppose that the oxygen nucleus is magnified until it appears to be the size of a golf ball. The golf ball, similarly magnified, would appear to have a diameter of about 100 million miles, or roughly the distance from the earth to the sun.

Atoms are quite *empty*. The nucleus and orbital electrons occupy but a very small fraction of space in matter. Further, most of the mass of matter is concentrated in the nucleus, which has a density of 2.4×10^{14} g/mL. For example, 1 mL of the substance of which nuclei are made would weigh over 200 million tons. It is with this very unusual material of the nucleus that we are concerned in nuclear reactions and radioactivity.

NUCLIDES AND ISOTOPES

In 1912, Thomson developed an analytical process known as *positive ray analysis* by which he could measure the mass of particles such as atoms. When he attempted to determine the mass of the neon atom, two lines appeared on the screen of his apparatus, indicating two types of neon atoms having masses of 20 and 22, respectively. Using a process that would be the forerunner of mass spectrometry, Thomson demonstrated the existence of nuclei possessing the same number of protons (and, hence, of the same chemical element) but a different number of neutrons (and, hence, of different mass). Soddy later called these *isotopes*.

The atomic number, Z, of neon is 10. From the relationship $A = Z + N$, we can deduce that the difference between these two forms of neon lies in the number of neutrons, N, in the nucleus:

$$A = 20 = 10 + N \therefore N = 10$$

$$A = 22 = 10 + N \therefore N = 12$$

Today, at least eight isotopes of neon are known. These are illustrated in Figure 29-2.

Isotopes are species of nuclides that possess the same number of protons but a different number of neutrons. That is, isotopes are nuclides of the same chemical element and, therefore, have the same chemical properties but differ in mass. They also may differ in stability. Certain mass numbers may represent stable nuclei, whereas other mass numbers may represent radioactive nuclei. A *nuclide* is any one of the more than about 2500 known species of atoms characterized by the number of protons and the number of neutrons in the nucleus. Nuclides that have the same mass are called *isobars*. Nuclides which possess the same number of neutrons are called *isotones*. The nuclides illustrated in Figure 29-3—^{1}H, ^{2}H (deuterium), and ^{3}H (tritium)—are isotopes; ^{3}He and ^{4}He are isotopes also. On the other hand, ^{3}H and ^{3}He are isobars, and ^{3}H and ^{4}He are isotones.

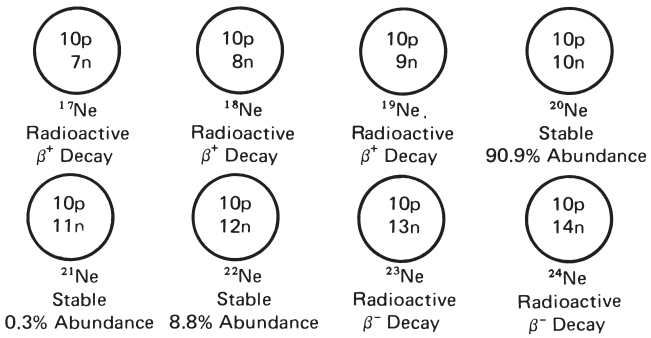

Figure 29-2. Isotopes of neon.

NUCLEAR NOTATION

In writing the symbol for a nuclide, the atomic number is written as a subscript preceding the symbol for the element, and the mass number is written as a superscript. Thus, the symbol $_{7}{}^{14}$N describes the nitrogen nucleus whose atomic number, Z, is 7 and whose mass, A, is 14.

$$^{A}_{Z}X_{N}$$

NUCLEAR EQUATIONS

A nuclear equation is a representation of a nuclear reaction. A nuclear reaction occurs when there is a change in the configuration of the nucleus of an atom. Nuclear reactions may occur spontaneously, as occurs during the decay of radionuclides; or they may be induced, as occurs during the production of artificial radionuclides. The nuclear equation expressing the first artificial transmutation observed by Rutherford is expressed by the notation:

$$^{14}_{7}N + {}^{4}_{2}He \rightarrow {}^{1}_{1}H + {}^{17}_{8}O$$

In this reaction, nitrogen of mass 14 is bombarded with a helium nucleus of mass 4 (ie, an alpha particle) to produce oxygen of mass 17 and a proton.

It will be noted that nuclear equations must balance. The sum of the masses on the left (14 + 4 = 18) must equal the sum of the masses on the right (1 + 17 = 18). Also, the sum of the atomic numbers on the left (7 + 2 = 9) must equal the sum of the atomic numbers on the right (1 + 8 = 9). This same nuclear reaction also may be represented by a *shorthand* notation:

$$^{14}N(\alpha, p)^{17}O$$

Target Nuclide (In, Out) Product Nuclide

RADIOACTIVE DECAY

STATISTICS

As stated previously, unstable nuclei that undergo a spontaneous nuclear reaction are said to be radioactive. If a single radioactive atom could be separated for observation, there would be no way to predict at which moment the decay of its nucleus would occur. If, however, a large number of similar radioactive atoms is considered, it becomes possible to predict how many will decay within a certain interval of time. This problem can be understood if a comparison is made to the similar situation existing with life insurance. Although the insuring company cannot predict when a particular policy holder will die, the fraction of a large group of policy holders who will die within a given time interval can be predicted. The larger the group considered, the more accurate the prediction. Such is the case with nuclei—the greater the number of nuclei considered, the more accurate the measurement of decay rate.

The need to recognize the influence of random decay upon analytical results is extremely important. When radioactivity is measured, the value μ, the true count, is required. Because radioactive decay is random, μ cannot be measured. It is expected that replicate measurements of count n_i of the same sample will give a range of values on either side of μ. The best estimate of μ is given by the average:

$$n = \sum_i n_i/N$$

where N is the number of replicate observations. The precision with which the decay rate can be measured is expressed by the standard deviation σ, which is a measure of the spread of data

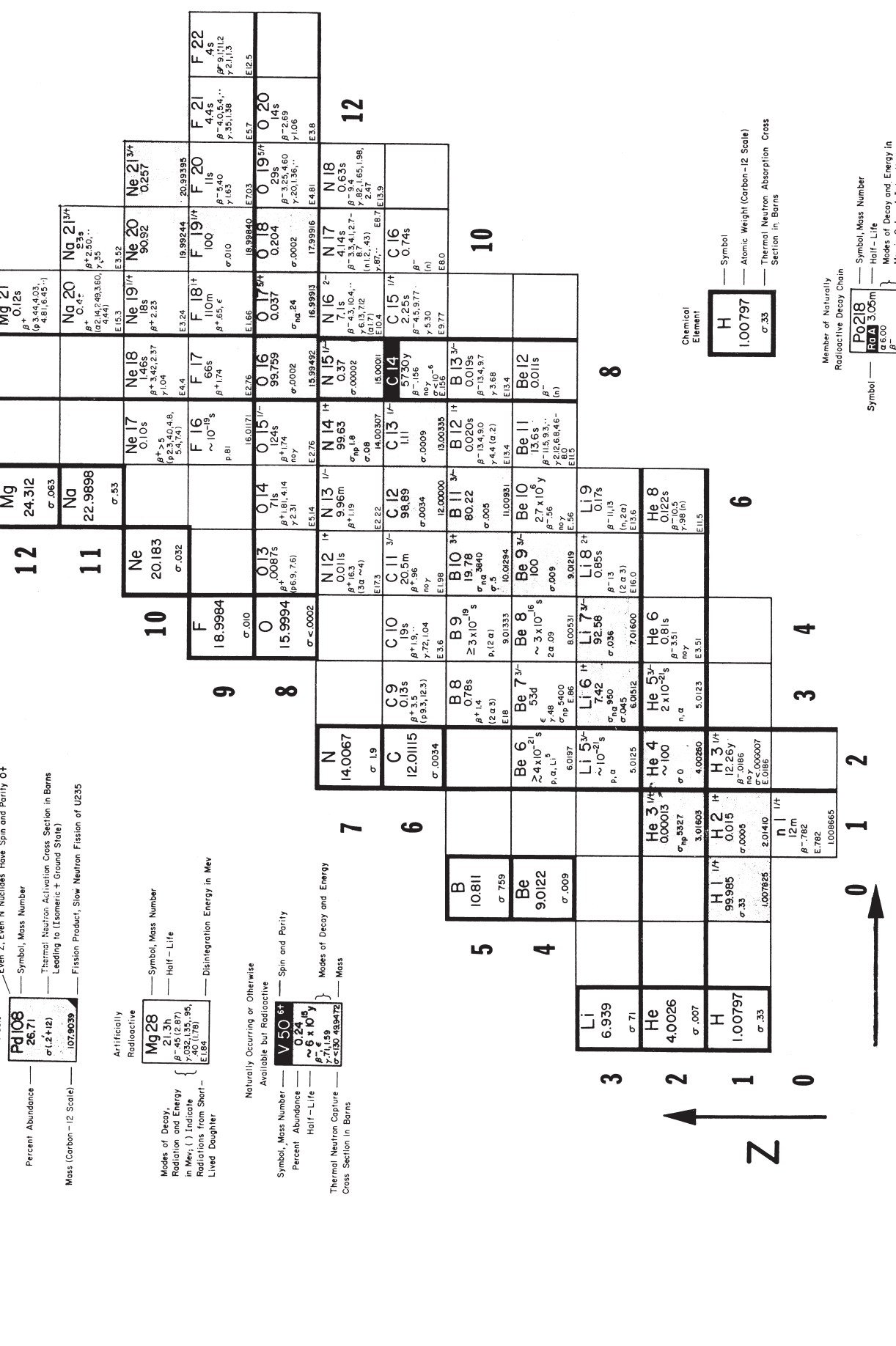

Figure 29-3. Chart of the nuclides—to mass number 21. Known nuclides now number about 2500 (courtesy, General Electric).

Table 29-1.

IF THE TOTAL NUMBER OF DECAYING ATOMS OBSERVED IS n THERE IS A 68% CHANCE THAT THE ERROR WILL BE LESS THAN $\sigma = \sqrt{n}$ OR A 68% CHANCE THAT THE OBSERVED VALUE IS IN ERROR BY NO MORE THAN $100\ \sigma/n$ %

n	σ	$100\ \sigma/n$%
50	7.07	14.14%
100	10.00	10.00%
500	22.36	4.47%
1000	31.62	3.16%
5000	70.71	1.41%
10000	100.00	1.00%
50000	223.60	0.44%

on either side of the mean. For radioactive decay, an estimate of σ is given by $\sqrt{n}$. There is a 68% chance that a particular measurement will fall within the range $n \pm \sigma$. About one-third of the observations result in values of n lying outside the range $n \pm \sigma$. The significance is illustrated by the statistical analysis in Table 29-1 and the normal probability curve depicted (refer to Chapter 12).

Assume that a radioactive sample is decaying at the rate of exactly 500 atoms per minute. If the number of decaying atoms during each of 100 different 1 minute intervals were measured, for 68 of these intervals the data would lie between $500 \pm \sqrt{500}$, or between 478 and 522. Data for the other 32% of the measurements will fall either below 478 or above 522, or greater than one standard deviation from the mean. Such variations, if truly of a statistical nature, should not be interpreted as indicating faulty equipment, faulty technique, or inaccurately calibrated samples. An increase in counting time to record a greater number of decay processes will result in an increase in counting accuracy.

When radionuclides are used in analytical procedures, the overall error in the measurement is due not only to random decay but also to instrument error, pipetting, weighing, and other procedural errors. The overall error can be estimated in terms of the sample standard deviation, s, where:

$$s = \sqrt{\frac{\sum_i (n_i - \bar{n})^2}{N - 1}}$$

If the only source of error is that due to random decay, the value of s should approach σ as N, the number of observations, approaches infinity.

KINETICS OF DECAY

Decay rate is the time rate at which atoms undergo radioactive disintegration. It is expressed by $-dN/dt$, where $-dN$ is the change in the number of atoms N, and dt is the change in the time t. The negative sign indicates merely that the number of atoms is decreasing in time. The rate of decay ($-dN/dt$) is proportional to the number of atoms N, present at any time t. Therefore, the rate of decay is expressed as:

$$-dN/dt = \lambda N$$

where λ is a proportionality constant usually called the *decay constant*. The decay of radioactive atoms, therefore, is a first-order reaction.

Integration of the equation above results in the useful relation:

$$\ln N_t/N_0 = -\lambda t$$

where N_0 is the number of atoms present at zero-time and N_t is the number of atoms present at time t. This relationship sometimes is used more conveniently in the exponential form, the "Common Radioactive Decay Equation":

$$N_t = N_0\, e^{-\lambda t}$$

which is illustrated graphically in Figure 29-4.

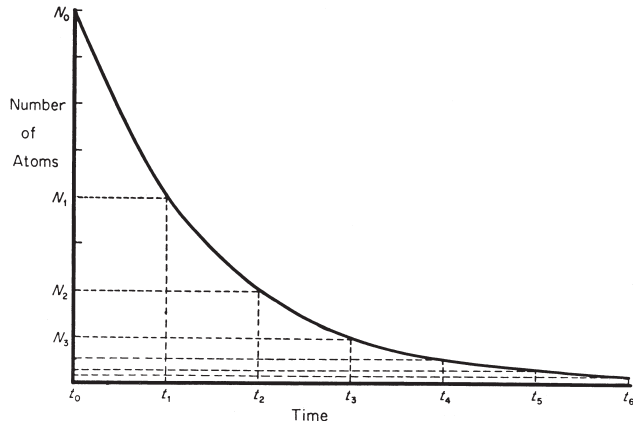

Figure 29-4. Energy-level diagram for the decay of phosphorus-32.

The rate of decay, $-dN/dt$, sometimes called the *activity,* is represented by the symbol A. Because the activity A is proportional to the number of atoms N, the following useful relationships also can be derived:

$$A = \lambda N$$

$$\ln A_t/A_0 = -\lambda t \quad \text{or} \quad A_t = A_0\, e^{-\lambda t}$$

or

$$\ln A_t = \ln A_0 - \lambda t$$

The last relationship is shown in Figure 29-5.

The *absolute activity* usually is expressed as disintegrations per sec (*d/s* or *dps*) or disintegrations per minute (*d/m* or *dpm*). The *observed activity*, which is less than the absolute activity by a factor equal to the efficiency of the counting system, is expressed in counts per second (*c/s* or *cps*) or in counts per minute (*c/m* or *cpm*).

The *half-life* of a radioactive species is the time required for one-half of a given number of atoms to decay. The half-life, $t_{1/2}$, is related to the disintegration constant, λ, by

$$t_{1/2} = 0.693/\lambda$$

where $0.693 = \ln 2$.

Consecutive, *sequential,* or *series decay* results when a parent nuclide A decays to produce a radioactive *daughter* or *progeny* B, which, in turn, decays to C:

$$A\ \lambda_A \rightarrow B\ \lambda_B \rightarrow C$$

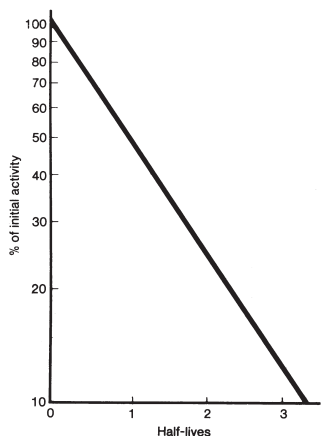

Figure 29-5. Radioactive decay curve.

If only atoms of A are present initially, the number of atoms of B present at time t is given by:

$$N_B = \lambda_A / \lambda_B - \lambda_A N_{Ao} (e^{-\lambda At} - e^{-\lambda Bt})$$

Of particular interest in nuclear medicine are combinations where the parent radionuclide has a relatively long half-life and the daughter radionuclide a short half-life, for example:

$$^{99}\text{Mo } 67 \text{ h} \rightarrow {}^{99m}\text{Tc } 6.0 \text{ h} \rightarrow {}^{99}\text{Tc}$$

After a time equal to many half-lives of the daughter, a state of *secular equilibrium* or *transient equilibrium* is achieved. At this time, *in-growth* of the daughter has reached a maximum. This process of series decay is used in *radionuclide generators* as a source of short-lived radionuclides. This topic is discussed further in the section on production of radionuclides.

UNITS OF RADIOACTIVITY

One gram of radium was selected as the unit of radioactivity and was called the *curie*. It has been extremely difficult to measure the absolute decay rate (dps) of a curie of radium, although the average of many measurements, using a variety of methods, is approximately 3.7×10^{10} dps. In view of these discrepancies, the International Radium Standards Commission has recommended the use of the arbitrary value of exactly 3.7×10^{10} until the third significant figure is agreed upon. Although originally defined in terms of radium, the curie has been used as a standard for the disintegration rate of any radionuclide. For example, 1 curie of carbon-14 means that amount of carbon-14 necessary to provide 3.7×10^{10} dps. Despite its continued use on a limited basis in the US, the curie has generally been replaced by the *becquerel,* Bq, named for Henri Becquerel, which is equal to an activity of one disintegrating atom per second (Table 29-2).

MODES OF RADIOACTIVE DECAY

When it is necessary to measure the absolute decay rate of a particular nuclear species, one must establish its mode of decay, or *decay scheme*, in order to determine the relationship of the number of particles or gamma rays emitted to the number of atoms actually undergoing decay. There are several important modes of decay.

Alpha decay is illustrated by the decay of polonium-210 to lead-206:

$$^{210}_{84}\text{Po} \rightarrow {}^{4}_{2}\text{He} + {}^{206}_{82}\text{Pb}$$

In this example, the nucleus of lead-206, which contains 82 protons and 124 neutrons, is stable and does not undergo further decay. The majority of nuclides that undergo alpha decay have atomic numbers greater than 82.

There are three types of *isobaric decay: negatron emission*, *positron emission,* and *electron capture*. If the ratio of neutrons to protons is too *high* for stability, a nucleus may decay by negatron emission (negatron decay). Decay by negatron emission is illustrated by the decay of phosphorus-32 to sulfur-32 (Fig 29-6):

$$^{32}_{15}\text{P} \rightarrow {}^{32}_{16}\text{S} + \beta^- + \nu$$

Note that the atomic number of the *daughter*, sulfur-32, is greater than that of the *parent*, phosphorus-32. In this process

Table 29-2. Becquerel Units

UNITS	SYMBOL	RADIOACTIVITY(dps)	CURIE EQUIVALENT
Becquerel	Bq	1	2.7×10^{-11} Ci
Kilobecquerel	kBq	10^3	2.7×10^{-8} Ci
Megabecquerel	MBq	10^6	2.7×10^{-5} Ci
Gigabecquerel	GBq	10^9	2.7×10^{-2} Ci
Terabecquerel	TBq	10^{12}	27 Ci

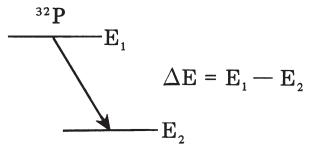

Figure 29-6. Energy level diagram.

a proton has been produced, but because a neutron has been consumed, there is no change in the mass number and thus the reaction is isobaric. This is explained by the *particle reaction:*

$$^{1}_{0}\text{n} \rightarrow {}^{1}_{1}\text{p} + \text{e}^- + \nu$$

which shows the decay of a neutron into a proton, a negative electron and a neutrino.

The beta particles emitted during the decay of a given radioactive species do not all possess the same energy but are emitted with a continuous energy distribution extending from zero to a specific maximum value, E_{max}. This posed an enigma for some time. The decay of phosphorus-32 of energy E_1 to sulfur-32 of energy E_2 should be associated with the release of energy equal to ΔE, where $\Delta E = E_1 - E_2$ (see Fig 29-6). A new particle, the *neutrino*, was postulated to explain the energy change not associated with the beta particle. Thus, the sum of the energies of the beta particle and its associated neutrino is equal to ΔE or E_{max} (Fig 29-7). Moreover, the average energy of a beta particle is equal to 1/3 E_{max}.

If the ratio of neutrons to protons is too *low* for stability, a nucleus may decay by *positron emission* (ie, *positron decay*):

$$^{11}_{6}\text{C} \rightarrow {}^{11}_{5}\text{B} + \beta^+ + \nu$$

In this instance the particle reaction that illustrates the change is:

$$^{1}_{1}\text{p} \rightarrow {}^{1}_{0}\text{n} + \text{e}^+ + \nu$$

Again, no change in mass number occurs (ie, the reaction is isobaric), since the decay of ^{11}C to ^{11}B is accompanied by the change of a proton into a neutron. The energies of the positrons extend from zero to E_{max} in a manner analogous to the energy distribution of negative beta particles because the neutrino is required to account for the balance of the energy.

An alternative to positron emission for increasing the neutron-to-proton ratio to a more stable condition is a process known as *electron capture*. In this process, an orbital electron is captured by the nucleus. An example is the decay of ^{201}Tl to ^{201}Hg:

$$^{201}_{81}\text{Tl} + \text{e}^- \text{(K)} \rightarrow {}^{201}_{80}\text{Hg}$$

The corresponding particle reaction is:

$$\text{e}^- + {}^{1}_{1}\text{p} \rightarrow {}^{1}_{0}\text{n}$$

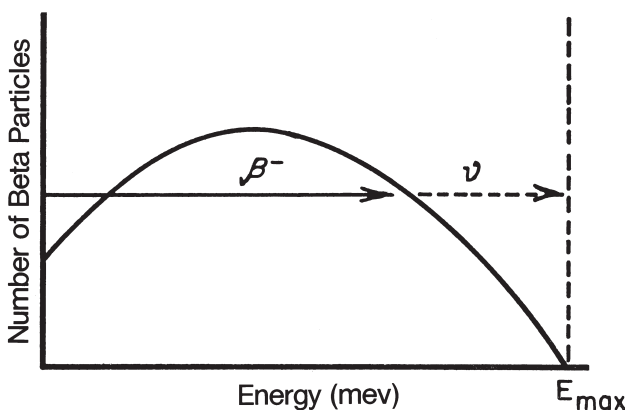

Figure 29-7. Typical beta spectrum.

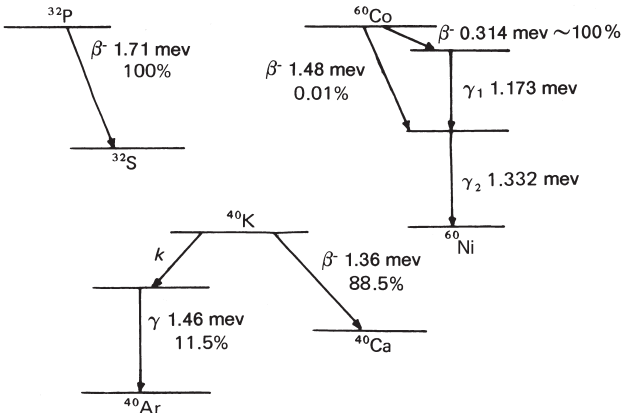

Figure 29-8. Modes of decay. Radioactive atoms may decay by any one of numerous processes. Negatron decay is shown by an arrow slanting to the right, electron or K-capture by an arrow slanting to the left and gamma emission by a vertical arrow.

Electron capture also has been called *K-capture* because the electron captured in the process is usually from the *K* shell. However, the electron may also come from the *L* or *M* shell.

The mode of decay is often represented by an energy-level diagram (Fig 29-8). Three different modes of decay are illustrated. The first is the simple beta decay of phosphorus-32. In this instance, each decaying atom of ^{32}P emits one beta particle. Thus, if the number of beta particles is measured, the number of decaying atoms also is known. The decay of an atom of cobalt-60 also results essentially in the emission of a single beta particle, but two gamma rays are also emitted. Thus, if the decay rate is measured by counting the number of beta particles emitted, a 1:1 ratio exists. If, on the other hand, the decay rate is determined from the number of gamma rays emitted, it must be remembered that the number of decaying atoms is equal to only one-half the number of gamma rays (neglecting a small correction for internal conversion). In the third example, the decay of ^{40}K results in the emission of beta particles in 88.5% of decay events. The other 11.5% of decay events are by electron capture. Thus, a microcurie of ^{40}K does not emit 3.7×10^4 beta particles per second, but only $0.885 \times 3.7 \times 10^4$ beta particles. Decay schemes for several radionuclides used in medicine are shown in Figure 29-9.

PRODUCTION OF RADIONUCLIDES

Most, if not all, radionuclides used in medicine and pharmacy are produced artificially. Table 29-3 is a compilation of medical radionuclides along with their physical properties. These radionuclides are produced by three general methods: (1) in a nuclear reactor as a fission by-product, (2) as the product of a neutron reaction—either by activation or transmutation, and (3) by use of a particle accelerator such as a cyclotron.

FISSION BY-PRODUCTS

Fission is a radioactive process in which a relatively heavy nucleus is divided into two new nuclei of nearly equal size with the simultaneous emission of two or three neutrons. Fission may be spontaneous, but normally the reaction is induced by bombardment of the parent nucleus with a neutron:

$$^{235}_{92}\text{U} + {}^{1}_{0}\text{n} \rightarrow X + Y + 2.5\ \text{n}$$

where *X* and *Y* are fission products (new nuclei) with a Z value of between 30 and 65 and a sum of 92. Fission reactions may be self-sustaining. For each neutron consumed, an average of 2.5 new neutrons are produced that may initiate the fission of other nuclei. Such a reaction is called a *chain reaction*. If at least one of the 2.5 neutrons produced is used to sustain the reaction, the reaction is said to be *critical*.

The following illustrates one of many combinations of fission reactions that are possible:

$$^{238}_{92}\text{U} + {}^{1}_{0}\text{n} \rightarrow {}^{131}_{50}\text{Sn} + {}^{106}_{42}\text{Mo} + {}^{1}_{0}\text{n} + {}^{1}_{0}\text{n}$$

The ^{131}Sn and the ^{106}Mo are very radioactive and have very short half-lives. They immediately decay by a series of beta decay processes:

$$^{131}_{50}\text{Sn} \rightarrow {}^{131}_{51}\text{Sb} \rightarrow {}^{131}_{52}\text{Te} \rightarrow {}^{131}_{53}\text{I}$$

$$^{106}_{46}\text{Mo} \rightarrow {}^{106}_{43}\text{Tc} \rightarrow {}^{106}_{44}\text{Ru} \rightarrow {}^{106}_{45}\text{Rh}$$

Both ^{131}I and ^{106}Ru are available commercially as fission-produced radionuclides, although ^{106}Ru is not routinely used for medical applications.

Before use, the desired nuclide must be chemically separated from a large number of other fission-produced radionuclides. For many of the radionuclides produced by fission, separation of the desired nuclide from the mixture of fission products is too difficult or costly.

NEUTRON REACTIONS

Many radioactive nuclides used in radiopharmaceuticals are prepared by neutron activation (n, γ) or transmutation (n, p) reactions by placing a suitable target material in a nuclear reactor where it is bombarded by neutrons. By means of (n, γ) and (n, p) reactions, reactors produce radionuclides having a high neutron-to-proton ratio that typically decay by emission of a negatron. For example, radioactive phosphorus (^{32}P) can be prepared from stable phosphorus (^{31}P) by *neutron capture:*

$$^{31}_{15}\text{P} + {}^{1}_{0}\text{n} \rightarrow {}^{32}_{15}\text{P} + \gamma$$

The disadvantage of this method is that the radioactive phosphorus (^{32}P) is highly diluted with stable ^{31}P. Phosphorus-32 of low specific activity can be used for certain purposes, such as the investigation of phosphate fertilizers, but would be less useful for many biological and medical applications.

Radioactive phosphorus can be made by transmutation if high specific activities are required:

$$^{32}_{16}\text{S} + {}^{1}_{0}\text{n} \rightarrow {}^{32}_{15}\text{P} + {}^{1}_{1}\text{p}$$

In this case, the radioactive phosphorus can be separated from the unreacted sulfur by chemical procedures. Where ^{32}P is made from ^{31}P, such chemical separations are not practical.

Transmutation is useful for the preparation of many radioactive nuclides, especially those of low atomic number. As the atomic number increases, (n, γ) reactions are favored over (n, p) reactions. For example, cobalt-60 is produced by the reaction ^{59}Co(n, γ)^{60}Co because the reaction ^{60}Ni(n, p)^{60}Co does not occur with sufficient frequency to make the process commercially feasible.

^{125}I($t_{1/2}$ = 60 d) is produced from ^{124}Xe:

$$^{124}\text{Xe(n, }\gamma)^{125}\text{Xe EC} \rightarrow {}^{125}\text{I}$$

Secondary neutron capture results in the side reaction ^{125}I(n, γ)^{126}I. Because ^{126}I($t_{1/2}$ = 14 d) is an undesirable impurity in ^{125}I, it is removed through its own decay.

CYCLOTRON-PRODUCED RADIONUCLIDES

Certain radionuclides are cyclotron-produced. The cyclotron and similar *particle accelerators* can be used only with charged particles such as electrons, protons, alpha particles, or deuterons because the operation of such machines depends upon the interaction of magnetic and/or electrostatic fields with

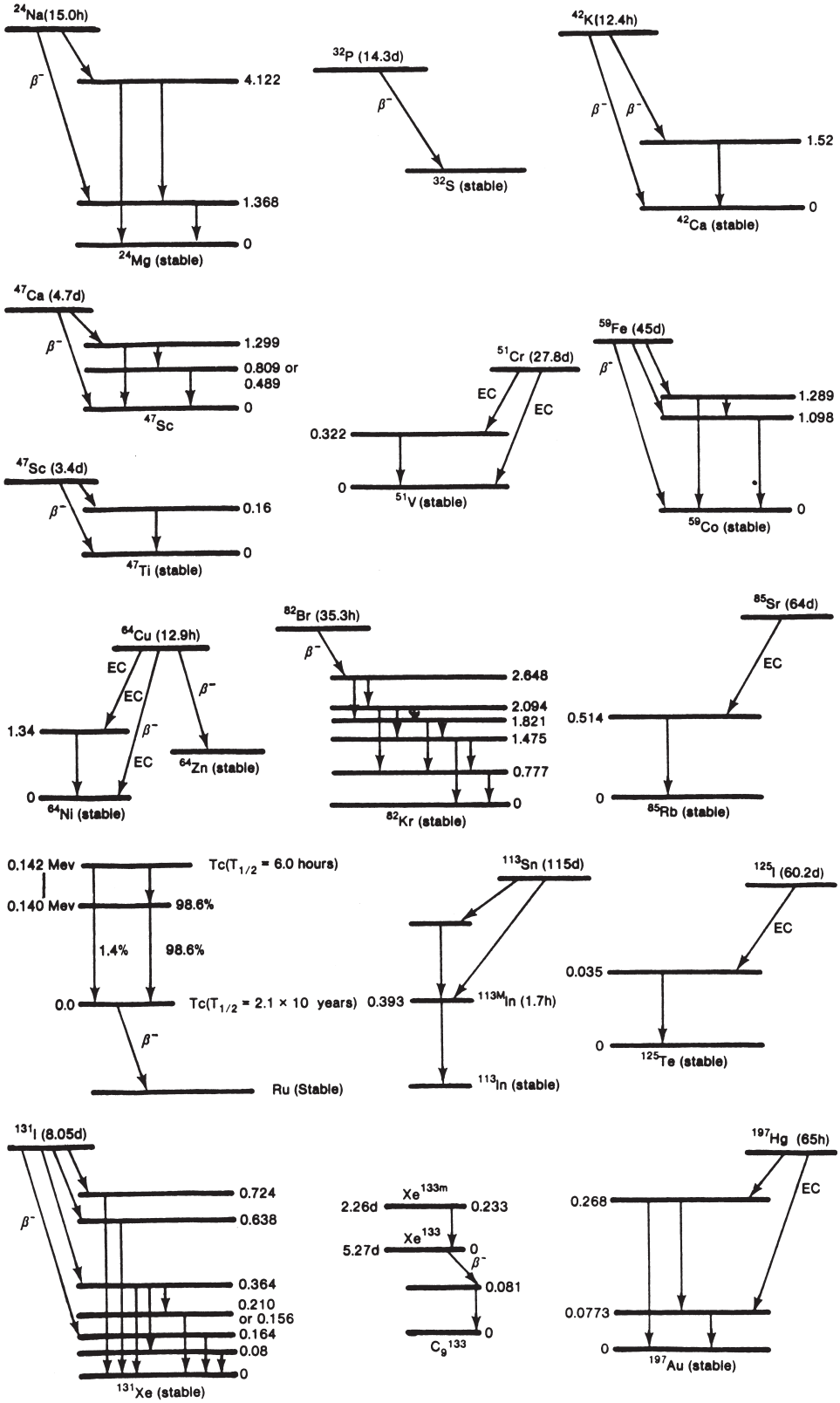

Figure 29-9. Decay schemes for nuclides commonly used in medicine.

Table 29-3. Physical Characteristics of Radionuclides Commonly Used in Medicine

NUCLIDE COMMON PRODUCTION	HALF-LIFE	DECAY MODE PRINCIPLE	EMISSIONS (MeV)	GAMMA RAY CONSTANT	R/mCi-HOUR AT 1 cm
^{11}C	$^{14}N(p, \alpha)^{11}C$	20.4 minutes	β^+	0.97 β^+ (100%) 0.511 γ (200%)	5.9
^{13}N	$^{16}O(p, \alpha)^{13}N$	10.0 minutes	β^+	1.2 β^+ (100%) 0.511 γ (200%)	5.9
^{14}C	$^{14}N(n, p)^{14}C$	5730 years	β^-	0.156 β^- (100%)	
^{15}O	$^{14}N(d, n)^{15}O$	2.05 months	β^+	1.74 β^+ (100%) 0.511 γ (200%)	5.9
^{18}F	$^{18}O(p, n)^{18}F$	110 minutes	β^+, EC	0.635 β^+ (97%) 0.511 γ (194%)	5.7
^{32}P	$^{31}S(n, p)^{32}P$	14.3 days	β^-	1.71 β^- (100%)	
^{51}Cr	$^{50}Cr(n, \gamma)^{51}Cr$	27.8 days	EC	0.320 γ (9%)	0.18
^{57}Co	$^{56}Fe(p, \gamma)^{57}Co$	271 days	EC	0.014 γ (9%) 0.122 γ (86%) 0.136 γ (10%)	0.57
^{60}Co	$^{59}Co(n, \gamma)^{60}Co$	5.27 years	β^-	0.31 β^- (99%) 1.173 γ (100%) 1.332 γ (100%)	13.2
^{67}Ga	$^{68}Zn(p, 2n)^{67}Ga$	78.3 hours	EC	0.093 γ (38%) 0.184 γ (20%) 0.300 γ (16%) 0.394 γ (5%)	1.6
^{68}Ga	^{68}Ge daughter	68.3 minutes	β^+, EC	1.9 β^+ (88%) 0.511 γ (176%)	5.4
^{81m}Kr	^{81}Rb daughter	13 seconds	IT	0.191 γ (66%)	1.6
^{82}Rb	^{82}Sr daughter	75 seconds	β^+, EC	3.15 β^+ (96%) 0.511 γ (192%)	6.1
^{89}Sr	$^{88}Sr(n, \gamma)^{89}Sr$	50.5 days	β^-	1.46 β^- (100%)	
^{90}Y	^{90}Sr daughter	64 hours	β^-	2.27 β^- (100%)	
^{99}Mo	fission	2.75 days	β^-	0.45 β^- (18%) 1.23 β^- (82%) 0.181 γ (6%) 0.740 γ (13%) 0.778 γ (5%)	1.8
^{99m}Tc	^{99}Mo daughter	6.02 hours	IT	0.140 γ (89%)	0.7
^{111}In	$^{112}Cd(p, 2n)^{111}In$	67.3 hours	EC	0.171 γ (90%) 0.246 γ (94%)	3.2
^{123}I	$^{127}I(p, 5n)^{123}Xe$ daughter	13.2 hours	EC	0.159 γ (83%) 0.027 $\times$ (71%)	1.6
^{125}I	$^{124}Xe(n, \gamma)^{125}Xe$ daughter	60.2 days	EC	0.036 γ (7%) 0.027 $\times$ (110%)	1.4
^{131}I	fission	8.04 days	β^-	0.61 β^- (90%) 0.284 γ (6%) 0.364 γ (82%) 0.637 γ (7%)	2.2
^{133}Xe	fission	5.25 days	β^-	0.35 β^- (100%) 0.081 γ (36%) 0.031 $\times$ (39%)	0.5
^{137}Cs	fission	30 years	β^-	0.51 β^- (94%) 1.18 β^- (6%) 0.662 γ (84%)	3.3
^{153}Sm	$^{152}Sm(n, \gamma)^{153}Sm$	46.3 hours	β^-	0.640 β^- (30%) 0.710 β^- (50%) 0.810 β^- (20%) 0.103 γ (29%)	0.9
^{186}Re	$^{185}Re(n, \gamma)^{186}Re$	3.72 days	β^-, EC	1.07 β^- (77%) 0.93 β^- (23%) 0.137 γ (9%)	0.08
^{201}Tl	$^{203}Tl(p, 3n)^{201}Pb$ daughter	73 hours	EC	0.135 γ (3%) 0.167 γ (10%) 0.070 $\times$ (74%) 0.080 $\times$ (20%)	0.47

Data from Madsen MT, Ponto JA. *Medical Physics Handbook of Nuclear Medicine,* Madison, WI: Medical Physics, 1992; and individual product package inserts.

the charge (either + or −) of the particle undergoing acceleration. When the particles have been accelerated to a high velocity, even approaching the velocity of light and representing enormous energies, they are caused to strike a target containing the atoms to be bombarded. Sodium-22 is prepared in this way, by the interaction of high-velocity deuterons with magnesium. The nuclear equation is:

$$^{24}Mg(d, \alpha)^{22}Na$$

Cyclotrons produce neutron-deficient isotopes; that is, the neutron-to-proton ratio is low. These nuclides usually decay by positron emission or electron capture. Cyclotron-produced radionuclides are generally carrier-free because they are normally produced by transmutation.

The following reactions are typical for the cyclotron production of some medically useful nuclides:

$$^{10}B(d, n)^{11}C$$

$$^{11}B(p, n)^{11}C$$

$$^{11}B(d, 2n)^{11}C$$

$$^{14}N(p, \alpha)^{11}C$$

$$^{10}B(\alpha, n)^{13}N$$

$$^{12}C(d, n)^{13}N$$

$$^{16}O(p, \alpha)^{13}N$$

$$^{14}N(d, n)^{15}O$$

$$^{15}N(p, n)^{15}O$$

$$^{16}O(p, pn)^{15}O$$

$$^{18}O(p, n)^{18}F$$

$$^{20}Ne(d, \alpha)^{18}F$$

$$^{70}Zn(p, \alpha)^{67}Cu$$

$$^{66}Zn(d, n)^{67}Ga$$

$$^{68}Zn(p, 2n)^{67}Ga$$

$$^{69}Ga(p, 2n)^{68}Ge$$

$$^{82}Kr(p, 2n)^{81}Rb \rightarrow {}^{81m}Kr$$

$$^{111}Cd(p, n)^{111}In$$

$$^{112}Cd(p, 2n)^{111}In$$

$$^{203}Tl(p, 3n)^{201}Pb \rightarrow {}^{201}Tl$$

Usually a nuclide can be made by more than one reaction. For example, ^{123}I can be prepared either directly or indirectly. Direct reactions include:

$$^{123}Te(p, n)^{123}I$$

$$^{121}Sb(^{4}He, 2n)^{123}I$$

$$^{122}Te(d, n)^{123}I$$

$$^{124}Te(p, 2n)^{123}I$$

Indirectly, the intermediate ^{123}Xe (or ^{123}Cs, which decays to ^{123}Xe) is prepared, which then decays to ^{123}I:

$$^{122}Te(^{4}He, 3n)^{123}Xe \rightarrow {}^{123}I$$

$$^{122}Te(^{3}He, 2n)^{123}Xe \rightarrow {}^{123}I$$

$$^{123}Te(^{3}He, 3n)^{123}Xe \rightarrow {}^{123}I$$

$$^{127}I(p, 5n)^{123}Xe \rightarrow {}^{123}I$$

$$^{124}Xe(p, 2n)^{123}Cs \rightarrow {}^{123}Xe \rightarrow {}^{123}I$$

RADIONUCLIDE GENERATORS

When clinical procedures require that a radionuclide be administered internally, it is advantageous to use a nuclide with a short half-life to minimize the radiation dose received by the patient. It is evident, however, that the shorter the half-life, the greater the problem of supply. One answer to this problem is the radionuclide generator, which uses the phenomenon of *sequential decay*. A radionuclide generator provides a mechanism for separating a clinically useful, short half-life daughter nuclide from a long-lived parent nuclide. Radioactive decay of the long-lived parent results in the production of a short-lived radioactive daughter nuclide that is *eluted* or *milked* from the generator by means of an appropriate eluant. Characteristics of a number of parent–daughter systems that have been used in radionuclide generators are found in Table 29-4.

The molybdenum-99/technetium-99m generator (Fig 29-10) consists of an alumina (Al_2O_3) column on which molybdenum-99 is adsorbed as ammonium molybdate. Radioactive decay of ^{99}Mo produces ^{99m}Tc, which is eluted from the column with0.9% sodium chloride, USP. Upon elution, the ^{99m}Tc is in the form of sodium pertechnetate ($Na^{99m}TcO_4$). Elution repeated every 24 hours provides a satisfactory balance between concentration and quantity of eluted ^{99m}Tc. If a high activity of ^{99m}Tc is not required, the generator can be eluted more frequently. A typical elution curve for a $^{99}Mo/^{99m}Tc$ generator is shown in Figure 29-11. Normally the generator must be replaced about once a week due to the decay of ^{99}Mo.

RADIOLABELING OF COMPOUNDS TO PREPARE RADIOTRACERS AND RADIOPHARMACEUTICALS

RADIOLABELING METHODS

For medical and pharmaceutical purposes, some radionuclides can be used in their elemental or salt forms, and thus do not require extensive processing beyond their separation and purification following production. However, most radionuclides must be incorporated into some molecule or compound to form a useful radiotracer or radiopharmaceutical. There are several ways that radionuclides are incorporated into the final radiopharmaceutical, a process known as *radiolabeling*. Some of the more common methods of radiolabeling include the following.

Introduction of a Foreign Label—For example, ^{99m}Tc is not a natural part of any medically useful compound, and thus a method must be developed to chelate ^{99m}Tc to various compounds of interest.

Table 29-4. Selected Radionuclide Generators

PARENT ISOTOPE	HALF-LIFE	DAUGHTER ISOTOPE	HALF-LIFE	MODE OF DECAY
^{68}Ge	271 d	^{68}Ga	68 m	β^+
^{81}Rb	4.7 h	^{81m}Kr	13 s	I.T.
^{82}Sr	25 d	^{82}Rb	1.3 m	β^+
^{87}Y	80 h	^{87m}Sr	2.8 h	I.T.
^{90}Sr	28 y	^{90}Y	64 h	β
^{99}Mo	67 h	^{99m}Tc	6.0 h	I.T.
^{109}Cd	453 d	^{109m}Ag	39.2 s	I.T.
^{113}Sn	118 d	^{113m}In	1.7 h	I.T.
^{115}Cd	53.4 h	^{115m}In	4.5 h	I.T.
^{122}Xe	20 h	^{122}I	3.6 m	β^+
^{132}Te	3.2 d	^{132}I	2.3 h	β^-
^{137}Cs	30 y	^{137m}Ba	2.6 m	I.T.
^{144}Ce	285 d	^{144}Pr	17.3 m	β^-
^{178}W	21.5 d	^{178}Ta	9.4 m	β^+
^{191}Os	16 d	^{191m}Ir	4.9 s	I.T.
^{195m}Hg	41 h	^{195m}Au	30.6 s	I.T.
^{225}Ac	10 d	^{213}Bi	45.6 m	α, γ, β^-

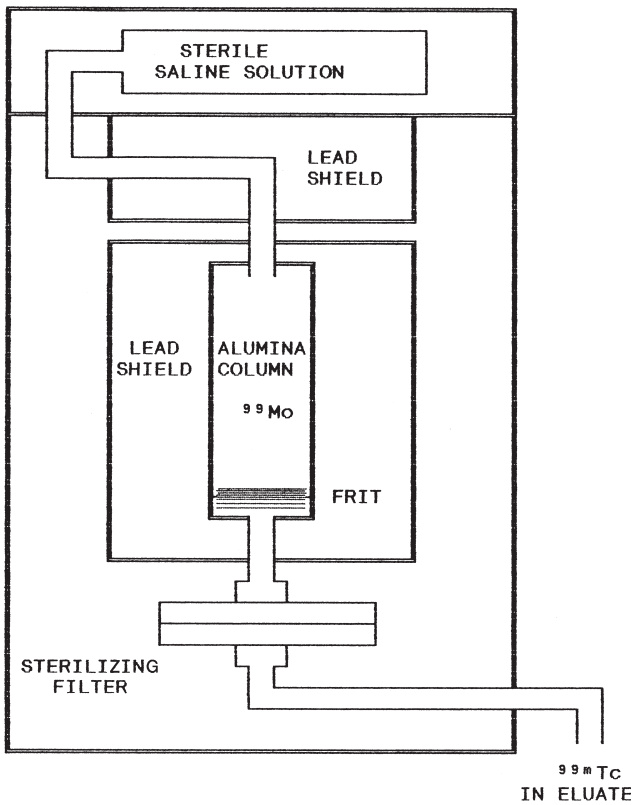

Figure 29-10. Schematic diagram of a radionuclide generator for the production of technetium-99m by elution from molybdenum-99 absorbed on an alumina column.

Isotope Exchange—This process occurs when a radioactive isotope is substituted for a stable atom of the same element that is already a natural part of the molecule. An example would be substituting ^{123}I for stable ^{127}I in some iodine containing molecule.

Labeling With Bifunctional Chelates—A *bifunctional chelate* is a molecule used to link another molecule with a radionuclide. An example would be linking ^{90}Y to a peptide without direct attachment to the peptide by using a compound such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

Biosynthesis—This reaction occurs when a radionuclide is incorporated into a molecule through some biosynthetic process. An example is when radioactive ^{57}Co is placed in the growth media of the bacteria that produces cyanocobalamin, vitamin B_{12}, as a metabolic by-product and yields radioactive vitamin B_{12} for use in the Schilling test.

DESIGN OF RADIOPHARMACEUTICALS

Not all radiopharmaceuticals use metal atoms as the radionuclide, but many do. When a molecule is radiolabeled with a metal atom, sometimes the metal atom does not change the biologic properties of the molecule into which it is incorporated; but sometimes it changes the biologic properties considerably. The result of the former instance is sometimes classified as a *metal-tagged* radiopharmaceutical, and the latter as a *metal essential* radiopharmaceutical. In the case of metal essential radiopharmaceuticals, the radioactive metal atom is absolutely essential in determining where that molecule will distribute in the body. Therefore, when designing a new radiopharmaceutical, one must be aware of how the addition of a metal atom (such as ^{99m}Tc) will affect the molecule in question.

In the design of radiopharmaceuticals, it is obviously important to select compounds that are likely to distribute to the organs or tissues of interest. As with nonradioactive drugs, computer modeling can quite often be helpful. It is not always easy to match a radionuclide that has appropriate physical properties with a candidate compound for a particular diagnostic or therapeutic purpose. It is important to make sure that the chemistries are compatible and that the resulting molecule has the desired biodistribution pattern.

With radiodiagnostic agents, structure–distribution relationships (SDR) are used to design candidate molecules. The SDR are similar to using structure–activity relationships for designing pharmacologically active drugs. The goal of SDR are to optimize target site delivery of the candidate radiopharmaceutical. This involves predicting, investigating, and determining changes in the biokinetics of a candidate radiopharmaceutical by effecting small changes in its structure, such as through the addition of functional groups to the compound. The newly altered candidate is tested for its pharmacokinetic behavior and compared with the prototype. Eventually, the most effective radiopharmaceutical candidate is selected for animal and human testing.

TECHNETIUM RADIOPHARMACEUTICALS

Technetium 99m (^{99m}Tc) is the most commonly used metal atom in radiopharmaceuticals; over 75% of all radiopharmaceuticals include ^{99m}Tc as the radionuclide. Technetium-99m has desirable physical properties for imaging purposes. It has a 6-hour half-life and a 140 keV gamma photon that is emitted with high abundance and it lacks particulate alpha and beta emissions. It also has a versatile chemistry that allows it to be chelated with a variety of compounds (but certainly not all compounds).

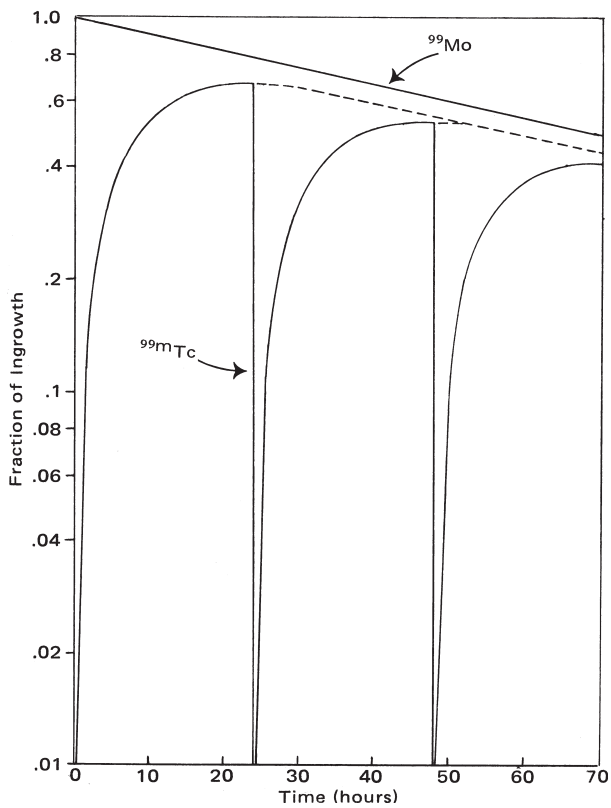

Figure 29-11. Elution curve. The lower solid lines show the theoretical activity of ^{99m}Tc in the generator as a result of ingrowth followed by elution of ^{99m}Tc at 24-hour intervals. If the generator were not eluted, ingrowth would follow the broken line and a transient equilibrium would be established. The upper solid line represents decrease in activity of ^{99}Mo, the parent nuclide, due to radioactive decay.

Table 29-5. Radiopharmaceutical Names

USAN/GENERIC NAME	LIGAND; COMMON CHEMICAL NAME	OTHER COMMON NAMES OR ABBREVIATIONS	COMMON TRADE NAMES
Albumin, aggregated iodinated I 131 serum[a]	macroaggregated albumin	I 131 MAA	Albumotope-LS; Macroscan-131
Albumin, chromated Cr 51 serum[a]		Cr 51 HSA	Tomatope
Albumin, iodinated I 125 serum	radio-iodinated serum albumin; iodinated human serum albumin	I 125 RISA; I 125 IHSA	Albumotope I 125; Jeanatope I 125
Albumin, iodinated I 131 serum	radio-iodinated serum albumin; iodinated human serum albumin	I 131 RISA; I 131 IHSA	Albumotope I 131; Megatope I 131
Ammonia N 13[a]	N 13 NH_3		
Carbon monoxide C 11[a]	C 11 CO		
Carbon C 14 urea	C 14 urea	PYtest	
Chromic phosphate P 32	P 32 colloid	Phosphocol	
Cyanocobalamin Co 57	vitamin B_{12}	Co 57 B_{12}	Rubratope
Cyanocobalamin Co 58/Co 57[b]	vitamin B_{12}/instrinsic factor	Co 58 B_{12}/Co 57 B_{12}-IF	Dicopac
Ferrous citrate Fe 59[a]	Fe 59 citrate	Ferrutope	
Fibrinogen I 125[a]	I 125 fibrinogen	Ibrin	
Fludeoxyglucose F 18[a]	2-fluoro-2-deoxy-D-glucose	F 18 fluorodeoxyglucose; FDG	
Fluorodopa F 18[a]	fluoro-levodopa	F 18 fluorodopa	
Gallium citrate Ga 67	Ga 67 citrate	Neoscan	
I 131 radiolabeled B1 monoclonal antibody[a]	iodinated IgG anti-B1 murine monoclonal antibody	I 131 anti-B1	Bexxar
Indium In 111 capromab pendetide	IgG 1 murine monoclonal 7E11-C5.3 conjugated with DTPA [antiprostate carcinoma monoclonal antibody]	In 111 CYT 356	ProstaScint
Indium In 111 chloride	In 111 Cl_3	Indiclor	
Indium In 111 imciromab pentetate[a]	IgG 2a murine monoclonal R11D10 Fab conjugated with DTPA [antimyosin monoclonal antibody]	In 111 antimyosin	Myoscint
Indium In 111 immune globulin intravenous pentetate[a]	immunoglobulin G (human polyclonal), disulfide with light chain, dimer, *N,N*-bis [2-[bis(carboxymethyl) amino]-ethyl] glycine conjugate	In 111 IgG	Macroscint
Indium In 111 oxyquinoline	8-hydroxyquinoline	In 111 oxine	
Indium In 111 pentetate	diethylenetriaminepentaacetic acid	In 111 DTPA	
Indium In 111 pentetreotide	octreotide-D-Phe-DTPA	In 111 octreotide	OctreoScan
Indium In 111 satumomab pendetide[a]	IgG1 murine monoclonal B72.3 conjugated with DTPA [anticolorectal/ovarian carcinoma monoclonal antibody]	In 111 CYT 099; CYT 103	OncoScint OR/OV
Iobenguane sulfate I 123[a]	*meta*-iodobenzylguanidine	I 123 MIBG	
Iobenguane sulfate I 131	*meta*-iodobenzylguanidine	I 131 MIBG	
Iocanlidic acid I 123[a]	iodobenzenepentadecanoic acid; (*p*-iodophenyl)pentadecanoic acid		
Iodocholesterol I 131[a]	19-iodocholest-5-en-3β-ol	I 131 iodocholesterol	
Iodohippurate sodium I 123[a]	*ortho*-iodohippurate	I 123 OIH	Nephroflow
Iodohippurate sodium I 131[a]	*ortho*-iodohippurate	I 131 OIH	Hippuran I 131; Hipputope
Iodomethylnorcholesterol I 131[a,b]	6-β-iodomethyl-19-norcholesto-5(10)en-3β-ol	NP 59	
Iofetamine hydrochloride I 123[a]	*N*-isopropyl-*p*-iodoamphetamine	I 123 IMP	Spectamine
Iothalamate sodium I 125	I 125 iothalamate	Glofil	
Krypton Kr 81m	Kr 81m		
Mesiperone C 11[a]	*N*-methylspiperone	C 11 NMSP	
Methionine C 11[a]	C 11 methionine		
Raclopride C 11[a]	C 11 raclopride		
Rhenium Re 186 etidronate[a]	ethylene hydroxydiphosphonate	Re 186 EHDP	
Rubidium chloride Rb 82	Rb 82	Cardiogen-82	
Samarium Sm 153 lexidronam pentasodium	ethylenediamine tetramethylene phosphonic acid	Sm 153 EDTMP	Quadramet
Selenomethionine Se 75[a]	Se 75 selenomethionine		
Sodium acetate C 11[a]	C 11 acetate		
Sodium chromate Cr 51	Cr 51 Na_2CrO_4	Chromitope	
Sodium fluoride F 18[a]	F 18 NaF		
Sodium iodide I 123	I 123 NaI		
Sodium iodide I 131	I 131 NaI	Iodotope	
Sodium pertechnetate Tc 99m	product from Mo-99/Tc-99m generator	Na^+ TcO_4^-	generators: Minitec; Technelite; Ultra-TechneKow
Sodium phosphate P 32	P 32 Na_3PO_4/Na_2HPO_4		
Stannic pentetate Sn 117[a,b]	tin (IV) diethylenetriaminepentaacetic acid	Sn 117 DTPA	

Table 29-5. Radiopharmaceutical Names *(continued)*

USAN/GENERIC NAME	LIGAND; COMMON CHEMICAL NAME	OTHER COMMON NAMES OR ABBREVIATIONS	COMMON TRADE NAMES
Strontium chloride Sr 89	Sr 89	Metastron	
Technetium Tc 99m albumin	Tc 99m HSA		
Technetium Tc 99m albumin aggregated	macroaggregated albumin	Tc 99m MAA	Pulmolite; Macrotec
Technetium Tc 99m albumin colloid[a]	Tc 99m AC	Microlite	
Technetium Tc 99m antimony trisulfide colloid[a]	Sb_2S_3	Tc 99m ASC	Lymph-Scan
Technetium Tc 99m apcitide	GP IIb/IIIa receptor peptide	Tc 99m P280	Accutech
Technetium Tc 99m arcitumomab	IgG murine monoclonal IMMU-4 Fab[anti-CEA monoclonal antibody fragment]	Tc 99m anti-CEA Fab	CEA-Scan
Technetium Tc 99m bectumomab[a]	IgG 2a murine monoclonal IMMU-LL2 Fab [anti-non-Hodgkin's lymphoma monoclonal antibody fragment]	Tc 99m IMMU-LL2	ImmuRaid-LL2
Technetium Tc 99m biciromab[a]	IgG murine monoclonal T2G1s Fab [antifibrin monoclonal antibody fragment]	Tc 99m antifibrin Fab	Fibroscint
Technetium Tc 99m bicisate	ethyl cysteinate dimer	Tc 99m ECD	Neurolite
Technetium Tc 99m depreotide			
Technetium Tc 99m disofenin	diisopropylacetanilidoiminodi-acetic acid	Tc 99m DISIDA	Hepatolite
Technetium Tc 99m etidronate[a]	ethylenehydroxydiphosphonate	Tc 99m EHDP	
Technetium Tc 99m exametazime	hexamethylpropyleneamineoxime	Tc 99m HMPAO	Ceretec
Technetium Tc 99m furifosmin[a]	ethylenebis(nitrilomethylidyne)bis (dihydrotetramethylfuranonato) bis(tris[methoxypropyl])-phosphine)	Tc 99m Q-12	TechneScan Q-12
Technetium Tc 99m gluceptate	glucoheptonate	Tc 99m GH; GHA	Glucoscan; TechneScan Gluceptate
Technetium Tc 99m lidofenin	dimethylacetanilidoimino diacetic acid	Tc 99m HIDA	TechneScan HIDA
Technetium Tc 99m mebrofenin	trimethylbromoacetanilidoimino-diacetic acid	Tc 99m BRIDA	Choletec
Technetium Tc 99m medronate	methylenediphosphonate	Tc 99m MDP	Osteolite; TechneScan MDP
Technetium Tc 99m mertiatide	mercaptoacetyltriglycine	Tc 99m MAG_3	TechneScan MAG3
Technetium Tc 99m nofetumomab merpentan	IgG murine monoclonal NR-LU-10 Fab [anti-small cell lung cancer mono-clonal antibody fragment]	Tc 99m NR-LU-10	Verluma
Technetium Tc 99m oxidronate	hydroxymethyldiphosphonate	Tc 99m HDP; HMDP	Osteoscan-HDP
Technetium Tc 99m pentetate	diethylenetriaminepentaacetic acid	Tc 99m DTPA	Techneplex
Technetium Tc 99m pyrophosphate		Tc 99m PYP	Phosphotec; Techne-Scan PYP
Technetium Tc 99m (pyro- and trimeta-) phosphates	Tc 99m PYP	Pyrolite	
Technetium Tc 99m red blood cells	Tc 99m RBC [in vitro]	UltraTag RBC	
Technetium Tc 99m sestamibi	hexakis(methoxyisobutyl)isonitrile	Tc 99m MIBI; hexamibi; RP 30A	Cardiolite; Miraluma
Technetium Tc 99m succimer	dimercaptosuccinic acid	Tc 99m DMSA	
Technetium Tc-99m sulesomab	IgG 1 murine monoclonal IMMU-MN3 Fab [anti-NCA-90 granulocyte cel antigen monoclonal antibody fragment]	Tc 99m IMMU-MN3	LeukoScan
Technetium Tc 99m sulfur colloid	Tc 99m SC	TechneColl; Tesuloid; TSC	
Technetium Tc 99m teboroxime[a]	boronic acid adduct of technetium dioxime; bis-cyclohexanedione dioxime methylborato-chlorotechnetium	SQ-30217; CDO-MEB; BATO	Cardiotec
Technetium Tc 99m tetrofosmin	1,2-bis[bis(2-ethoxyethyl)phos-phino] ethane	Tc 99m P53	Myoview
Thallous chloride Tl 201	Tl 201		
Water 0 15[a]	O 15 H_2O		
Xenon Xe 127[a]	Xe 127		
Xenon Xe 133	Xe 133		

[a] Not commercially available (investigational, discontinued, or extemporaneously compounded).
[b] Official generic name not yet established.
Source: Table courtesy of James A Ponto.

Technetium-99m is derived from the decay of ^{99}Mo. Since ^{99}Mo is a decay product of ^{99m}Tc, it is chemically separated and used to make various ^{99m}Tc radiopharmaceuticals. This separation process occurs in what is known as a $^{99}Mo/^{99m}Tc$ radionuclide generator system, as was discussed in a previous section. The ^{99m}Tc is eluted from the generator in the form of sodium pertechnetate in the +7 oxidation state. As such, it is not very chemically reactive and will not bind to other compounds. The oxidation state of technetium must be reduced to a lower value in order to make it chemically reactive. This is typically done by using a reducing agent such as stannous ion.

Manufacturers develop compounds that can be labeled with ^{99m}Tc and used for imaging various organ systems or tissues. These compounds are frequently available in what are known as *reagent kits*. The reagent kits are vials containing the particular compound, usually in freeze-dried form, along with the stannous ion and any other necessary ingredients such as buffers or preservatives. The radioactive ^{99m}Tc, as pertechnetate, is added to the reagent kit vial and the stannous ion reduces the technetium, allowing it to chelate with the compound. Binding occurs through coordinate covalent bonds with certain moieties on the compound molecule, known as *ligands*. Some of the more common ligands that bind to technetium are $—NH_2$, $—NH_3^+$, —CN, —SH, —COO—, —CO—, and —OH, among others. The radiolabeling of certain ^{99m}Tc radiopharmaceuticals involves the formation of an intermediate compound with a subsequent ligand exchange process (which usually requires a heating step) to form the final product.

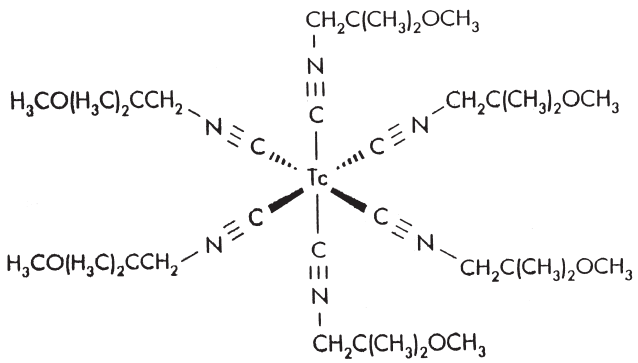

Figure 29-12. Tc-hexakis-2-methoxyisobutylisonitrile (Tc-sestamibi).

Technetium, in its various oxidation states, has a variety of coordination numbers. Compounds will complex with technetium in specific ways, depending on the oxidation state of technetium and the associated coordination number. Figure 29-12 illustrates how isonitrile molecules are complexed with ^{99m}Tc in the +1 oxidation state.

PREPARATION OF RADIOPHARMACEUTICALS

Some radiopharmaceuticals are prepared in their final form at the manufacturing site, whereas others are compounded at a nuclear pharmacy or nuclear medicine department. There are several levels of sophistication in compounding these agents, ranging from simple addition of radiopertechnetate to the reagent kit vial, to radiolabeling of autologous blood cells, custom radiolabeling of peptides and antibodies, and rapid *hot lab* chemistry compounding of short-lived positron-emitting radiopharmaceuticals. Different diagnostic and therapeutic needs require the use of different preparation techniques. Table 29-5 includes a list of radiopharmaceuticals currently in use.

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PART **4**

Pharmaceutical Testing, Analysis, and Control

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CHAPTER 30

Analysis of Medicinals

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From the time of the early apothecaries, who worked with meager equipment in small laboratories, pharmacists have made important contributions in the field of medicinal chemistry, both in discovering or isolating new therapeutic agents and in developing methods for standardizing and controlling medicinals. Today, such activity is rarely a function of the practicing pharmacist in the prescription laboratory or the industrial pharmacist in manufacturing laboratories. Rather, analytical chemists specializing in chromatographic, spectroscopic, and wet-chemical analyses perform this function. Some of the testing still involves classical titrimetric or gravimetric techniques. Other analytical techniques, such as two-dimensional nuclear magnetic resonance (NMR) spectroscopy and time-of-flight mass spectrometry (MS), are often performed by scientists with graduate and post-doctoral training in the methodology. But whether or not pharmacists may have occasion to conduct analyses, they at least should understand the basic principles involved in the standardization and control of the medicinal agents dispensed.

VALIDATION OF ANALYTICAL METHODS

The use of an analytical method is justified only after it has been found to be valid (has been *validated*). Both the Food and Drug Administration (FDA) and United States Pharmcopeia (USP) are vitally interested in formal assay method validation to be certain that methods are as they purport to be. In a section entitled *Validation of Compendial Methods,* the USP[1] describes analytical performance parameters that must be measured to validate an analytical procedure. Similar descriptions can be found in ICH Guidances.[2]

The degree to which a method is validated depends on the phase of development. All pharmaceutical companies have well-defined Standard Operating Procedures (SOPs) that state their validation requirements for different phases of development. Minimal validation is usually needed for preclinical, Phase I, and Phase II development. Typically the method's selectivity (ability to measure analyte in presence of any possible impurities, as in a stability-indicating assay), linearity (the concentration range over which concentration and response are related linearly), recovery (accuracy; the concentration of analyte measured relative to the concentration of analyte spiked into the sample), and repeatability (precision) are assessed. The stability of standard and sample solutions is also evaluated. Additional validation requirements are needed for methods used to support Phase III clinical studies, product registration, and clearance of drug substance and commercial drug product: limit of detection (concentration that gives the smallest perceptible response); limit of quantitation (lowest concentration measurable with good precision and accuracy); intra-laboratory reproducibility (different instruments, columns, analytical chemists within a laboratory); robustness (the capacity of a method to remain unaffected by small, but deliberate variations in method parameters); and reproducibility (method crossover between two laboratories). In the later stages of development, method validation is performed under a pre-approved validation protocol with defined procedure and acceptance criteria.

Compendial analytical methods usually do not require validation. Compendial microbial methods, however, may require validation as directed by individual company SOPs. Physical test methods, such as viscosity, pH, tablet hardness, melting point, require minimal or no validation prior to use.

INSTRUMENT QUALIFICATION

Instrumentation must be qualified prior to GMP use. An installation qualification (IQ) provides documented verification that all key aspects of a facility, utility system, or equipment installation adhere to appropriate codes, safety standards, approved design intentions, and that manufacturer's specifications for installation have been suitably considered. An operation qualification (OQ) provides documented verification that a facility, utility system, or equipment performs as intended throughout all anticipated established limits and tolerances. Performance qualification (PQ) provides documented verification that a facility, utility system, or equipment performs as intended under load conditions. Two documents are essential for any qualification: the qualification protocol and the qualification report. The qualification protocol describes the objectives, test procedures, and acceptance criteria. This document must be approved prior to execution of the qualification procedure. The qualification report summarizes the results of the qualification protocol versus the pre-determined acceptance criteria.

CALIBRATION, MAINTENANCE, AND USE

Instrumentation intended for GMP use must be calibrated to assure that equipment performs properly for the intended use. Calibration schedules are usually established so that instruments are calibrated on a monthly, quarterly, semi-annual, or annual basis. Between calibrations, company SOPs describe the frequency at which the instrument must be checked to assure that it is still working properly. For example, an analytical balance that is calibrated quarterly is usually checked on a weekly basis by weighing a NIST-traceable weight. Calibrations and calibration checks are recorded into a log book, as is preventative and corrective maintenance of instrumentation. Each sample analyzed is also logged. Detailed instrument

records assist the analytical chemist during investigations of out-of-specification or out-of-trend results.

ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

The FDA issued 21 CFR Part 11, which provides criteria for FDA acceptance of electronic records, electronic signatures, and handwritten signatures, in 1997.[3] Analytical development, pharmaceutics, and quality control laboratories that use computers for instrument control, data acquisition, data evaluation, data transfer, data management, or data archiving must comply with Part 11. All computer systems used to generate, maintain, or archive electronic records must be validated. Access to the validated system must be limited to trained and authorized users; individual password-protected user accounts are required. Computer-generated, time-stamped audit trails that record the date and time of data acquisition, modification, or deletion by an authorized user are required. In addition, the integrity of original data files cannot be obscured. Standard Operating Procedures are required to manage and archive electronic files. Complete and accurate copies of the electronic records must be readily retrievable for agency inspection or review. Finally, policies that hold individuals responsible and accountable for actions initiated under their electronic signatures are required. An electronic signature is a computer data compilation of symbols that is executed, adopted, or authorized by an individual and is the legally binding equivalent of the individual's handwritten signature. In 2003, the FDA issued a new guidance[4] that limited the scope of Part 11 to apply only to records required by a predicate rule and when one or both or the following conditions apply: (1) Electronic records are used instead of paper; or (2) persons make printouts but still rely on the electronic records to perform regulated activities.[5]

ANALYTICAL BALANCES

The analytical balance is an indispensable requirement for any analytical procedure whether the method is a classic or stoichiometric analysis or a modern, instrumental method of a nonstoichiometric nature. If the determination of mass is not accurate and precise, the ultimate analytical result is unacceptable.

An analytical balance differs from a high-class prescription balance in the matter of sensitiveness. A satisfactory analytical balance is sensitive to the tenth of a milligram and should never be used for weighing a total load greater than that specified. The electronic analytical balance is of the null type, but the restoring torque is not applied by adding or removing weights but rather by varying a current applied to a coil in a magnetic field. The great advantage of the electromagnetic principle is the freedom from drift or change in sensitivity. The balances have a digital display, and tare-out capabilities, as well as internally programmed test and calibration routines. Some balances have small maximum capacity (about 0.1 to 1.0 g). Other electronic analytical balances using load cells are available with capacities of up to 200 g and a readability of ± 0.10 mg or ± 0.01 mg and have data outputs making them capable of incorporation into automated systems. Microbalances, which are useful when limited material is available, can be read to the nearest microgram.

SOURCES OF INFORMATION

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Specialized Analytical Methods and Equipment

In the following section some important analytical methods used by pharmaceutical manufacturers are discussed. Practicing pharmacists do not, as a rule, require such sophisticated apparatus as is used for analysis, but they should at least be familiar with the types of analyses conducted with each instrument.

Some of the medicinal products are still being assayed by the time-honored procedures of gravimetric and titrimetric analysis, although here, too, the use of electronic balances and the recording titrator have improved these classic procedures considerably.

Familiar examples of analytical methods that are purely physical in their nature include those that involve the use of the microscope, the polarimeter, or the refractometer. The identity, relative purity, and crystallinity of many substances often are determined by microscopical examination. The polarimeter has long been recognized for its usefulness in assaying certain liquids, such as dextrose solutions, by determining their ability to bend or rotate the plane of polarized light. Polarimeters are available that measure the rotation of polarized light at wavelengths in addition to the D line of sodium (589 nm).

The determination of the moisture content in various substances involves several types of analytical measurement. These methods include drying in a desiccator or in a heated oven, either under ordinary atmospheric conditions or in

vacuum under reduced pressure. A moisture balance, in which the sample pan is directly heated by an infrared lamp, eliminates removal of the sample from the balance. Other procedures involve distillation of vegetable drugs with toluene or with benzene, then noting the volume of water that separates in a graduated tube containing the distillate. A more specific and convenient procedure for determining water in many substances is the Karl Fischer titrimetric method. In this procedure, the water is quantitatively measured by titration under anhydrous conditions by the use of a reagent containing iodine, sulfur dioxide, pyridine, and methanol. The endpoint may be detected visually, or preferably by the use of the electrometric and automatic titration assembly. Some instruments use coulometric titration to generate the reagent at an electrode surface. Electrical methods for determining water are being applied now to a variety of industrial products, in some cases during continuous processing operations. These are based upon the principle that if a substance is placed between two condenser plates, the capacitance will vary with the dielectric constant of the medium between the plates. Because the dielectric constant of water is greater than that of other substances, the capacitance will vary with the amount of moisture present. Water content in granulations and solid-dosage forms can also be measured easily using near-infrared spectroscopy.

The determination and adjustment of pH or hydrogen ion concentration (activity) has become an important function in the control analysis of medicinal products. For a discussion of pH determination see Chapter 33. The use of microelectrodes allows pH to be measured in small volumes (0.5 mL) of solution.

Separation techniques, particularly chromatographic methods, are necessary and valuable in the analysis of pharmaceuticals. The partitioning of a solute between two immiscible solvents is used many times to isolate a drug from other components in a mixture. Open column chromatographic methods, once a mainstay in purification, have been replaced with preparative chromatographic techniques to isolate, purify, and often, concentrate drug, degradation product, or synthetic impurity from a dosage form matrix or a natural biological environment. Other separations such as solvent–solvent extraction, thin-layer chromatography, solid-phase extraction, or solid-phase micro-extraction may be required as a preparatory step when spectrometric analysis is to follow.

Gas chromatography (GC) and high-performance liquid chromatography (HPLC) represent two nonstoichiometric methods that have achieved very great popularity because of their capabilities. In GC, any compound, directly or with derivatization, can be analyzed if it has a perceptible vapor pressure and if a suitable column can be found. The use of various detectors adds another element of selectivity to the procedure. HPLC has been rapidly developing with the introduction of gradient pumping systems, integrated instrument control and data acquisition systems, a larger variety of columns, and sophisticated detectors. But the great attraction of chromatographic techniques to the industrial laboratory is the possibility of automation. The chromatographic procedure and instrumentation may be so designed that the method largely may be automated, involving automated sampling, separations, detection, recording, and finally, calculation and printing of results, leaving only the preparation of drug substance or of dosage form solutions to be done by the analytical chemist. Diode array detectors allow data acquisition over a range of analytical wavelengths. Mass spectrometric detectors can be used to obtain nominal masses of eluting substances or can be tuned to the mass of interest to quantify a substance that is not adequately separated from other substance or its matrix. Small-bore columns often afford shorter run times and conserve on solvent use. The subject of chromatography is discussed in Chapter 32.

Mass spectrometers and nuclear magnetic resonance (NMR) spectrometers are valuable instruments to identify new degradation products, extractables, leachables, and other impurities in drug substances and drug products. Organic and analytical chemists can often identify possible structures of an unknown molecule by re-constructing the molecule from its fragmentation pattern obtained from MS-MS analysis. The structures can be confirmed by two-dimensional proton and carbon-13 Fourier Transform NMR spectroscopy. High-frequency magnetic fields, complex pulse sequences, and innovative probes, like the cryoprobe, have greatly improved the sensitivity of NMR spectroscopy in recent years.

The modern spectrometer, which incorporates such features as microprocessor control and diode array detectors, has become an especially useful instrument for analysis, as it enables analytical chemists to seek the answers to their analytical problems with *eyes* that see not only in the visible range, but throughout the electromagnetic spectrum. The analytical possibilities in this direction can be understood more readily when one considers that the ultimate molecules and atoms that make up a material transmit, absorb, and scatter radiation according to their individual natures. Assay methods based upon absorption in the ultraviolet, infrared, and visible portions of the spectrum are used extensively. The principles underlying such determinations are discussed in Chapter 33. In some spectrometric analytical procedures, a colorless substance that must be analyzed is converted to a derivative having color, the intensity of the color being measured in a suitable spectrometer and compared with that developed by a known amount of a *reference standard* grade of the same substance.

Other widely used instruments which are quite suitable for routine colorimetric measurements are the colorimeter and the combination nephelocolorimeter, which is of considerable value in making quantitative turbidimetric measurements. High-through put robotic systems have added capability to analyze compounds synthesized using combinatorial methods. These systems require milligram quantities of drug and can analyze up to 96 compounds in a single sample plate. These systems have been interfaced to mass spectrometers for molecule identification and purification, X-ray diffractometers for salt selection and polymorph screening, and spectrophotometers and nephelometers for solubility and permeability measurements.

The fluorometer provides for measurement of fluorescence that may be present in the sample or that may be developed in the sample through derivatization. This method provides a means of evaluating the potency of many pharmaceutical products, as, for example, those containing thiamine hydrochloride. A solution in which the thiamine has been converted quantitatively into thiochrome is placed in the fluorometer where it is caused to fluoresce on exposure to light. This fluorescence intensity is compared with readings obtained on standard control samples prepared and observed under exactly the same conditions. This comparison serves as a basis on which the potency of the unknown vitamin sample can be calculated readily. At the opposite end of the electromagnetic spectrum are the infrared radiations. These are heat rays and their utilization marks another important contribution to analytical research. Infrared spectrometry involves placing the sample in a cell that is traversed by radiation from an infrared source. The transmitted radiation on passing into the spectrometer is dispersed into a spectrum by a prism of sodium chloride, or other salt, or by a diffraction grating. Fourier transform infrared spectrometers are available that can acquire an infrared spectrum very rapidly (see Chapter 33). An important application of infrared spectrometry in the USP is in the fingerprinting of organic compounds, by which means they may be identified. Pattern recognition techniques and the use of neural networks to compare spectra are very impressive.

The ability to detect and measure elements in a complex dosage-form system is very important because some elements such as the heavy metals, which may have been used in the synthesis, are toxic. The emission spectrograph is used for identification and for the quantitative measurement of many elements by providing photographic records of their emission spectra. These elements include most metals and some nonmetals, such as boron, silicon, and phosphorus. By determining the wavelengths of the lines, the various elements present in the sample may be determined by reference to wavelength

tables. By the use of a densitometer, which measures the relative darkness of the lines, the quantitative evaluation is accomplished.

An emission technique that is largely solution based and is newer than emission spectroscopy is inductively coupled plasma optical emission spectrometry (ICP-OES). In this technique the sample solution is aspirated into an inductively-coupled plasma (argon gas), a medium whose temperature is about 10,000 K, a condition that results in atomization and excitation of even the most refractory elements (eg, sulfur). The results provide both qualitative and quantitative data in a rapid, efficient manner, identifying and measuring multiple elements from a single sample. The disadvantage of this technique is its high instrumental cost and its operating expense. The flame spectrometer serves a useful purpose in some industrial and hospital laboratories for making routine emission determinations, particularly of alkali metals and alkaline earth metals.

Electrochemical methods offer a level of selectivity that some spectroscopic analyses cannot provide. Ion-specific electrode potentiometry measures free-unbound species rather than the total amount of metal ion in a solution. The polarograph provides for rapid qualitative and quantitative analyses by automatic recording of current-voltage curves. In the operation of this instrument, reducible ions and organic compounds are reduced at the dropping mercury electrode, yielding polarograms that serve as records of the analysis. The polarogram establishes the identity of the substance by its half-wave potential, while the height of the step in the curve is taken as a direct measurement of concentration. Variations of polarography, such as differential pulse polarography, increase the sensitivity of quantitative analysis, whereas cyclic voltametry provides a means whereby the qualitative oxidation–reduction behavior of a species may be examined.

The nonstoichiometric methods used in drug analysis are discussed in Chapters 31, 32, and 34, and the stoichiometric analyses are treated in this chapter as they apply to specific drug substances and to specific dosage forms.

OFFICIAL PHYSICAL AND CHEMICAL ASSAYS

There appears to be a misconception on the part of some individuals concerning the assay procedures of the official compendia. A material may well fall within the assay limits stated in the individual monograph for a particular substance, and yet *not* be of suitable quality to conform to the complete specifications indicated for the compound, even though the assay is performed exactly as indicated in the official method. It is essential, then, to realize that even though a substance meets the purity specifications of an official monograph, as established by a chemical or physical assay procedure, it is *not* of USP quality unless it conforms to *all* of the specifications contained in the monograph for that material. Also, some official substances do not have an assay procedure, as such, listed in the monograph for the basic drug. A quantitative analytical method is not required in such cases because other specifications in the monograph serve to characterize the substance both quantitatively and qualitatively.

As dosage forms become more complex and active pharmaceutical ingredients become more potent, pharmaceutical companies may include additional testing or stricter acceptance criteria to ensure functionality of compendial excipients. For example, residual peroxide content of polyoxoether excipeints or of vehicles containing oxygen atoms may need to be monitored closely before the excipient is used to manufacture a drug that can easily oxidize. Another example is that lot-to-lot variation in polymers used in tablet coating may cause variation in dissolution behavior. Here the coating thickness may need to be adjusted during the manufacturing process in order to meet release-rate specification criteria.

In the following sections, various aspects of the official drug analyses are considered. The classic titrimetric and gravimetric methods are considered in some detail and, even though the subjects are treated in Chapters 32 and 33, some aspects of instrumental procedures are examined. Tables 30-3 and 30-4 contain the indicators and other reagents; some examples of the various classes of analyses are presented, together with an explanation of the chemical principles or other pertinent detail. A comprehensive tabulation of all official assays, which uses the classification outline of Appendix A, is found in Appendix B at the end of this chapter.

Because of the selectivity, specificity, and sensitivity that can be achieved by HPLC methods, there has been a definite tendency to choose HPLC procedures for the analysis of many drugs, as may be seen for USP-NF analyses in Appendix B. Chapter 32 presents a detailed consideration of HPLC.

THE PREPARATION OF SOLUTIONS

The preparation of a solution of a drug substance is vital to many methods of analysis. The nature of the system chosen to express the concentration of the solute is important, particularly in stoichiometric methods, because the nature of a chemical reaction is used to calculate the analytical result. The useful concentration systems, molarity, formality, molality, normality, and titer, are defined here.

Molarity = Mols of solute/liter = Millimols of solute/millimeter.
Formality = Number of formula weights/liter.
Formula Weight = Molecular weight in grams.
Molality = Mols of solute/1000 grams of solvent.

The most useful concentration system is normality, because the reaction capability of a reagent or an analyte is taken into account when solutions are prepared.

Normality = Number of equivalents/liter.
Equivalent = Grams of drug or reagent used/equivalent weight.
Milliequivalents = Grams of drug or reagent used/milliequivalent weight.
Equivalent Weight = Molecular weight in grams/n.
Milliequivalent Weight = Equivalent weight/1000.
n = number of reacting entities per reagent aggregate.

The number of reacting entities per reagent aggregate for acids is the number of accessible protons. For bases, it is the number of available basic anions or pairs of unshared electrons that can accept a proton. For oxidizing or reducing agents, it is the number of electrons that an aggregate can lose or gain in an electron transfer reaction as is seen from a half-reaction; for example, $MnO_4^- + 5\,e^- + 8\,H_3O^+ = Mn^{2+} + 12\,H_2O$. Textbooks that provide tables of standard oxidation or reduction potentials may be consulted for half reactions. The values of n for reagents are shown in Table 30-1.

A number of equations are useful when calculations in volumentric analysis are needed.

$$(\text{milliliters}_{\text{reagent}})(\text{normality}_{\text{reagent}}) = \frac{\text{grams}_{\text{analyte}}}{\text{milliequivalent weight}_{\text{analyte}}}$$

$$\frac{\text{grams}_{\text{analyte}}}{\text{grams}_{\text{sample}}} \times 100 = \%\ \text{analyte in sample}$$

Table 30-1. Reaction Capacity Values (n) for Selected Reagents

ACIDS	BASES	ELECTRON TRANSFER
HCl – 1	NaOH – 1	$KMnO_4$ – 5 ($MnO_4^- - Mn^{2+}$)
H_2SO_4 – 2	NH_3-H_2O – 1	I_2 – 2 (I_2 — $2I^-$)
H_3PO_4 – 2	Ba $(OH)_2$ – 2	$Na_2S_2O_3$ – 2 ($2S_2O_3^{2-} - S_4O_6^{2-}$)
HOAc – 1	$CH_3CH_2NH_2$ – 1	$Na_2Cr_2O_7^{2-}$ – 6 ($Cr_2O_7^{2-} - 2Cr^{3+}$)

The concept of titer is very useful because it allows a titrant to be labeled in terms of the analyte and simplifies calculations.

$$titer = \frac{\text{milligrams of analyte}}{\text{milliliter of titrant}}$$

For a titrant whose normality is 0.1000, the calculation is

(1.00) (0.1000) (milliequivalent weight of analyte) = titer

The USP-NF uses titer in titrimetric assays. Some examples are given in Table 30-2.

Titrimetric Assay Methods

The titrimetric assay procedure is the one most frequently encountered by the pharmaceutical chemist in the standardization of official products. Every titrimetric assay is based on the determination of the volume of a solution of known strength required to complete a chemical reaction with the substance being analyzed. Such a solution is called a *standard* or *volumetric solution* and is commonly referred to by the abbreviation *VS*.

Indicators for Determining Endpoints

It is imperative to avoid the error of using an insufficient amount of a volumetric solution, thus failing to complete a reaction; it is equally necessary to guard against overstepping a reaction by adding too much of the volumetric solution. To meet this situation, a group of chemicals known as *Indicators* is used. These are substances that show when the endpoint of a reaction has been reached, either by a change in color or by the formation of a precipitate.

INDICATOR SOLUTIONS

Solutions of indicators used for volumetric determinations are referred to as *Test Solutions* (TS), and those used for determination of hydrogen ion concentration are termed *pH indicators*.

Table 30-2. Titer Values for Selected Pharmaceuticals

ANALYTE	NATURE OF ANALYTICAL REACTION	n	TITRANT	TITER (1.00 mL =), mg
Ascorbic acid mw = 176.13	ET[a]	2	0.1*N* I_2	8.806
Chlorpromazine mw = 318.87	NAB[b]	1	0.1*N* $HClO_4$	31.89
Hydrogen peroxide concentrate mw = 34.01	ET	2	0.1*N* $KMnO_4$	1.701
Betaine hydrochloride mw = 153.61	NAB	1	0.1*N* $HClO_4$	15.36
Butabarbital mw = 224.26	P[c]	1	0.1*N* $AgNO_3$	22.43
Calcium acetate mw = 158.17	Complex[d]	1	0.05 *N* EDTA	7.909
Sodium hypochlorite solution mw = 74.44	ET	2	0.1 *N* $Na_2S_2O_3$	3.722
Sulfabenzamide mw = 276.32	NAB	1	0.1 *N* NaOMe	27.63
Zinc oxide mw = 81.39	AB[e]	2	1 *N* H_2SO_4	40.69

[a] ET indicates electron transfer.
[b] NAB indicates nonaqueous acid-base.
[c] P indicates precipitation.
[d] Complex indicates complex formation.
[e] AB indicates aqueous acid-base.

The indicators used for colorimetric pH determinations are either weakly acid or weakly basic. However, most indicators used for this purpose, such as the phthaleins and sulfonated phthaleins, behave like weak acids.

The usual concentration of the indicator solution is 0.05%. From 0.1 to 0.2 mL of the indicator solution is generally used for 10 mL of the liquid being examined.

Solutions of indicators of the basic type and of the phthaleins are prepared by dissolving them in alcohol. In preparing solutions of indicators containing an acid group, this group must first be neutralized with sodium hydroxide.

Unless otherwise stated each acid–base indicator solution is so adjusted that when 0.15 mL of the indicator solution is added to 25 mL of carbon dioxide-free water, 0.25 mL of 0.02 *N* acid or alkali, respectively, will develop the characteristic color changes.

The solutions should be kept in glass-stoppered bottles, and must be protected from light.

Indicators for Reactions Involving Neutralization

In the USP, indicators are used either to indicate the completion of a chemical reaction in volumetric analyses or to indicate the hydrogen ion concentration (pH) of solutions. Most of the indicators for acid–base titrations and for pH measurement are acidic. They contain a carboxyl, a sulfonic or a phenolic group. In many instances the same indicator is applicable either to acid–base titrations or to pH measurements, the difference being only in the preparation of the indicator solution. The following are the pH indicators of the Pharmacopeia; in each case Test Solutions (TS) of the following indicators are used.

Bromocresol Green (Bromocresol Blue: *Tetrabromo-m-cresolsulfonphthalein*)—Transition interval: from pH 4.0 to 5.4. Color change: from yellow to blue.

Bromocresol Purple (*Dibromo-o-cresolsulfonphthalein*)—Transition interval: from pH 5.2 to 6.8. Color change: from yellow to purple. This solution and the next two are satisfactory in the titration of weak bases.

Bromophenol Blue (*Tetrabromophenolsulfonphthalein*)—Transition interval: from pH 3.0 to 4.6. Color change: from yellow to blue.

Bromothymol Blue (*Dibromothymolsulfonphthalein*)—Transition interval: from pH 6.0 to 7.6. Color change: from yellow to blue.

Cresol Red (*o-Cresolsulfonphthalein*)—Transition interval: from pH 7.2 to 8.8. Color change: from yellow to red.

Cresol Red-Thymol Blue TS—Transition interval: from pH 7.7 to 9.1. Color change: from yellow to violet.

Malachite Green—The oxalate salt is used. Transition interval: from pH 0.0 to 2.0. Color change: from yellow to green.

Methyl Orange (*Helianthin* or *Tropaeolin D*)—The sodium salt of dimethylaminoazobenzenesulfonic acid or dimethylaminoazobenzene sodium sulfonate. Transition interval: from pH 3.2 to 4.4. Color change: from pink to yellow. Useful in the titration of weak bases.

Methyl Red (*Dimethylaminoazobenzene-o-carboxylic acid; o-carboxybenzeneazodimethylaniline*)—Transition interval: from pH 4.2 to 6.2. Color change: from red to yellow. Useful in the titration of weak bases.

Methyl Red-Methylene Blue TS—Transition interval: from pH 4.8 to 6.2. Color change: from red-violet to green.

Methyl Yellow (*p-Dimethylaminoazobenzene*)—Transition interval: from pH 2.9 to 4.0. Color change: from red to yellow.

Phenolphthalein—Use *Phenolphthalein USP*. Transition interval: from pH 8.0 to 10.0. Color change: from colorless to red. Useful in the titration of acids with strong bases.

Phenol Red—Use Phenolsulfonphthalein USP. Transition interval: from pH 6.8 to 8.2. Color change: from yellow to red.

Quinaldine Red (*5-Dimethylamino-2-styrylethylquinolinium iodide*)—Transition interval: pH 1.4 to 3.2. Color change: from colorless to red.

Thymol Blue (*Thymolsulfonphthalein*). *Acid*—Transition interval: from pH 1.2 to 2.8. Color change: from red to yellow. *Alkaline*—Transition interval: from pH 8.0 to 9.2. Color change: from yellow to blue.

Thymolphthalein—Transition interval: from pH 9.3 to 10.5. Color change: from colorless to blue.

Indicators for Reactions Involving Precipitation

Dichlorofluorescein TS.
Eosin Y (Sodium Tetrabromofluorescein) TS.
Ferric Ammonium Sulfate TS—8% in water. This indicator, well-known as *Ferric Alum,* generally is used when titrating with standard ammonium thiocyanate in the presence of silver nitrate. A red color of the ferric thiocyanate complex forms immediately when the silver thiocyanate has been completely precipitated.
Potassium Chromate TS—10% in water. This indicator gives a red precipitate of silver chromate in a neutral or slightly alkaline solution, after silver halides have been completely precipitated by titration with standard silver nitrate.
Sodium Alizarinsulfonate TS.
Tetrabromophenolphthalein TS.
Tetrabromophenolphthalein, Ethyl Ester TS.
Indicators for Nonaqueous Titrations
Azo-violet.
Crystal Violet (TS)—1% in glacial acetic acid.
Malachite Green—Use Malachite Green TS.
Methyl Red—Use Methyl Red TS.
Methyl Violet—Use Methyl Violet TS.
***p*-Naphtholbenzein**—4-[α-(4-hydroxy-1-naphthyl)benzylidene]-1-(4*H*)[naphthalenone].
Phenol Red—Use Phenol Red TS.
Quinaldine Red—Use Quinaldine Red TS.
Thymol Blue—Use Thymol Blue TS.

Indicators for Complexometric Titrations

Diphenylamine TS.
Dithizone (*Diphenylthiocarbazone*) **TS.**
Eriochrome Black TS—0.05% aqueous solution (should be freshly prepared but can be stabilized).
Hydroxynaphthol Blue.
Murexide (*Acid Ammonium Purpurate*)
Used as a powder; usually mixed with an inert carrier (potassium sulfate) to facilitate handling.
Naphthol Green TS.
1-(2-Pyridylazo)-2-naphthol.

Indicators for Reactions Involving Changes in Valence

2,6-Dichloroquinone-chlorimide (*Dichlorophenolindophenol*)— Usually used as the sodium salt in a solution containing sodium bicarbonate to titrate ascorbic acid dosage forms. In oxidized form, it is blue in alkaline and rose-pink in acid solution; when reduced, it is colorless.

Dicyanobis(1,10-phenanthroline)iron II Dihydrate—An indicator that reacts similarly to ortho-phenanthroline.

Diphenylamine—Employed in titrations involving potassium dichromate as titrant. In reduced form it is colorless; in a reversible oxidation reaction it produces a brilliant violet diphenylbenzidine derivative.

Iodine—Free iodine serves as its own indicator in assays where it is liberated and determined volumetrically by titration with standard potassium iodate. The endpoint is the disappearance of the violet color of iodine in chloroform added to the mixture being titrated for the purpose of dissolving and concentrating the iodine.

Methyl Orange—Used as a test solution in titrations with potassium bromate; the color of this external indicator is discharged by excess titrant.

Nitrophenanthroline—An indicator that reacts similarly to *ortho*-phenanthroline.

***Ortho*-phenanthroline—**Used in 1.5% concentration in 1.5% ferrous sulfate solution as an indicator in titrations involving standard ceric sulfate solution. The color changes from red to pale green when the slightest excess of ceric sulfate is added to the oxidized solution.

Oxalic Acid VS—This standard solution generally is used without an indicator because most reactions in which it takes part depend on decolorization of potassium permanganate.

Potassium Permanganate VS—This highly colored solution is decolorized on being reduced, so a separate indicator is not required.

Potassium Thiocyanate—Used in conjunction with ferric chloride volumetric solution, a red compound is produced at the endpoint.

Starch Iodide Paste TS—Approximately 5% suspension of potato starch in 0.75% potassium iodide with zinc chloride preservative. May be used as an external indicator for titrations with sodium nitrite VS. Starch iodide paste test solution must show a definite blue streak when a glass rod, dipped in a mixture of 1 mL of 0.1 *M* sodium nitrite, 500 mL of water, and 10 mL of hydrochloric acid is streaked on a smear of the paste.

Starch-Potassium Iodide TS—0.5% KI in Starch TS. Must be freshly prepared.

Starch TS—A 0.5% suspension of arrowroot starch in water, freshly prepared. A blue color is produced by starch in the presence of free iodine.

INDICATOR PAPERS

Strong, white filter paper is treated with hydrochloric acid and washed with water until the washings no longer show an acid reaction to methyl red. It then is treated with ammonia TS and again washed with water, until the washings are no longer alkaline toward phenolphthalein. It then is dried thoroughly.

The dry paper is saturated with the proper strength indicator solution and carefully dried by suspending the paper in a room free from acid or alkali fumes.

The papers so prepared are kept in glass-stoppered bottles, and must be protected from light and moisture.

Lead Acetate Test Paper—Prepared from lead acetate TS.

Litmus Paper, Blue—Usually in the form of strips about 50 mm in length and 6 mm in width.

Litmus Paper, Red—Usually in the form of strips about 50 mm in length and 6 mm in width.

Mercuric Bromide Test Paper—Prepared from alcoholic mercuric bromide TS.

Phenolphthalein Paper—Prepared from a 0.1% solution of phenolphthalein in diluted alcohol.

Potassium Iodate-Starch Paper—Strips of white filter paper impregnated with a solution prepared by mixing a 5% solution of potassium iodate with an equal volume of freshly prepared starch TS.

Starch Iodate Paper—Strips of white filter paper impregnated with a mixture of equal volumes of starch TS and potassium iodate solution (1 in 20).

Starch Iodide Paper—Strips of white filter paper impregnated with a solution of 500 mg of potassium iodide in 100 mL of freshly prepared starch TS.

Turmeric Paper—Strips of white filter paper impregnated with turmeric solution prepared as directed in the USP.

Potentiometric Determination of Endpoints

The detection of the endpoint in titrimetric assays by use of colorimetric indicators may sometimes be difficult, especially if the solution being titrated is colored or turbid. In some instances, titration to the equivalence or true endpoint is essential, a requirement that is not met conveniently when an indicator is employed. In such cases the endpoint may be indicated potentiometrically, most commonly employing the millivolt scale of a pH meter. The potentiometric determination of endpoints depends on the fact that in most titrations the potential across two suitable electrodes immersed in the solution being titrated undergoes a sharp change at the true endpoint (equivalence point); this change corresponds to the point where an indicator undergoes marked change of color. In some titrations neither the change of color nor the change of potential is sharp at the endpoint, in which case titration to a predetermined voltage or voltage deflection is necessary. As it generally is more convenient to do this potentiometrically, rather than colorimetrically, this electrochemical method is employed. Suitable electrodes, such as a combination glass-calomel electrode, serve as a means of *detecting* the endpoint by sensing ionic activities.

It may be pointed out here that the change of other electrical properties, such as resistance or the amount of current flowing in a solution being titrated, may be used to indicate the endpoint in a titration. The general term *electrometric titrations* sometimes is applied to such titrations; specific

titrations in this category are referred to as *amperometric, conductometric,* and *high-frequency titrations.*

Titrimetric Procedures

Table 30-3 contains the indicator abbreviations used in these sections. See Appendix A for explanation of abbreviations in parentheses appearing at the end of headings used throughout the rest of this chapter.

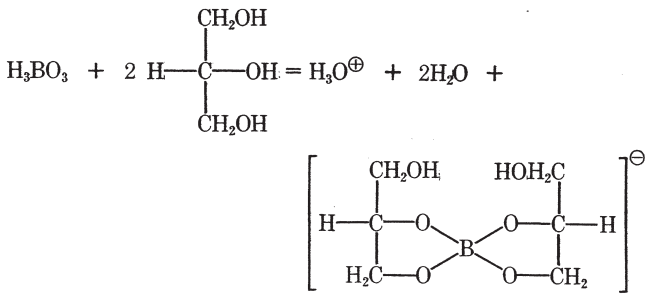
ACID–BASE REACTIONS

DIRECT OR RESIDUAL TITRATION OF AN ACID BY BASE (IA1A,IA2A)

In this category a free acid is titrated directly using the method indicated in the monograph to determine the endpoint.

Phosphoric Acid—Titrated in water with 1 *N* NaOH to a TP endpoint.

Boric Acid—The use of glycerin increases the acid strength of the boric acid by formation of a glycero-borate complex according to the equation given here.



Cellulose Acetate Phthalate—Phthalyl content.

Dibasic Sodium Phosphate—Treatment of the salt with hydrochloric acid forms phosphoric acid and the endpoint is determined potentiometrically from pH readings. Only one hydrogen of phosphoric acid is titrated in this procedure.

Oxyphenbutazone—Even though a phenol, it is sufficiently strong to be titrated directly.

Potassium Phosphate, Monobasic—See *Sodium Phosphate,* above.

Sodium Citrate and Citric Acid Oral Solution—For citric acid, titration to a phenolphthalein endpoint.

Sodium Phosphates Enema and Oral Solution—After the addition of a standard base, the solution is titrated potentiometrically, with standard acid, to two inflection points in the titration curve.

Sulfinpyrazone—The sulfonyl group (—SO_2—) makes the alpha-hydrogen sufficiently acid so that it may react with base.

Sulfur—Sulfur is oxidized to sulfuric acid by the *oxygen flask technique,* then titrated. In the *oxygen flask technique,* the sample is burned in a thick-walled iodine flask in an atmosphere of oxygen, in the presence of an absorbing solution (the nature of which depends on the sample being analyzed). After combustion the flask is shaken to absorb any gaseous product and treated as directed in the specific monograph.

TITRATION OF A LIBERATED ACID BY A BASE (IA1AI)

Cellulose, Oxidized—The sample is shaken with calcium acetate solution, to exchange calcium ion for hydrogen ion of the free carboxyl groups. The liberated hydrogen ion is then titrated with standard base.

Phenacemide (and Tablets)—The amide is hydrolyzed to phenylacetic acid, extracted with chloroform, evaporated, and the free acid titrated.

SØRENSEN FORMOL TITRATION (IA1AII)

Meprobamate (and Oral Suspension)—After hydrolysis of the ester.

Protein Hydrolysate Injection—For alpha-amino nitrogen.

In each case the free amino acid is treated with formaldehyde to form the methylimino or methylol derivative, reducing the basicity of the amino group so that the free carboxyl group may be titrated.

$$RCH(NH_2)COOH + HCHO = RCH(NHCH_2OH)COOH \text{ or } RCH(N{=}CH_2)COOH$$

RESIDUAL TITRATION OF EXCESS BASE AFTER INTERACTION WITH ACID (IA2B)

In this type of assay a measured excess of standard base is added to the prepared sample and the excess titrated with standard acid. Quite often a blank titration is performed, whereby the same volume of base, which was added to the sample, is titrated with standard acid. The difference in the volume of titrant used for the blank and sample is the volume of titrant equivalent to the sample.

Chloral Hydrate (and Capsules and Syrup)—The chloral-containing compounds are treated with excess standard sodium hydroxide which hydrolyzes the chloral to chloroform and sodium formate. Excess base is titrated with standard acid.

$$CCl_3CHO \cdot H_2O + NaOH = CHCl_3 + HCOONa + H_2O$$

With Chloral Hydrate Syrup a correction must be made for original acidity by a preliminary titration of the sample with base.

Ethyl Chloride—For ethyl chloride the halogen is hydrolyzed with excess standard alcoholic alkali and the excess titrated with acid.

Formaldehyde Solution—The formaldehyde is oxidized to formic acid with peroxide in the presence of excess standard base and the excess titrated.

Glutaral Concentrate—to a solution of hydroxylamine hydrochloride, neutralized to BpB with triethanolamine, a measured excess of triethanolamine is added, followed by the sample. The HCl liberated in the following reaction combines with triethanolamine and the excess is titrated with standard sulfuric acid. A blank is run on the reagents.

$$OHC(CH_2)_3CHO + 2NH_2OH \cdot HCl = HON{=}CH(CH_2)_3CH{=}NOH + 2H_2O + 2HCl$$

Methenamine and Monobasic Sodium Phosphate Tablets—for sodium biphosphate.

All of the phosphates above are assayed by first precipitating ammonium phosphomolybdate from a dilute nitric acid solution of the sample:

$$AlPO_4 + 12(NH_4)_2MoO_4 + 24HNO_3 = (NH_4)_3PO_4 \cdot 12MoO_3 + 21NH_4NO_3 + Al(NO_3)_3 + 12H_2O$$

The precipitated yellow molybdate is filtered, washed free of adhering nitric acid, and dissolved in an excess of standard alkali:

$$(NH_4)_3PO_4 \cdot 12MoO_3 + 23NaOH = 11Na_2MoO_4 + NaNH_4HPO_4 + (NH_4)_2MoO_4 + 11H_2O$$

Excess standard alkali then is titrated with standard acid.

DIRECT TITRATION OF BASE BY ACID (IA1B)

Oxtriphylline—For choline, using MeB.

Potassium Hydroxide—For potassium hydroxide using Phth and for potassium carbonate content using MeO.

Tromethamine (and for Injection)—For tromethamine using BcP.

TITRATION OF VOLATILE BASES AFTER DISTILLATION (IA2AI,IA1C)

Compounds in this category usually are hydrolyzed by boiling with strong alkali, and the ammonia or amines formed are distilled into excess standard acid or into a saturated boric acid solution. In either case, the excess standard acid is titrated with standard base, or the ammonia-boric acid complex titrated with acid; methyl red is the indicator for either method.

If the nitrogen content only is determined, the Kjeldahl procedure is used. The general procedure for the Kjeldahl method involves digestion of the sample with a mixture of sulfuric acid and potassium sulfate in the presence of a catalyst. Copper, selenium, or mercury salts have been used as catalysts. After conversion of the organic nitrogen to ammonia (ammonium ion in the acidic medium), alkali is added and the liberated ammonia is distilled and collected in standard sulfuric acid or in boric acid. Titration of the residual sulfuric acid or the ammonium ion in the boric acid solution allows calculation of the nitrogen content (IA1c).

Calcium Pantothenate—Nitrogen content by Kjeldahl method.

Glucagon—Nitrogen content by Kjeldahl method.

Ichthammol (and Ointment)—For ammonia; make alkaline and distill into excess standard acid.

Neostigmine Methylsulfate—Dimethylamine distilled.

Pyrazinamide—Amide hydrolyzed and ammonia distilled.

TITRATION OF METAL SALTS WITH ACID (IA1BI)

Caffeine and Sodium Benzoate Injection—The caffeine is extracted with chloroform, ether is added to the residual aqueous solution,

Table 30-3. Indicators, Color Developing Reagents, and Techniques[a]

AAP	4-Aminoantipyrine
AAPF	4-Aminoantipyrine and potassium ferricyanide
AC	Antimony trichloride
ACBD	4-Amino-6-chloro-1,3-benzenedisulfonamide (diazotized)
ACT	Ammonium cobaltothiocyanate
AMDB	Alkaline metadinitrobenzene
ANB	Alpha-nitroso-beta-naphthol (diazotized)
ANS	1,2,4-Aminonaphtholsulfonic acid
AP	Alkaline picrate, TS
AS	Ammonium molybdate and stannous chloride
AT	Ammonium thiocyanate
AV	Azoviolet
BcB	Bromocresol blue
BcG	Bromocresol green
BcP	Bromocresol purple
BF	Basic fuchsin
BM	Bratton-Marshall reagent; *N*-(1-naphthyl)ethylenediamine added to the diazotized solution
BnF	Beta-Naphthoquinone sulfonate—formaldehyde
BpB	Bromophenol blue
BPy	2,2′-Bipyridine
BT	Blue tetrazolium
BtB	Bromothymol blue
CAN	Ceric ammonium nitrate, TS
C-S	Cyanogen bromide—sulfanilic acid
CR	Cresol red, TS
CRTB	Cresol red—thymol blue, TS
CrV	Crystal violet, TS
CTA	Chromotropic acid
DCF	Dichlorofluorescein
DC	Diphenylcarbazone, TS
DBP	Dicyanobis(1,10-phenanthroline)iron II dihydrate
DBQ	2,6-Dibromoquinone chlorimide
DcD	2,6-Dichloroquinone chlorimide
DNP	2,4-Dinitrophenylhydrazine
DP	Diphenylamine, TS
DT	Dithizone
EBT	Eriochrome black T
EY	Eosin Y, TS
FAS	Ferric ammonium sulfate, TS
FC	Ferric chloride, acid, TS
FCiT	Ferrocitrate reagent
FCP	Folin-Ciocalteau-Phenol, TS
FEH	Ferric chloride and hydroxylamine
FEN	Ferric nitrate
FET	Ferrous tartrate reagent
HDA	Hexanitrodiphenylamine
HNB	Hydroxynaphthol blue
HQ	8-Hydroxyguinoline
IN	Isoniazid reagent
IP	Iron-phenol reagent
MaG	Malachite green, TS
MDB	Metadinitrobenzene
MeB	Methylene blue
MeO	Methyl orange
MeP	Methyl purple, TS
MeR	Methyl red, TS
MeY	Methyl yellow (*p*-dimethylaminoazobenzene)
MP	Molybdophosphotungstate, TS
MRB	Methyl red—methylene blue, TS
MV	Methyl violet, TS
Nb	Para-Naphtholbenzein
NiB	Nile blue hydrochloride
Np	Nitrophenanthroline, TS
ON	Oxidized nitroprusside solution
ONA	Ortho-Nitroaniline
Op	Ortho-Phenanthroline, TS
PAN	1-(2-Pyridylazo)-2-naphthol
PBA	Para-Bromoaniline
PC	Potassium chromate, TS
PDA	Para-Dimethylaminoazobenzene
PDB	Para-Dimethylaminobenzaldehyde
PdC	Palladium chloride
PDS	Phenoldisulfonic acid
PH	Phenylhydrazine hydrochloride
Phth	Phenolphthalein
Poten	Potentiometric determination of the endpoint
PR	Phenol red
PTB	Phenolphthalein—thymol blue
PTC	Potassium thiocyanate
PyA	Pyridine-acetic anhydride
QR	Quinaldine red
R	Reinecke's salt
SA	Sulfuric acid in methanol
SAF	Sodium acetate-potassium ferricyanide
SAS	Sodium alizarinsulfonate, TS
SD	Sudan IV
SN	Sodium nitrite in acid solution
SNF	Sodium nitroferricyanide, TS
SaO	Safranin O
SPI	Starch-potassium iodide, TS, or paper or paste
ST	Starch, TS
TB	Thymol blue
TBP	Tetrabromophenolphthalein, TS
TBPE	Tetrabromophenolphthalein, ethyl ester, TS
TNP	Trinitrophenol (picric acid)
TP	Thymolphthalein
TTC	Triphenyltetrazolium chloride
UV	Ultraviolet radiation
VS	Vanadyl sulfate
XyO	Xylenol orange

[a] These are coded in the last column of Appendix B. They usually are employed as solutions, and often are the official Test Solutions (TS).

and the mixture is titrated with acid, shaking vigorously. As free benzoic acid is liberated by titration with hydrochloric acid, it is immediately extracted into the ether phase. As the endpoint is exceeded, excess titrant causes the indicator (MeO) to change.

RESIDUAL TITRATION OF EXCESS ACID AFTER INTERACTION WITH BASE (IA2a)

For this category, a basic substance is treated with a measured excess of standard acid and the excess acid titrated with standard base.

Ammonia Spirit, Aromatic—For the total ammonia assay, the sample is boiled with excess standard acid and the excess titrated with sodium hydroxide. The ammonium carbonate is converted into an equivalent amount of sodium carbonate.

Magnesium Trisilicate—For magnesium oxide (MeO).

Zinc Undecylenate—Excess standard sulfuric acid is boiled with the salt, the liberated undecylenic acid is extracted with hexane, and the aqueous phase is titrated with standard base (MeO).

RESIDUAL TITRATION OF EXCESS ACID FOLLOWING LIBERATION OF A BASE BY A STRONGER BASE (IA2A)

Assays of this kind also are applied to extractions made of vegetable drugs containing alkaloidal principles and to the pharmaceutical preparations obtained from them.

All of the assays are based on the principle that relatively weak organic bases are displaced readily from their salts by a stronger base, such as sodium hydroxide, sodium carbonate, or ammonium hydroxide.

The last compound is more generally employed to liberate alkaloids from their salts. The liberated free bases are then extracted into an organic solvent (ether or chloroform) and the separated organic phase evaporated.

TITRATION OF CARBONATE RESIDUES FROM IGNITED SALTS (IA2AII)

In general the ignition of an alkali metal salt of a carboxylic acid forms sodium carbonate, carbon dioxide and water as exemplified by sodium citrate:

$$2Na_3C_6H_5O_7 + 9O_2 = 3Na_2CO_3 + 9CO_2 + 5H_2O$$

Excess standard acid is added to the ignition residue and the residue titrated with base. The volume of standard acid consumed is multiplied by the appropriate conversion factor to determine the amount of alkali salt in the sample taken.

Magnesium Citrate Oral Solution—For citric acid (Phth), after precipitation of calcium citrate and ignition of the filtered salt.

RESIDUAL TITRATION INVOLVING SAPONIFICATION OF AN ESTER (IA2bi)

In general, esters are determined by a saponification procedure of boiling the sample in excess standard alcoholic alkali, which acts as a mutual solvent. The excess alkali is determined with standard acid. A blank usually is run on the same volume of alkali used for the saponification procedure.

Oxandrolone—The ester is present in lactone form.

Peppermint Oil—For total menthol content. The free menthol first is acetylated with acetic anhydride to form the ester, menthyl acetate. After purification to remove excess acetic acid and water, the ester is subjected to the saponification procedure.

Polysorbates—Saponification value.

Polyvinyl Alcohol—Degree of hydrolysis.

Storax—Saponification value.

Tolu Balsam—Saponification value.

RESIDUAL TITRATION FOLLOWING AN ACYLATION REACTION (IA2aiii)

The general method involves the treatment of an alcohol with an acylating reagent, usually acetic anhydride or phthalic anhydride in pyridine. Any excess anhydride remaining after the esterification reaction is converted to the free acid with water, and the acid titrated with standard base. A blank usually is run employing all the reagents except the sample. The difference in titer between the blank and the sample is the volume of base equivalent to the alcohol content of the sample taken.

Polyethylene Glycol—For average molecular weight, using phthalic anhydride in pyridine.

RESIDUAL TITRATION FOLLOWING THE HYDROLYSIS OF ALKOXYL GROUPS (IA2bii)

A previously neutralized sample is saponified with excess standard base, and the excess is determined in the usual manner.

Pectin—For methoxyl groups (galacturonic acid).

PRECIPITATION REACTIONS

TITRATION OF LIBERATED NITRIC ACID (IB1E)

In assays of this type, silver nitrate reacts with the substance being assayed to form an insoluble silver derivative, simultaneously releasing an equivalent amount of nitric acid, which is titrated with standard alkali.

Oxtriphylline—For theophylline. The solution from the choline assay is treated with silver nitrate and the above method followed.

DIRECT TITRATION OF A THEOPHYLLINE–SILVER COMPLEX (IB1BI)

The theophylline–silver complex is separated by filtration, dissolved in nitric acid, and the liberated silver ion titrated with thiocyanate (FAS indicator).

Aminophylline—Some dosage forms, for theophylline.

RESIDUAL TITRATION OF A THEOPHYLLINE–SILVER COMPLEX (IB2ai)

The insoluble silver complex is precipitated from an ammoniacal solution of the sample by warming with excess standard silver nitrate. After filtration, the excess silver ion is determined in the filtrate by titration with thiocyanate (FAS indicator).

Dimenhydrinate—For 8-chlorotheophylline.

DIRECT TITRATION OF HALOGEN (IB1a)

These assays may involve the conversion of organic halogen to halide ion (if covalently bound) before titration. Silver nitrate is the titrant in all cases.

The following are titrated without previous treatment:

Anticoagulant Heparin Solution and Heparin Lock Flush Solution—For NaCl.

The following require hydrolysis with alkali:

Melphalan.

Methyclothiazide—Although two chlorine atoms occur in the molecule, only the benzylic halogen is sufficiently active to be hydrolyzed and then titrated with silver nitrate.

The following require refluxing with zinc and alkali to liberate the halogen:

Diatrizoate Meglumine (and Injection).

Diatrizoate Meglumine and Diatrizoate Sodium Injection—The assay gives both compounds and a correction is made for Diatrizoate Meglumine.

Diatrizoate Sodium (and Injection and Solution).

Diatrizoic Acid.

Iocetamic Acid (and Tablets).

Iodipamide.

Iodipamide Meglumine Injection.

Iopanoic Acid.

Iothalamate Meglumine Injection.

Iothalamate Meglumine and Iothalamate Sodium Injection.

Iothalamate Sodium Injection.

Iothalamic Acid.

Ipodate Calcium (and for Oral Suspension).

Ipodate Sodium (and Capsules).

RESIDUAL TITRATION OF HALOGEN (IB2aii)

Excess standard silver nitrate is added to a solution of the prepared sample containing ionic halogen. The excess silver nitrate is then titrated with standard ammonium thiocyanate. This method is known as the Volhard procedure. Nitrobenzene is added, in the titration involving silver chloride, to prevent its interaction with thiocyanate. Ferric Alum (FAS) is the usual indicator. Quite often the ionic halogen must be liberated from an organic compound.

Chlorobutanol—After hydrolysis with base.

Mannitol in Sodium Chloride Injection—For sodium chloride.

Sodium Chloride and Dextrose Tablets—For sodium chloride.

TITRATION WITH THIOCYANATE (IB1b)

Silver ion or mercury(II) ion is titrated with thiocyanate. With silver, insoluble silver thiocyanate is formed; with mercury(II) un-ionized mercuric thiocyanate is produced. Ferric alum (FAS) is the usual indicator.

Nitromersol (and Solution)—The sample is digested with sulfuric acid and peroxide, and oxidized with permanganate to form mercuric ion.

Phenylmercuric Acetate and Phenylmercuric Nitrate—Both are decomposed with formic acid to release mercury, which is scavenged with zinc metal and then dissolved in nitric acid.

TITRATION WITH THORIUM(IV) (IB1d)

Sodium Monofluorophosphate—The sample, acidified with sulfuric acid, is distilled and the fluoride-containing distillate is titrated with thorium nitrate solution, using sodium alizarinsulfonate indicator. Insoluble thorium tetrafluoride is formed in the acid solution, and when all the fluoride ion is precipitated the pink-red thorium salt of the indicator is produced.

REDOX REACTIONS

TITRATIONS INVOLVING DIRECT OXIDATION WITH CERIC SULFATE (IC1a)

Ceric sulfate is of value in titrating iron(II) salts in mixtures that contain excipients or diluents that have a reducing action on permanganate, but have no effect on ceric sulfate. The equation that applies is

$$2FeSO_4 + 2Ce(SO_4)_2 = Fe_2(SO_4)_3 + Ce_2(SO_4)_3$$

Ferrous Fumarate—Prior to titration with ceric sulfate, stannous chloride is added to ensure that all the iron is in the reduced state; excess tin is removed by precipitation with mercuric ion.

Homatropine Hydrobromide—Following hydrolysis with base, the mandelic acid thereby liberated is oxidized by the titrant.

Menadione—The quinone groups are reduced with zinc and acid to hydroquinone and then reoxidized with the titrant.

DIRECT TITRATION WITH POTASSIUM PERMANGANATE (IC1b)

The sample is oxidized directly by the permanganate titrant. No indicator is required, as a slight excess of permanganate imparts a distinct pink color indicating the endpoint.

Hydrogen Peroxide Concentrate (and Topical Solution).

TITRATION USING FERRIC ALUM AND PERMANGANATE (IC1bi)

In this reaction category an excess of ferric ammonium sulfate is added to the sample, which reduces the ferric iron to iron(II), and the latter is titrated with permanganate.

Titanium Dioxide—The sample is dissolved by heating with sulfuric acid and ammonium sulfate; the titanium(IV) is reduced to titanium(III) with zinc amalgam, and ferric alum is added to reoxidize the titanium with simultaneous formation of an equivalent amount of ferrous ion, which is titrated with permanganate.

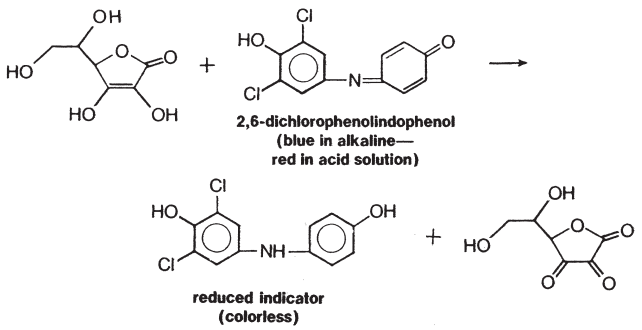
RESIDUAL TITRATION USING OXALIC ACID AND PERMANGANATE (IC2e)

Potassium Permanganate—An excess of standard oxalic acid is reacted with a warm, acidified solution of the sample; the excess oxalic acid then is titrated with permanganate.

Sodium Nitrite—The nitrite first is oxidized to nitrate with an excess of standard permanganate and the unreacted permanganate is reduced with an excess of oxalic acid, which is titrated with more standard permanganate. The reason for using an excess of permanganate in the first step is to prevent loss of nitrous acid on acidifying the sodium nitrite; the addition of an excess of oxalic acid is to ensure reduction of permanganate to manganous ion rather than an intermediate of higher valence.

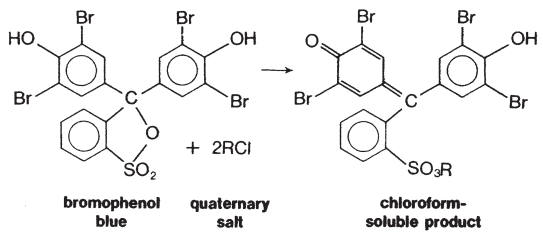
DICHLOROPHENOL-INDOPHENOL TITRATION (IC1c)

Ascorbic acid in Ascorbic Acid Injection may be oxidized quantitatively by titration with dichlorophenol-indophenol volumetric solution, which also serves as its own indicator. During the titration, the blue color of the dichlorophenol-indophenol solution is discharged by the reducing action of the ascorbic acid; when the endpoint is reached, a permanent reddish color is imparted by the slightest excess of titrant. The reaction is explained as



SODIUM TETRAPHENYLBORON TITRATION (IE1)

Quaternary ammonium salts are capable of forming chloroform-soluble compounds with bromophenol blue as



The product is extracted from alkaline solutions into chloroform. Titration with sodium tetraphenylboron removes the quaternary salt from the product, discharging the color from the chloroform layer. In this assay, the quaternary salt and bromophenol blue, in a mixture of chloroform and water, are titrated with the sodium tetraphenylboron solution.

ASSAYS INVOLVING DIPHASIC AMINE-SURFACTANT TITRATION (IE2 AND 3)

Cetylpyridinium Chloride Lozenges—See *A*, below.
Docusate Calcium—See *B*, below (TBA).
Docusate Potassium—See *B*, below (TBA).
Docusate Sodium—See *B*, below (TBA).
Methylbenzethonium Chloride Dosage Forms—See *A*, below.

***A.*—**In th—is type of assay, the amine salt is dissolved in chloroform, the indicator is added, and the mixture is shaken. The indicator dissolves in the organic phase. Titration of this two-phase system (with adequate shaking) with a surfactant solution, such as sodium lauryl sulfate, produces a water-soluble complex between amine and surfactant. As the endpoint is exceeded, the excess surfactant reacts with the basic dye (in the organic layer) and the indicator color changes from pale yellow to red (MeY), blue (BpB), or pink (SaO). Standardization of the titrant is effected using a pure sample of the substance being assayed as the standard.

***B.*—**In this modification, the surfactant is the substance being assayed and is added to the chloroform-water–indicator mixture. The titration is now performed using a solution of a quaternary amine (cetalkonium chloride-CAC or tetrabutylammonium iodide-TBA) and the endpoint is reached when the color *disappears* from the chloroform layer.

DIRECT TITRATION WITH TITANIUM TRICHLORIDE (IC1f)

These titrations depend on the reduction of the colored sample and subsequent discharge of the color at the endpoint.

RESIDUAL TITRATION WITH TITANIUM TRICHLORIDE (IC2d)

The sample is heated with excess standard titanium trichloride, in an inert atmosphere. Excess reagent is determined by titration with ferric ammonium sulfate; as the indicator, thiocyanate ion gives a red endpoint.

TITRATION OF IODINE LIBERATED FROM POTASSIUM IODIDE (IC1lii)

Assays in this category involve addition of the substance being assayed to an acidified solution of potassium iodide as exemplified by the equation with cupric sulfate:

$$2CuSO_4 + 4KI = 2CuI + I_2 + 2K_2SO_4$$

The liberated iodine is titrated with thiosulfate; starch is employed as the indicator:

$$I_2 + 2Na_2S_2O_3 = 2NaI + Na_2S_4O_6$$

In many cases the sample requires an initial special treatment.

Ethiodized Oil Injection—See *A*, below.
Ethylcellulose—For ethoxyl, by the Zeisel alkoxy procedure.
Ferric Oxide—As for Ferrous Fumarate Tablets, replacing nitric acid with hydrochloric acid.
Ferrous Fumarate Tablets—The sample is decomposed with nitric and perchloric acids. Addition of KI to the iron(III) solution causes reduction of the iron and liberation of free iodine, which is titrated with thiosulfate.
Iodoquinol (and Tablets)—See *A*, below.
Iophendylate and Injection—Treatment with sodium biphenyl in toluene liberates iodide ion, which is extracted into dilute phosphoric acid. Addition of hypochlorite then liberates free iodine.
Methylcellulose Ophthalmic Solution and Oral Solution—Methoxyl; see *Ethylcellulose,* above.
Propyliodone (and dosage forms)—See *A*, below.
Selenium Sulfide (and Lotion)—After treatment with fuming nitric acid to form selenious acid. Potassium iodide then reduces the selenium, liberating iodine:

$$H_2SeO_3 + 4KI + 4H^+ = Se + 2I_2 + 4K^+ + 3H_2O$$

***A.*—**Substances in this category are initially decomposed using the *Oxygen Flask Combustion Method,* and the sample is treated with bromine, as directed for *B,* below.

***B.*—**The sample is fused with potassium carbonate, acidified, and oxidized with bromine to form iodate and bromide ions. The solution is boiled to expel bromine; phenol or formic acid is added to scavenge any remaining halogen; then KI is added and the iodate ion liberates free iodine, which is titrated.

TITRATIONS WITH POTASSIUM IODATE (IC1n)

When potassium iodate solution is titrated into an acidified solution of an alkali metal iodide, free iodine is liberated according to

$$5KI + KIO_3 + 6HCl = 6KCl + 3I_2 + 3H_2O$$

When this step of the reaction is complete, and if a sufficiently high concentration of hydrochloric acid is present, the liberated iodine is converted into iodine monochloride, as is shown by

$$KIO_3 + 2I_2 + 6HCl = KCl + 5ICl + 3H_2O$$

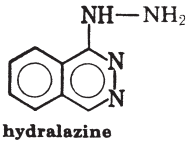
Combining both reactions,

$$KIO_3 + 2KI + 6HCl = 3KCl + 3ICl + 3H_2O$$

The endpoint of this titration is the disappearance of the iodine color from a few milliliters of chloroform, added to serve as an indicator.

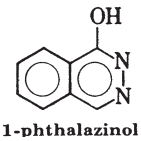
Benzalkonium Chloride (and Solution)—Each equivalent of the quaternary chloride yields one equivalent of iodide ion, which is titrated according to the above reaction.

Hydralazine Hydrochloride Injection—The hydrazino group of hydralazine is oxidized by potassium iodate to nitrogen and is replaced by a hydroxyl group on the phthalazine ring in accordance with



hydralazine

$$+ KIO_3 + 2HCl =$$



1-phthalazinol

$$KCl + ICl + N_2 + 2H_2O$$

Iodine Topical Solution—For sodium iodide; free iodine is first reduced by titration with arsenite.

Strong Iodine Solution—For potassium iodide; as for *Iodine Topical Solution.*

Iodine Tincture, Strong Iodine Tincture—For sodium iodide and potassium iodide; as for *Iodine Topical Solution.*

Stannous Fluoride—For tin(II); in HCl solution, KI is added and iodide is converted to iodine, which is titrated with iodate.

REACTION OF KI WITH EXCESS PERIODATE (IC1Liii)

Mannitol Injection—An acidified solution of the prepared sample is heated with periodate and acid, oxidizing the mannitol as

$$C_6H_{14}O_6 + 5HIO_4 = 2HCHO + 4HCOOH + 5HIO_3 + H_2O$$

The excess periodate and the iodate formed in the reaction react with KI to liberate iodine

$$HIO_3 + HIO_4 + 12HI = 7I_2 + 7H_2O$$

A blank is performed and the difference in the volumes of thiosulfate titrant is equivalent to the mannitol in the sample.

Mannitol in Sodium Chloride Injection—For Mannitol Injection, as above.

DIRECT TITRATION OF IODINE WITH THIOSULFATE (IC1l)

No preliminary preparation of the sample is necessary, as the iodine is present in the free state.

Povidone-Iodine—For available iodine.

RESIDUAL TITRATION OF IODINE FOLLOWING DICHROMATE PRECIPITATION (IC2ai)

These assays are based on the insolubility of the dichromate precipitated from an aqueous solution of the sample on the addition of excess standard potassium dichromate. After removal of the precipitate, the excess dichromate in the filtrate is determined by adding excess KI, which liberates free iodine and is titrated with thiosulfate.

$$Cr_2O_7^{2-} + 14H^+ + 6I^- = 3I_2 + 2Cr^{3+} + 7H_2O$$

RESIDUAL TITRATION OF EXCESS STANDARD IODINE (IC2a,f)

A sample of the assay material is oxidized or converted to a periodide or iodine substitution product with standard iodine, and the excess iodine is determined by titration with thiosulfate.

Phenelzine Sulfate—The hydrazine is oxidized by iodine as indicated by

$$C_6H_5CH_2NHNH_2 \cdot H_2SO_4 + 2I_2 + 5NaHCO_3 = C_6H_5CH_2I + 3NaI + Na_2SO_4 + 5CO_2 + 5H_2O + N_2$$

IODIMETRIC DETERMINATION OF PHENOLS (IC2a,c)

In these assays a bromophenol derivative is precipitated by adding a bromine (potassium bromate–potassium bromide) volumetric solution to a solution of the sample and acidifying to release free bromine, according to

$$5KBr + KBrO_3 + 6HCl = 6KCl + 3Br_2 + 3H_2O$$

The free bromine immediately reacts with the phenolic substance, as in the following equation using phenol as an example:

$$C_6H_5OH + 3Br_2 = C_6H_2Br_3OH + 3HBr$$

Potassium iodide then is added, and the excess bromine liberates free iodine:

$$2KI + Br_2 = 2KBr + I_2$$

It is titrated with thiosulfate. A blank is run on the same quantity of reagents, omitting the sample.

DIRECT TITRATION WITH STANDARD IODINE (IC1k)

The sample is titrated directly; starch TS is usually employed as the indicator.

Ascorbic Acid—A direct titration. If ascorbic acid is present in a multiple vitamin preparation, the dichlorophenol-indophenol procedure is employed.

Echothiophate Iodide (and for Ophthalmic Solution)—The ester first is hydrolyzed with pH 12 buffer to yield the free mercaptan, which then is oxidized, by titration with iodine, to the disulfide. Any free mercaptan in the original sample is corrected for by a preliminary titration. The following equations apply:

$$[(C_2H_5O)_2(PO)—S—CH_2CH_2N(CH_3)_3]^+I^- + H_20$$

Echothiophate

$$= [HSCH_2CH_2N(CH_3)_3]^+I^- + (C_2H_5O)_2(PO)OH$$

$$2[HSCH_2CH_2N(CH_3)_3]^+I^- + I_2$$

mercaptan

$$= 2[—SCH_2CH_2N(CH_3)_3{}^+]I^- + 2HI$$

Sulfur Dioxide—On absorption in sodium hydroxide, bisulfite ion is produced and then titrated with iodine.

RESIDUAL TITRATION OF EXCESS THIOSULFATE WITH IODINE (IC2b)

Mechlorethamine Hydrochloride and Mechlorethamine Hydrochloride for Injection—Thiosulfate reacts with the active chlorine atoms according to

$$CH_3N(CH_2CH_2Cl)_2 \cdot HCl + NaHCO_3 + 2Na_2S_2O_3 = CH_3N(CH_2CH_2S_2O_3Na)_2 + 3NaCl + CO_2 + H_2O$$

DIRECT TITRATION OF IODINE WITH ARSENITE (IC1m)

Free or liberated iodine is titrated with a standard sodium arsenite solution.

Iodine Topical Solution—For iodine.

Iodine Solution, Strong—For free iodine.

Iodine Tincture and Strong Iodine Tincture—For free iodine.

DIRECT TITRATION WITH FERRIC CHLORIDE (IC1g)

Articles in this category are titrated with ferric chloride using thiocyanate indicator.

DIRECT TITRATION WITH STANDARD BROMINE (IC1h)

Thymol—A warm solution of the sample is titrated to produce a bromo-derivative, analogous to the determination of phenols. However, an excess is not employed, because methyl orange, whose color is bleached as the equivalence point is exceeded, is used as an indicator.

TITRATIONS INVOLVING SODIUM NITRITE SOLUTION (IC1J)

Most compounds in this group, being primary aromatic amines or derivatives that may be converted to such amines, are capable of undergoing quantitative diazotization of the amino group substituted on the aromatic ring, as illustrated by the following equation using *p*-aminobenzoic acid.

$$H_2NC_6H_4COOH + NaNO_2 + 2HCl = ClN_2C_6H_4COOH + NaCl + 2H_2O$$

The titration with sodium nitrite is performed potentiometrically in a solution containing crushed ice (to prevent decomposition of the diazonium salt), or until a drop of the titrated solution produces an immediate blue color with starch iodide paste used as an external indicator. Sulfonamides in which the reactive amino group is acylated must first be hydrolyzed to release the free amine form of the sulfonamide prior to diazotization.

Primaquine Phosphate (and Tablets)—This substance contains a secondary amino group and nitrosation rather than diazotization occurs, the ═NH group being converted to ═N—NO (*N*-nitroso).

Procaine and Tetracaine Hydrochlorides, Procaine and Tetracaine Hydrochlorides, and Levonordefrin Injection—For procaine and tetracaine, after removal as the thiocyanate.

COMPLEXATION REACTIONS

DIRECT WITH ETHYLENEDIAMINETETRAACETIC ACID (EDTA) (ID1a,IDib)

EDTA complexes with many polyvalent metals to form an undissociated chelate. A buffered solution of the sample is titrated with EDTA (as the disodium salt). The indicator used is a dye that forms a weak chelate with the analyte metal. At the endpoint the color changes when the indicator-metal complex can no longer exist.

Alumina and Magnesia Oral Suspension (and Tablets)—For magnesium hydroxide, using ammonium hydroxide and ammonium chloride buffer (EBT).

Calcium Pantothenate (and Tablets)—For calcium content.

Calcium Pantothenate, Racemic—For calcium content.

Edetate Calcium Disodium (and Injection)—Mercury(II) nitrate is the titrant.

Edetate Disodium (and Injection)—Primary standard calcium carbonate, after suitable preparation, is titrated with a solution of the *Assay Preparation*.

Edetic Acid—Calcium carbonate (primary standard) is titrated with a solution of the *Assay Preparation*.

Magaldrate (and Oral Suspension and Tablets)—For magnesium hydroxide.

Magnesia and Alumina Oral Suspension (and Tablets)—For magnesium hydroxide.

RESIDUAL TITRATION INVOLVING EDTA (ID2a)

To assay for aluminum, in many combinations containing both magnesium and aluminum a residual method is employed. Excess EDTA is added to a suitably buffered sample, and the excess determined by titration with standard zinc sulfate solution. By use of proper buffers and masking agents (weak complexing materials), it often is possible to determine mixtures of calcium and aluminum, calcium and magnesium, or zinc and aluminum without preliminary separation.

Alumina and Magnesia Oral Suspension (and Tablets)—For aluminum hydroxide (DT).

Aluminum Acetate Topical Solution—For aluminum oxide (DT).

Aluminum Subacetate Topical Solution—For aluminum oxide (DT).

Magaldrate (and Oral Suspension and Tablets)—For aluminum hydroxide (DT).

Magnesia and Alumina Oral Suspension (and Tablets)—For aluminum hydroxide (DT).

Acid–Base Reactions in Nonaqueous Solvents

Titrimetric methods employing nonaqueous solvents are used extensively for the assay of certain materials that cannot be titrated easily in aqueous systems. Water is a leveling solvent, and many weak acids or bases do not give a sufficiently sharp break in the titration curve to evidence a distinct endpoint. However, in a nonaqueous solvent such as glacial acetic acid, weak organic bases and their salts can be titrated with an acetic acid solution of perchloric acid. The strongest acid available in aqueous medium is the oxonium ion, H_3O^+, in acetic acid, but the proton of perchloric acid forms the acetacidium ion, $CH_3C(OH)_2^+$.

$$CH_3COOH + HClO_4 = CH_3C(OH)_2^+ + ClO_4^-$$

The reaction between acetacidium ion and an amine (a weak base) is illustrated by the following equation, forming the ammonium ion and acetic acid.

$$CH_3C(OH)_2^+ + RNH_2 = CH_3COOH + RNH_3^+$$

No difficulty is experienced in the titration of amine salts other than salts of halogen acids. In the latter case, mercury(II) acetate is added to form undissociated mercury(II) halide, thus preventing interference by the halogen acid, which would be liberated in its absence (Pifer–Wollish method).

Weak organic acids, such as carboxylic acids, phenols, barbiturates, sulfonamides, or enols, also may be titrated in nonaqueous medium using a strong base. These include the sodium or lithium salts of methanol or ethanol, and the reaction is of the ordinary neutralization type, as illustrated below for an organic acid with sodium ethoxide.

$$RCOOH + C_2H_5ONa = RCOONa + C_2H_5OH$$

In both types of titration, acid or base, the endpoint may be determined with indicators or potentiometrically as depicted in the accompanying chart (Table 30-4) taken from the USP.

TITRATION OF BASIC SUBSTANCES (IA1BII)

Dimenhydrinate—For diphenhydramine (poten).

Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution and Tablets—For diphenoxylate hydrochloride.

Mepivacaine Hydrochloride and Levonordefrin Injection—For mepivacaine.

Potassium Acetate—Titration of a salt of a carboxylic acid.

Potassium Sorbate—See Potassium Acetate.

Table 30-4. Systems for Nonaqueous Titrations

TYPE OF SOLVENT	ACIDIC (FOR TITRATION OF BASES AND THEIR SALTS)	RELATIVELY NEUTRAL (FOR DIFFERENTIAL TITRATION OF BASES)	BASIC (FOR TITRATION OF ACIDS)	RELATIVE NEUTRAL (FOR DIFFERENTIAL TITRATION OF ACIDS)
Solvent[a]	Glacial acetic acid Acetic anhydride Formic acid Propionic acid Sulfuryl chloride	Acetonitrile Alcohols Chloroform Benzene Chlorobenzene Ethyl acetate Dioxane	Dimethylformamide *n*-Butylamine Pyridine Ethylenediamine Morpholine	Acetone Acetonitrile Methyl ethyl ketone Methyl isobutyl ketone *tert*-Butyl alcohol
Indicator	Crystal violet Quinaldine red *p*-Naphtholbenzein Alphazurine 2-G Malachite green	Methyl red Methyl orange *p*-Naphtholbenzein	Thymol blue Thymolphthalein Azo violet *o*-Nitroaniline *p*-Hydroxyazobenzene	Azo biolet Bromothymol blue *p*-Hydroxyazobenzene Thymol blue
Electrodes	Glass-calomel Glass-silver-silver chloride Mercury-mercuric acetate	Glass-calomel Calomel-silver-silver chloride	Antimony-calomel Antimony-glass Antimony-antimony[b] Platinum-Calomel Glass-calomel	Antimony-calomel Glass-calomel Glass-platinum[b]

[a] Relatively neutral solvents of low dielectric constant such as benzene, chloroform, or dioxane may be used in conjunction with any acidic or basic solvent to increase the sensitivity of the titration endpoints.
[b] In titrant.

TITRATION OF ACIDIC SUBSTANCES (IA1AIII)

A strong base is used to titrate very weak acids. Special precautions must be employed to exclude atmospheric carbon dioxide, which interferes with the titration. The titrants used frequently are indicated. Titrants employed are

1—Lithium methoxide solution.
2—Sodium methoxide solution.
3—Tetrabutylammonium hydroxide solution.
4—Tributylethylammonium hydroxide solution.

GRAVIMETRIC METHODS

In gravimetric methods of analysis, the assay results generally are obtained by determining either the weight of a substance in the sample, or the weight of some other substance derived from the sample, the equivalent weight of which serves as the basis for calculating the result. Separation of the substance ultimately weighed is accomplished frequently by purely physical methods. On the other hand, there are many instances in which it is necessary to use a chemical reaction to convert the substance to a corresponding amount of some other substance that can be separated, purified, and weighed. The various types of official gravimetric assays may be grouped conveniently into the following categories.

WEIGHING THE ACTIVE INGREDIENT AFTER SEPARATION (IIA)

The active principle is separated, dried and, weighed.

Caffeine and Sodium Benzoate Injection—For caffeine, after solution of the sodium benzoate in water.

Collodion—Pyroxylin is precipitated by water, dried, and weighed.

Estrone Injection—An elaborate purification procedure is involved whereby the estrone is converted to a water-soluble derivative using trimethylacethydrazide ammonium chloride (Girard's reagent for carbonyl compounds); the aqueous extract contains only ketonic material, as the reagent reacts only with carbonyl compounds. The aqueous extract then is decomposed with acid to regenerate estrone, which is extracted into chloroform; the solvent is removed and the residue weighed.

PRECIPITATION AND WEIGHING OF A DERIVATIVE OF THE ACTIVE INGREDIENT (IIB)

Anticoagulant Citrate Phosphate Dextrose Solution—For dextrose, a precipitate of Cu_2O, from reaction with Fehling's solution, is weighed.

Barium Sulfate—The sample is fused with sodium carbonate, forming barium carbonate, which is dissolved in acid; the barium is precipitated as the chromate, and is weighed.

Camphor Spirit—For camphor, as the 2,4-dinitrophenylhydrazone.

Ichthammol (and Ointment)—For total sulfur as barium sulfate after oxidation with nitric acid and perchlorate (see *Sulfur Ointment*).

Lanolin Alcohols—The cholesterol content is determined by precipitation as digitonide.

Magnesium Citrate Solution—For MgO as the 8-hydroxyquinolate.

Parachlorophenol, Camphorated—For *para*-chlorophenol: silver chloride is precipitated after release of chloride by oxidation with hot permanganate. For camphor: as the 2,4-dinitrophenylhydrazone.

Potash, Sulfurated—For sulfur by treatment with copper(II) sulfate to precipitate copper(II) sulfide, which is ignited to oxide and weighed.

Sorbitan Esters—The sample is saponified, the fatty acid is separated from the acidified aqueous solution, and it is weighed. The aqueous phase is concentrated and extracted with ethanol; the extract is concentrated to yield the *polyols,* which are weighed.

Sulfur Ointment—The sample is oxidized with nitric acid to convert sulfur to sulfate, which is precipitated and weighed as barium sulfate.

WEIGHING OF THE RESIDUE AFTER IGNITION OF THE SAMPLE (IIC)

Aluminum Monostearate—As aluminum oxide.

Silica Gel—See *Silicon Dioxide, Colloidal.*

Silicon Dioxide, Colloidal—Silica is determined by difference; the sample is weighed before and after treatment with hydrofluoric acid, which converts silica into the volatile silicon tetrafluoride. The difference in weight represents the silica content of the sample.

Zinc Oxide and Salicylic Acid Paste—For total zinc, as the oxide.

SPECTROMETRIC METHODS

Photometric analysis depends upon the measurement of the amount of light absorbed by a solution (*spectrophotometry*), a suspension (*turbidimetry*), the amount of light scattered by a suspension (*nephelometry*), or the intensity of the light emitted by an element when subjected to high temperatures (*flame photometry*). The measurement of light in the visible region (*colorimetry*) may be accomplished using a colorimeter or spectrometer or less accurately by visual comparison with color standards. See Chapter 33 for a more detailed treatment.

Radiant energy waves that are of importance to spectrophotometry range from 200 to 400 nm in the ultraviolet, from 400 to 750 nm in the visible range, and from 750 to 25,000 nm in the near infrared and infrared regions. The relatively large number of spectrometric assays that are described now in the official compendia testifies to the widespread development and general acceptance of the analytical methods that belong in this category.

VISIBLE ABSORPTION (COLORIMETRY) ASSAYS (IIIA)

If an absorption spectrometric analysis is specified in the USP-NF, a formula is provided to ensure accuracy in the calculation of the analytical result. In most cases, a numerical constant is found in the formula and may be deduced as follows. As Beer's Law holds for both the analyte (A) and standard (S) solutions, Equations 1 and 2 may be written

$$A_A = abc_A \quad (1)$$

$$A_S = abc_S \quad (2)$$

where A_A is the absorbance of the analyte solution whose concentration is C_A; A_S is the absorbance of the standard solution whose concentration is C_S; and a is the absorptivity of the drug substance, and b is the path length or cell thickness. If cells of the same thickness are used, Equation 1 may be divided by Equation 2 and the resulting expression solved for C_A to give

$$C_A = \frac{A_A}{A_S} C_S \quad (3)$$

For a solution to have a proper concentration such that the absorbance may be in the range of the spectrometer, an initial analyte sample, large enough to minimize weighing errors, is chosen and the initial solution is then carried through a series of dilutions to produce the final desired solution concentration. The final analytical measurement should be related back to the original analyte sample, W_A, in milligrams; thus, Equation 4 may be written to indicate the total volume V_A in liters of solution of concentration, C_A in milligrams per liter, which would result if the entire quantity W_A were diluted directly.

$$W_A = V_A C_A \quad (4)$$

Equation 4 may be solved for C_A and substituted into Equation 3 to yield Equation 5. Thus, the constant V_A is the numerical constant that is found in spectrometric analyses and represents the total volume of solution of concentration C_S that could be made from the entire initial analyte sample, W_A.

$$W_A = V_A \frac{A_A}{A_S} C_S \quad (5)$$

It should be carefully noted that the spectrophotometric measurement allows the calculation of the mass of absorbing material, W_A. If the original sample is not pure drug substance but is a dilution, such as drug substance plus excipients, it should be clear that the percentage of the analyte in the sample taken, W_{sample}, is given by Equation 6.

$$\frac{W_A}{W_{\text{sample}}} \times 100$$

Under this heading are considered those assays that depend on the development of color or upon the color of the substance being assayed. The absorbances are measured accordingly at wavelengths that are within the visible range of the spectrum. These colorimetric assays generally consist of adding a reagent to the assay preparation or to the substance being tested, to produce a color that is compared with that of a standard preparation that has been prepared simultaneously and contains approximately an equal quantity of a reference standard. When the

absorbance of a frequently assayed substance has been found to conform to Beer's law over a reasonable range of concentration, it is considered permissible to use a standard curve, prepared with the respective reference standard, for interpolation of the data obtained with the assay preparation.

In some instances characteristic colors are developed in *flame photometers* by subjecting an inorganic element or its compound in solution to an intensely hot flame. The intensity of the colors (radiations) is compared photometrically in a suitable spectrometer with standard solutions containing the same element.

The various models of available spectrometers are suitable for making these colorimetric measurements. Photoelectric colorimeters of the filter type, in which the light absorption is measured by sensitive photoelectric cells, also are used largely for making these determinations and several of these are commercially available.

DYE-COMPLEX METHOD (IIIA2)

Quaternary salts and many amines are capable of forming chloroform-soluble complexes with indicators, such as bromophenol blue. The usual procedure is to shake a mixture of the assay preparation, chloroform, and a buffer containing the indicator. The dye-complex partitions into the organic layer, which is separated and filtered to remove any adhering aqueous phase; the absorbance is then determined.

COLORIMETRY INVOLVING A CHROMOGENIC REAGENT (IIIA1,4)

When a three-digit number followed by a letter code is given, this indicates the analytical wavelength and color-developing reagent employed.

Anticoagulant Citrate Phosphate Dextrose Solution—For monobasic sodium phosphate; 660, ANS. For citrate; 425, PyA.

Carbachol Ophthalmic Solution—Hypochlorite is employed to form the *N*-chloroamide and this derivative with KI forms free iodine which reacts with starch TS, 590.

Mepivacaine Hydrochloride and Levonordefrin Injection—For levonordefrin; 530, FCiT.

Methenamine and Monobasic Sodium Phosphate Tablets—For methenamine; 570, CTA.

Norgestrel and Ethinyl Estradiol Tablets—For ethinyl estradiol; 536, H_2SO_4.

Procaine and Phenylephrine Hydrochlorides Injection—For phenylephrine; 500, AAP.

Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection—For levonordefrin; 530, FCiT.

Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection—For levonordefrin; 530, FCiT.

Propoxycaine and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection—For norepinephrine; 530, FCiT.

Propoxyphene Napsylate and Aspirin Tablets—For aspirin; 530, FEN.

Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets—For reserpine; 390, SN. For hydralazine hydrochloride; 510, FAS-Op.

Terpin Hydrate and Dextromethorphan Hydrobromide Elixir—For dextromethorphan; 420, BcG.

SPECTROMETRIC ASSAYS IN THE ULTRAVIOLET (IIIB)

Spectrometric assays in which the absorbances are measured directly in the ultraviolet range are described in official monographs.

Applied to solutions, spectrometry is more specific than colorimetry because the absorption depends upon wavelength in a complicated manner that is generally characteristic of the chemical composition of the absorbing substance. Measurement of absorption at several wavelengths may permit identification of the solute as well as the determination of its concentration. Tests of this kind are made usually on solutions, rarely on pure liquids or solids.

Solvents used for dilution usually require special purification that is often exacting and different from the requirements for other uses. Some assays direct that blank runs be made on the solvent and reagents used to obtain a correction for their inherent absorbances.

REFERENCE STANDARDS

In practically all cases a *reference standard* is used in conjunction with the sample under assay. The standard preparation is prepared and observed in the same manner as the test specimen. The purpose of this specification is to avoid errors due to wavelength or slit-width variation among various spectrophotometers, as well as to avoid errors arising from differences in transmittance and placement of cells.

INFRARED ASSAYS (IIIC)

The quantitative estimation of compounds by infrared methods is quite similar to the techniques employed in the ultraviolet and visible regions. However, due to the difficulties involved in measuring the absolute absorbance at a particular absorbance maximum, the *baseline* technique often is used. In this method a synthetic *baseline* is constructed between the minima at the sides of the absorption maximum, and a vertical line, intersecting the peak of the maximum, is erected perpendicular to the abscissa. The length of the vertical line, measured from the intersection of the synthetic baseline and the peak of the absorption maximum, is used as the absorbance in quantitative calculations, as illustrated in Figure 30-1. For a further discussion of the theory involved in infrared absorption, see Chapter 33.

ASSAYS INVOLVING FLAME PHOTOMETRY (IIID)

The *flame photometry method* deals with the emission of energy of a particular wavelength when a dilute solution of a metallic ion is sprayed into a colorless flame. The intensity of the emitted radiation is determined by a suitable spectrometer and compared to standards. Sodium, at 588 nm, and potassium, at 766 nm, are determined by this technique for the official substances indicated below.

Potassium Citrate and Citric Acid Oral Solution—For potassium.

Ringer's Injections and Irrigation—For potassium and sodium.

FLUOROMETRIC ASSAY METHODS (IIIE)

Riboflavin is assayed quantitatively by measuring its degree of fluorescence. Thiamine also is assayed by a fluorometric method, the principal difference from the riboflavin assay being that thiamine is oxidized first to thiochrome, the fluorescence of which is quantitatively measured in isobutyl alcohol solution. The intensity of fluorescence is measured at right angles to the incident monochromatic radiation in an instrument known as a fluorometer, or in certain spectrometers equipped with the required accessories. Quantitative evaluation of the fluorescence data is achieved through comparison with similar data obtained from solutions containing known amounts of the reference standard thiamine hydrochloride.

ATOMIC ABSORPTION ANALYSIS (IIIF)

Atomic absorption analysis is similar to flame photometry except that the photometer determines the decrease in intensity of a beam of energy passed through a flame into which the metallic ion under test is sprayed. The incident radiation is generated by a lamp, the cathode of which is fabricated from the same metal as the ions of the solution being assayed. See Chapter 33 for a detailed discussion.

NUCLEAR MAGNETIC RESONANCE METHODS (IIIG)

With NF XIV, a new spectrometric technique for the assay of organic pharmaceuticals was employed. Because this technique is an absorptive process, the area under the resonance peak is related to the concentration of that substance. The methods are similar to infrared or ultra violet techniques, and an *internal standard* often is employed. See Chapter 33 for further discussion.

Amyl Nitrite (and Inhalant)—Benzyl benzoate internal standard.

POLAROGRAPHIC ANALYSIS (IVA1)

Quantitative polarographic methods of analysis are specified for several official substances. The *diffusion current* (i_d) is proportional to the concentration of the electroactive species under test, whereas the *half-wave potential* ($E_{1/2}$) is characteristic of the kind of electroactive species and is independent of concentration. In the official assay methods the diffusion current of a sample and a reference standard solution is measured under identical conditions, and the concentration of the sample is calculated from the ratio of the sample to reference standard diffusion currents. A review of the theory of polarography can be found in Chapter 33.

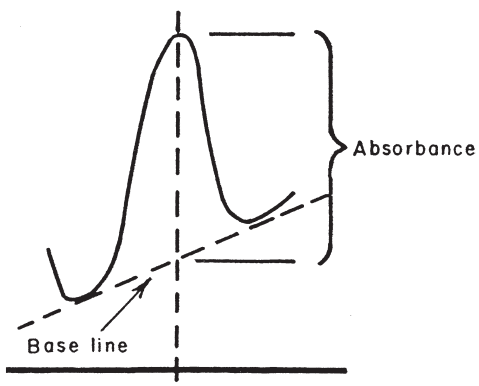


Figure 30-1. Illustration of baseline technique.

MISCELLANEOUS METHODS

GASOMETRIC ASSAY METHODS (VIA)

Gasometric methods of analysis depend on the measurement of the volume of a gas liberated under the conditions that are described in the assay, or of the decrease in volume of a gas when a suitable reagent is used to remove one of the gases present. These determinations usually are conducted in a gas buret or nitrometer, which is provided with a two-way stopcock and a two-way outlet and is properly connected with a balancing tube.

Carbon Dioxide—The sample is absorbed in 50% potassium hydroxide, and the volume of residual gas is measured.

Cyclopropane—The sample is absorbed by concentrated sulfuric acid, and the residual volume is measured.

Oxygen—The gas sample is exposed to the action of an ammoniacal copper solution, which reacts with oxygen. The residual volume is a measure of the impurities present.

ASSAYS INVOLVING VOLUMETRIC MEASUREMENTS (VIB)

Assays that depend on the separation and measurement of oily or aqueous immiscible layers are considered here. In general, these volumetric measurements are made possible as the result of processes that involve solvent separations, steam distillations, or chemical changes, in which an important constituent of the official substance (ie, volatile oil), such as an aldehyde, a ketone, or a phenol, is converted purposely to a water-soluble substance. In the latter case, the volume of residual oil is measured, and the assay result then is determined by difference.

Peppermint Spirit—For mixed oils; the oils are separated in a Babcock bottle after first mixing and centrifuging with kerosene and an acidified, saturated calcium chloride solution. A correction in the measured volume is made for the kerosene used.

ASSAYS DEPENDING ON MEASUREMENT OF OPTICAL ROTATION (VIC)

Many organic substances, or their solutions, have the property of rotating the plane of polarized light either to the right or to the left; this property is referred to as the optical activity or rotation of that substance. Measurement of this rotatory power serves as the basis for determining the purity, as well as the identity, of a number of official substances as the optical activity is a function of their chemical constitution, as well as their concentration. When the rotation is to the right, the dissolved substance is said to be dextrorotatory; whereas levorotatory substances are those that rotate the plane of polarized light to the left. The extent of observed rotation is measured and expressed in terms of degrees, and the instrument used in making these measurements is called a *polarimeter*.

The term *optical rotation* when used in the official monographs refers to *angular rotation,* and this represents the number of degrees a substance, or its solution, under specified conditions of wavelength of the polarized light, concentration, temperature, and length of the tube, will rotate the plane of polarization.

The *specific rotation,* $[\alpha]$, of a liquid is defined as the angular rotation in degrees through which the plane of polarization of polarized monochromatic light is rotated by passage through 1 decimeter (100 mm) of the liquid, calculated on the basis of a specific gravity of 1. In the case of solutions of an optically active substance, the specific rotation is calculated on the basis of a concentration of 1 g of solute in 1 mL of solution.

For calculating the specific rotatory power of an optically active liquid substance, or the solution of an optically active solid, the following formulas apply generally:

$$\textit{For liquid substances, } [\alpha]_D^t = \frac{a}{ld}$$

$$\textit{For solutions, } [\alpha]_D^t = \frac{100a}{\text{lpd}}$$

$$\text{or } [\alpha]_D^t = \frac{100a}{\text{lc}}$$

where

a = the observed rotation in degrees of the liquid at a temperature t, using a sodium light.
l = the length of the tube in decimeters.
d = the specific gravity of the liquid or solution at the temperature of observation.
p = the concentration of the solution expressed as the number of grams of active substance in 100 g of solution.
c = the concentration of the solution expressed as the number of grams of active substance in 100 mL of solution.
t = temperature of measurement.
D = D line of sodium (light source).

Anticoagulant Citrate Dextrose Solution—For dextrose.

Dextrose and Sodium Chloride Injection—For dextrose.

Diatrizoate Meglumine and Diatrizoate Sodium Injection—For diatrizoate meglumine.

Epinephrine Inhalation Solution, Sterile Oil Suspension, Nasal Solution—Rotation of the triacetyl derivative.

Epinephryl Borate Ophthalmic Solution—As for Epinephrine Nasal Solution.

Iothalamate Meglumine and Iothalamate Sodium Injection—For iothalamate meglumine.

Sodium Chloride and Dextrose Tablets—For dextrose.

Sterile Epinephrine Oil Suspension.

SPECIFIC GRAVITY (VID)

Many substances are mixtures of several compounds and can have varied composition. A simple assay procedure will not establish the purity or efficacy of such a material; therefore, they are characterized quite often by physical methods, one of which may be specific gravity.

ASSAYS INVOLVING MEASUREMENT OF RADIOACTIVITY (VIE)

In this type of assay, the radioactivity of a sample and of a calibrated radioactive standard are determined at the same time and under identical geometric conditions, as outlined in Chapter 29.

The radiochemical purity of many official radioactive substances is determined by first chromatographing the substance on a paper strip, then determining the radioactive distribution on the developed chromatogram.

ASSAYS OF ENZYME-CONTAINING SUBSTANCES (VIF)

The official enzymatic assays depend on the ability of enzymes to catalyze reactions of a certain type under the conditions that are described in the assay. These enzymes that bring about the conversion of starch into water-soluble sugars are known as diastatic enzymes. Other official enzyme-containing substances are those that digest proteins and peptides, changing them into peptones and eventually amino acids. These are called proteolytic enzymes. A third type of enzyme encountered in the official assays is the one that causes or prevents the coagulation of serum. In all of these assays the enzymatic activity of the sample is determined by comparison with that of a reference standard.

Chymotrypsin—A dilute hydrochloride solution of the sample is incubated with buffered *N*-acetyl-L-tyrosine ethyl ester in a spectrometer cell with the instrument set at 237 nm. The change in absorbance with respect to time is noted. One Chymotrypsin Unit is the activity causing a change in absorbance of 0.0075/min under the conditions of the assay.

Heparin Sodium (and Injection, Anticoagulant Heparin Solution, Heparin Calcium and Injection, and Lock Flush Solution)—The anticoagulant activity of heparin sodium is determined by its ability to inhibit the clotting of sheep plasma *in vitro*. Assay preparations are compared to a reference standard, and the calculation of potency is based on determinations of the extent of clotting which has occurred 1 hour after addition of heparin and calcium chloride to samples of citrated plasma.

Hyaluronidase Injection (and for Injection)—Hyaluronidase activity is assayed on the basis of the ability of preparations of the enzyme to decrease the turbidity of colloidal suspensions of a substrate consisting of potassium hyaluronate and protein *in vitro*. Assay preparations are compared to a reference standard, and the calculation of potency is based on measurements of the absorbance of solutions containing hyaluronidase, potassium hyaluronate, hydrolyzed gelatin, phosphate buffer, and serum.

Pancreatin (and for Capsules and Tablets)—The *starch digestive power* (amylase activity) is determined on a prepared sample by testing its quantitative ability to hydrolyze starch to the extent that no blue or reddish color develops upon the addition of iodine. The *casein digestive power* (protease activity) is determined by placing a suitably prepared casein solution in each of two tubes. To one tube is added a solution of Pancreatin and to the other tube is added a similar amount of Pancreatin Reference Standard. Both mixtures are diluted and incubated at 40°C for 1 hour. The addition of alcoholic acetic acid solution produces no more haze in the tube containing Pancreatin than in that containing the Reference Standard, indicating that the proteolytic activity of the former is at least as great as that of the latter. The *fat digestive power* (lipase activity) is determined on an olive oil substrate by titration of liberated fatty acid with base. The activity is determined from a standard curve in *mean acidity released* per minute.

Pancrelipase (and Capsules and Tablets)—The amylase activity is measured by hydrolysis of starch, after which the starch substrate is reacted with iodine. The lipase activity is determined by the digestion of olive oil and the concomitant production of acid. The protease activity is determined by the digestion of casein, after which the hydrolysis products are measured spectrophotometrically.

Protamine Sulfate (and Injection and for Injection)—The activity of Protamine Sulfate Injection is assayed on the basis of its ability to nullify the anticoagulant action of sodium heparin *in vitro*. Varying concentrations of sodium heparin are added to a series of test tubes containing uniform amounts of citrated sheep plasma, calcium chloride-thromboplastin solution, and Protamine Sulfate Injection. Calculation of potency is based on that amount of heparin sodium that results in a clotting time most nearly approaching the clotting time observed in the control tube.

Sutilains (and Ointment)—Using a casein substrate and a tyrosine reference standard, the amount of tyrosine cleared per unit time, measuring the absorbance at 275 nm, is related to the enzyme activity.

Trypsin, Crystallized (and for Inhalation Aerosol)—The method is similar to that used for *Chymotrypsin*; *N*-benzoyl-L-arginine ethyl ester hydrochloride is the substrate measured at a wavelength of 253 nm. One Trypsin Unit is the activity causing a change in absorbance of 0.003/min under the conditions of the assay.

PROXIMATE ASSAYS (VIG)

At one time the extensive use of vegetable drugs, extracts, and other galenicals in pharmacy required that the analyst be concerned with a great many *proximate assays*. Currently, more specific, well-defined medicinals, usually of synthetic origin, are in common use, so the proximate assay is required to a much lesser degree. By proximate assay is meant the determination of the amount of any organic constituent that may be present in any vegetable drug or plant to which its value or therapeutic activity is attributed. The separations depend mainly on the use of a variety of solvents selected after elaborate and painstaking research. Acid and alkali solutions, chloroform, ether, alcohol, or many other organic solvents play an important role in proximate assays.

Although largely associated with the alkaloidal content of vegetable drugs, proximate assays also include the determination of alcohol-soluble, ether-soluble, or water-soluble constituents of various drugs by solvent extraction.

ALKALOIDAL DRUG ASSAYS (VIG1)

Alkaloidal assays present the most important application of proximate assay methods with which the pharmaceutical chemist has to deal. Quantitative experiments necessarily must be done with great care, and in conducting proximate assays of alkaloidal drugs particular attention must be paid to all details. The alkaloidal substances to be separated are organic chemical compounds that are difficult to extract from the drug. They are present in comparatively small quantities and in many cases are easily destroyed by improper manipulation.

These assays are conducted largely through the use of immiscible solvents, such as chloroform, ether, or amyl alcohol, except where the properties of the alkaloid sought necessitate a special method, as for morphine in opium. Advantage is taken of the fact that the free alkaloids are practically insoluble in water (except colchicine, ephedrine, sparteine, nicotine, and a few others), whereas they are very soluble in one or more of the immiscible solvents such as chloroform or ether. The salts of the alkaloids behave in the reverse manner, being practically insoluble in the immiscible solvents and soluble in water. There are several exceptions, such as the salts of caffeine, theobromine, or colchicine; their bases are feebly basic, and the salts hydrolyze readily with the liberation of the free alkaloid.

Three general steps are required for the separation and estimation of alkaloids in vegetable drugs.

1. Extraction of the drug.
2. Subsequent separation and purification of the alkaloid.
3. Determination of the amount of alkaloid obtained, either by gravimetric or titrimetric means.

Extraction of the Crude Drug

After reduction to proper fineness by grinding, the drug may be *defatted* by extraction with petroleum benzin, or directly treated with a solvent to extract the active constituent. Depending on the alkaloid present, the drug is treated in one of the following methods:

1. Extraction with an organic solvent, after addition of ammonia to ensure the complete liberation of the basic alkaloid (belladonna and ipecac).
2. Extraction with water (morphine in opium).
3. Extraction with acidulated water, if the alkaloid is present as such or in the form of weakly combined organic salts.

The extraction procedure usually is accomplished by use of separatory funnels (separators) with mechanical agitation or in a Soxhlet extraction apparatus.

The assay processes for extracts, fluidextracts, tinctures, and powdered extracts of an alkaloidal drug are in general similar to those described for the crude drug. *Powdered and pilular extracts* usually are liquefied by the use of an appropriate solvent and then extracted directly. *Fluidextracts* often are diluted with water, and *tinctures* are concentrated to a small volume by means of a preliminary evaporation. After the mixture is made alkaline it is extracted, directly, with the most suitable solvent.

Automatic Extraction Apparatus—The need for an automatic extraction apparatus for use in the assay of alkaloidal galenicals prompted the design of an improved apparatus. The simple type is constructed easily, requires only a small amount of solvent and practically no attention, and gives a clear extraction in one operation.

In the simple type of apparatus (Fig 30-2) the same jacket, condenser, and boiling flask are used for light and heavy solvent. For light solvents, the funnel tube containing very small openings at its lower end is used in the jacket, as shown in *B*. For heavy solvents, as shown in *A*, the wide tube open at both ends is used.

The illustration shows the manner in which the extractors function. In both cases the extracting solvent is returned continuously to the boiling flask and reused. In *A*, the chloroform returns to the boiling flask under the bottom and around the inner jacket; in *B*, the nonaqueous layer is always on top and is returned by overflow.

Separation and Purification of the Alkaloid

The extract of the crude drug or galenical usually contains impurities that may interfere with the ultimate method of assay, especially in the case of extraction with immiscible solvents, whereby oils, tannins, and soluble coloring matter can obscure the endpoint in a titration or add to the weight of a gravimetric method. For these reasons, purification of the alkaloidal extract is accomplished by crystallization (as in the case of morphine in opium), removal of associated alkaloids by chemical methods, or by use of immiscible solvents. This latter method most often is employed and involves repeated extraction of the alkaloid from aqueous and organic solvent. For example, the original organic solvent extract containing the basic alkaloid is shaken with dilute acid, thus transferring the alkaloid to the aqueous layer due to the formation of the more polar acid salt. The aqueous acid layer then is made basic with ammonia (or a stronger base if required) and again extracted into an immiscible organic solvent as the free base. This process is repeated until the alkaloid is sufficiently pure for the final assay.

Estimation of the Alkaloid

Final determination of the alkaloid is accomplished either by a quantitative gravimetric or volumetric procedure, the latter being preferred. In the gravimetric method all, or a definite fraction (aliquot), of the solution containing the extract is evaporated to dryness in a tared

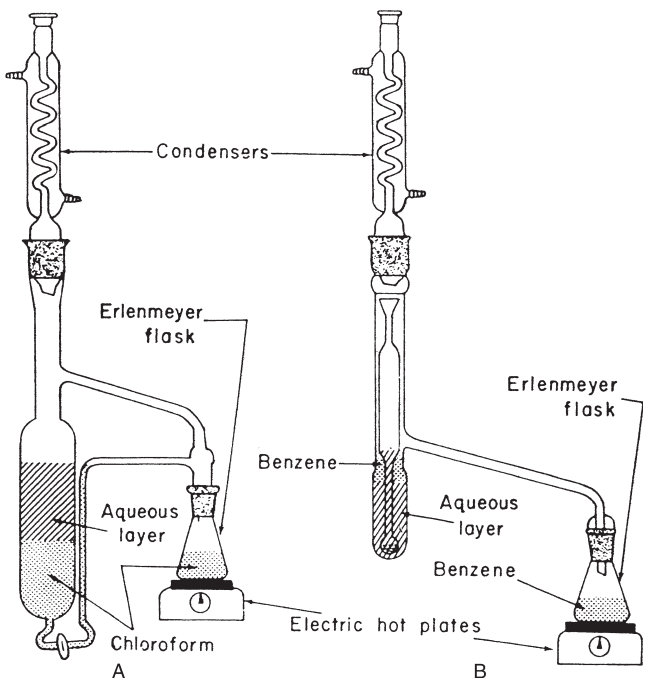


Figure 30-2. Automatic extraction apparatus for alkaloids.

container, the increase in weight of the container representing the weight (or some fraction thereof) of the alkaloid in the sample.

In the volumetric method the solvent is evaporated carefully to a small volume and an excess of standard acid plus a small amount of alcohol is added and the evaporation continued. The residual titration method is used, because the acid, by converting the alkaloid(s) to salt(s), prevents loss of some alkaloids that are fairly volatile in the form of the free base.

MISCELLANEOUS ASSAY METHODS OR FUNCTIONAL TESTS (VIK,M)

Barium Hydroxide Lime—The weight of carbon dioxide absorbed under specified conditions of rate of gas flow and time is determined.

Charcoal, Activated—The adsorptive power with respect to alkaloids (strychnine) and dyes (methylene blue) is determined by measuring the amount (if any) of unadsorbed material.

Mecamylamine Hydrochloride—Phase solubility analysis is applied to 50- to 250-mg portions of sample by equilibration with isopropyl alcohol and determination of the solution concentrations of the portions. From a plot of these concentrations versus the system concentrations, the purity of the sample may be calculated (see Chapter 16).

Soda Lime—See *Barium Hydroxide Lime,* above.

Sodium Alginate—The carbon dioxide, liberated when the sample is heated with hydrochloric acid in a special apparatus for alginates assay, is drawn into an excess of standard base and the excess titrated with acid (IA2b).

BIOLOGICAL ASSAYS (VIH)

Substances in this category may not need to be assayed by a chemical or physical method. If a biological assay is required, information concerning it may be found in Chapter 31. Some of these substances require batch certification by either the US Food and Drug Administration or the National Institutes of Health.

MULTIVITAMIN AND MULTIMINERAL DOSAGE FORMS (VIL)

The analysis of vitamins in a mixture of vitamins may be different from the procedures used when the individual vitamins or minerals are alone. The following methods are used in multivitamin and multimineral mixtures.

Vitamins

Vitamin A	HPLC; VB1a, 325 nm.
Vitamin D	HPLC; VB1a, 265 nm.
Vitamin E	HPLC; VB1b, 254 nm.
Vitamin K	HPLC; VB1b, 325 nm.
β-Carotene	Spectrometry; III A4, 452 nm.
Vitamin C	Titration; ICIK.
Biotin (1)	HPLC; VB1b, 200 nm.
Biotin (2)	Microbial; VIL.
Vitamin B_{12} (1)	HPLC; VB1b, 280 nm.
Vitamin B_{12} (2)	Microbial; VIL.
Folic Acid	HPLC; VB1b, 280 nm.
Calcium Pantothenate (1)	HPLC; VB1b, 210 nm.
Calcium Pantothenate (2)	Microbial; VIL.
Dexpanthenol or **Panthenol**	Microbial, VIL.
Niacin or **Niacinamide**	HPLC; VB1b, 280 nm.
Pyridoxine	HPLC; VB1b, 280 nm.
Riboflavin	HPLC; VB1b, 280 nm.
Thiamin	HPLC; VB1b, 280 nm.

Minerals

Metals—Atomic Absorption Spectroscopy, III F1, at λ given, in nanometers: Ca 422.7; Cr 357.9; Cu 324.7; Fe 248.3; Mg 285.2; Mn 279.5; Mo 313; K 766.5; Zn 213.8. Additional Mo: spectroscopy, III A4, 465 nm.

Nonmetals—F, potentiometry, IVB1; I, titration, IC10; P, spectroscopy, IIIA4, 650 nm; Se, (1) Atomic Absorption Spectroscopy, III, F1, 196 nm, (2) spectroscopy, III, B1, 380 nm, (3) fluorescene, III, E2, excitation 366 nm, emission 525 nm.

Dosage Forms

Minerals Capsules and Tablets
Trace Elements Injection
Oil-soluble Vitamin Capsules and Tablets
Water-soluble Vitamin Capsules and Tablets
Oil-and Water-soluble Vitamin Capsules and Tablets
Oil-and Water-soluble Vitamins with Minerals Capsules and Tablets
Water-soluble Vitamins with Minerals Capsules and Tablets

FIXED OILS AND WAXES (VII1)

The fixed oils (corn, cottonseed, olive) and waxes are composed largely of mixtures of fatty acid esters, and it is possible that each component has a relatively wide concentration limit without sacrificing the quality of the oil. It is for this reason that a single-substance assay is of little value; many parameters are necessary to stipulate the quality of the oil. Some of the many kinds of tests performed on the materials in this category include saponification value, acid number, acetyl value, iodine number, specific gravity, and melting range of fatty acids.

PENICILLIN CLASS ANTIBIOTIC ASSAYS (VIN2,3)

Penicillin G Determination

Penicillin G determination is a reversed-phase HPLC procedure that can measure the penicillin G content in an antibiotic drug substance by measuring responses of the major peaks in the chromatogram.

Iodometric Assay—Antibiotics

Treatment of penicillins with alkali or penicillinase causes the β-lactam to open, yielding a derivative with an acidic and an amine function (eg, penicillin yields penicilloic acid). The derivative consumes iodine, whereas the initial intact penicillin antibiotic does not. This behavior forms the basis for the iodometric assay.

Hydroxylamine (Hydroxamic Acid) Assay—Antibiotics

When penicillins are reacted with hydroxylamine, the β-lactam is opened and a hydroxamic acid derivative forms. The derivative reacts with iron III to produce a color whose intensity is used as a measure of the penicillins. This method is specific, because the β-lactam must be intact for the hydroxamic acid derivative to form. This assay has been automated.

MONOGRAPHS FOR COMPOUNDED PREPARATIONS

The USP has undertaken the development of monographs for compounded preparations. These compounded preparations represent those dosage forms that are not commercially available but for which there is a demonstrated need. The concept of a compliance assay has been introduced, and an assay is included in the monograph. The pharmacist who is compounding the preparation is not required to analyze the preparation; however, it is expected that the compounded preparation which results when the compounding directions are followed will meet the purity rubric requirements as determined by the compliance assay. The compliance assay is used in stability studies of the compounded preparation and provides the data from which a beyond-use date is specified in the monograph.

An example of a compounded preparation is Sodium Hypochlorite Topical Solution. The compliance assay is of the class IcIii and the beyond-use date is 7 days after that day on which the preparation was compounded. Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution, Hydralazine Hydrochloride Oral Solution, and Rifampin Oral Suspension are other compounded preparations whose monographs do not yet specify an assay, but each of which has a beyond-use date of 30 days. Other monographs will be added.

MONOGRAPHS FOR BOTANICALS AND NUTRITIONAL SUPPLEMENTS

The Revision Committee of the USP continues to provide monographs for botanicals and nutritional supplements. The list of monographs is growing with each supplement to the USP. The following is a partial list: Calcium with Vitamin D Tablets, Chamomile, Cranberry Liquid Preparation, Feverfew, Powdered Feverfew, Garlic, Powdered Garlic, Ginkgo, Oriental Ginseng, Powdered Oriental Ginseng, Milk Thistle, Powdered Milk Thistle, Saw Palmetto, Powdered Saw Palmetto, St John's Wort, Powdered St John's Wort, Valerian, Powdered Valerian, and Vitamins.

The approaches to qualitative and quantitative analysis in these botanical monographs are very similar. Thin-layer chromatography is used in all but one monograph (Cranberry Liquid Preparation) to identify plant principles. In some cases, characteristic color tests are used to supplement identification. For quantitative analysis, the quantity of a particular plant principle is determined by high-performance liquid chromatography (HPLC), using spectrophotometric detection in all but two cases. For Cranberry Liquid Preparation, there is an HPLC procedure that uses a refractive index detector to determine dextrose and fructose. In the monographs for Saw Palmetto and Powdered Saw Palmetto, gas chromatography (GC) is used to measure 11 methyl esters of fatty acids using flame ionization detection.

REFERENCES

1. United States Pharmacopeia 24/National Formulary 19 (USP24/NF19). Rockville, MD: United States Pharmacopeia Convention, 2002.
2. ICH Guidance for Industry Q2B Validation of Analytical Procedures: Methodology, November 1996.
3. FDA. Code of Federal Regulations, Title 21, Part 11 Electronic Records, Electronic Signatures–Final Rule. Federal Register, 1997; 62(54): 13429–13466.
4. FDA Guidance for Industry Q2B Part 11, Electronic Records, Electronic Signatures–Scope and Application, August 2003.
5. For a practical reference regarding Part 11 requirements, see Huber L, Winter, W. *BioPharm International*, February 2004 Supplement, S-4–S-9.

Classification Used for Official Assays

APPENDIX A

For the purpose of this chapter, the official chemical, physicochemical, and physical assay methods have been classified in an outline form. The first two classes are stoichiometric analyses; the next three are modern or nonstoichiometric analyses; the last class encompasses miscellaneous methods, including many older procedures and some more modern ones.

I. Titrimetric Methods
- A. Acid–Base Reactions
  - 1. Direct Titrations
    - a. Titration of an acid by a base
      - i. Titration of a liberated acid
      - ii. Sørenson–Formol titration
      - iii. Nonaqueous titration
    - b. Titration of a base by an acid
      - i. Titration of metal salts
      - ii. Nonaqueous titration
      - iii. Nonaqueous titration—Pifer–Wollish reagent
    - c. Kjeldahl Determination
  - 2. Residual Titrations
    - a. Titration of excess acid by a base
      - i. After distillation of a volatile base
      - ii. After addition to carbonate residues
      - iii. After acylation reactions
      - iv. Nonaqueous titration
    - b. Titration of excess by an acid
      - i. After saponification of an ester
      - ii. After hydrolysis of an alkoxyl group
      - iii. After distillation of a volatile base
- B. Precipitation Reactions
  - 1. Direct Titrations
    - a. With silver nitrate
    - b. With thiocyanate
      - i. Of theophylline–silver compound
      - ii. Of halogen
      - iii. Of mercury
      - iv. Of silver
    - c. Of a halogen with mercuric ion
    - d. Of a halogen with thorium (IV)
    - e. Of liberated nitric acid
    - f. Of thiol with mercuric ion
  - 2. Residual Titrations
    - a. With thiocyanate
      - i. Of theophylline–silver compound
      - ii. Of silver
- C. Redox Reactions
  - 1. Direct Titrations
    - a. Involving ceric sulfate or ceric ammonium nitrate
    - b. Involving potassium permanganate
      - i. Using ferric alum and potassium permanganate
    - c. Involving dichlorophenol-indophenol
    - d. Involving potassium dichromate
    - e. Involving ferrous ammonium sulfate
    - f. Involving titanium trichloride
    - g. Involving ferric chloride
    - h. Involving standard bromine
    - i. Involving potassium ferricyanide
    - j. Involving sodium nitrate
    - k. With iodine
    - l. Involving iodine and thiosulfate
      - i. Iodimetric determination of phenols
      - ii. Titration of iodine liberated from potassium iodide
      - iii. Reaction of potassium iodide with excess periodate
    - m. Of iodine with arsenite
    - n. Involving potassium iodate
    - o. With thiosulfate
  - 2. Residual Titrations
    - a. Of excess standard iodine
      - i. Titration of iodine following dichromate reaction
    - b. Of excess thiosulfate with iodine
    - c. Of generated iodine with thiosulfate
    - d. Of residual titanium with iron (III)
    - e. Of residual oxalic acid by potassium permanganate
    - f. Of residual iodine by sodium thiosulfate
- D. Complexation Reactions
  - 1. Direct Titrations
    - a. With EDTA
    - b. With miscellaneous titrant
  - 2. Residual Titrations
    - a. With EDTA
    - b. With metal ion
- E. Large Anion Reagent and Large Cation Reagent Reactions
  - 1. Titrations with sodium tetraphenylboron
  - 2. Titration with sodium lauryl sulfate
  - 3. Titration with *tetra*-*n*-butyl ammonium iodide
  - 4. Titration with dioctyl sodium sulfosuccinate

II. Gravimetric Methods
- A. Weighing Drug after Separation
- B. Weighing a Derivative after Separation
- C. Weighing a Residue after Ignition

III. Spectrometric Methods
- A. Visible Absorption (Colorimetry)
  - 1. Steroid
  - 2. Dye–complex
  - 3. Direct
  - 4. Derivative formed
  - 5. Starch-iodine reaction
- B. Ultraviolet (UV) Absorption
  - 1. Direct
  - 2. Derivative formed
  - 3. Amphetamine
- C. Infrared (IR) Absorption
  - 1. Direct
  - 2. Derivative formed
- D. Flame Photometric Emission
- E. Fluorometric Emission
  - 1. Native fluorescence
  - 2. Fluorescent derivative formed
- F. Atomic Absorption (AA)
  - 1. Flame
  - 2. Furnace used
- G. Nuclear Magnetic Resonance (NMR) Absorption
  - 1. Absolute method
  - 2. Relative method

IV. Electrochemical Methods
- A. Voltammetry
  - 1. Polarography
  - 2. Differential pulse polarography
  - 3. Use of electrodes other than DME
- B. Potentiometry
  - 1. Ion-selective electrodes

V. Chromatographic Methods
- A. Gas Chromatography (GC)
  - 1. Direct assay
  - 2. Derivative formed

B. High-Performance Liquid Chromatography (HPLC)
   1. Direct assay
      a. Normal phase
      b. Reverse phase
   2. Derivative formed
      a. Normal phase
      b. Reverse phase
C. Thin-Layer Chromatography (TLC)
   1. Mobile phase
      a. Normal
      b. Reverse

VI. Miscellaneous Methods

A. Gasometric Assay
B. Assays Involving Liquid Volume Measurements
C. Assays Involving Optical Rotation
   1. Direct
   2. Derivative formed for assay
D. Assays Involving Specific Gravity
E. Assays of Radioactivity
F. Enzyme Assay
G. Proximate Assay
   1. Alkaloid assay
H. Biological Assay
I. Miscellaneous
   1. Fixed oils and waxes
J. Distillation
K. Functional Test
L. Vitamin Assays
M. Phase Solubility
N. Antibiotic Assays
   1. Microbial
   2. Iodometric
   3. Hydroxylamine
O. See individual components

Assay Index of Official USP-NF Drugs

APPENDIX **B**

This appendix presents a classification of the assay for the majority of official drugs taken from USP24–NF19. In column 1, the drug substance or dosage form is listed. Column 2 gives the assay category whose interpretation may be taken from Appendix A. Column 3 gives the analytical wavelength for spectrometric analyses (Class III) in nanometers for visible and ultraviolet regions and in micrometers for the infrared; it also gives the detector type that is used for chromatographic methods (Class V). For example, for GC methods, FID-P represents a flame ionization detector—temperature programmed mode, whereas TC-I means thermal conductivity detector—isothermal mode. For HPLC, UV-280 means UV detector used at 280 nm, RI indicates refractive index, and EC electrochemical detectors. Finally, column 4 lists the indicator employed in titration procedures or the internal standard, where used, for the chromatographic procedures and for the quantitative NMR analyses.

Appendix B. Assay Index of Official USP-NF Drugs

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Acebutolol Hydrochloride	VB1b	UV-254	
Acepromazine Maleate	VB1b	UV-280	
Injection	VB1b	UV-280	
Tablets	VB1b	UV-280	
Acetaminophen	IIIB1	244	
Capsules	VB1b	UV-243	
for Effervescent Oral Solution	VB1b	UV-243	
Oral Solution	VB1b	UV-243	
Oral Suspension	VB1b	UV-243	
Suppositories	VB1b	UV-243	
Tablets	VB1b	UV-243	
and Aspirin Tablets	VB1b	UV-280	benzoic acid
Aspirin and Caffeine Tablets	VB1b	UV-275	benzoic acid
and Codeine Phosphate Oral Solution	VB1b	UV-280	
and Codeine Phosphate Oral Suspension	VB1b	UV-220	
and Codeine Phosphate Capsules	VB1b	UV-280	
and Codeine Phosphate Tablets	VB1b	UV-280	
and Diphenhydramine Citrate Tablets	VB1b	UV-254, 265	guafenesin, xylometazoline
and Pseudoephedrine Tablets	VB1b	UV-214	
Capsules containing at least three of the following—acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	VB1b	UV-214, 280	
Oral Solution containing at least three of the following—acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	VB1b	UV-214, 280	
Tablets containing at least three of the following—acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	VB1b	UV-214, 280	
Capsules containing at least three of the following—acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Pseudoephedrine	VB1b	UV-214, 280	
Oral Powder containing at least three of the following–acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Pseudoephedrine	VB1b	UV-214, 280	
Oral Solutions containing at least three of the following—acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Pseudoephedrine	VB1b	UV-214, 280	
Tablets containing at least three of the following—acetaminophen, and salts of chlorpheniramine, Dextromethorphan, and Pseudoephedrine	VB1b	UV-214, 280	
Acetazolamide	IIIC1	7.38	
Tablets	IVA1		
Acetazolamide for Injection	IIIB1	265	
Acetic Acid	IA1a		Phth
Glacial	IA1a		Phth
Irrigation	IA1a		Phth
Otic Solution	IA1a		Phth
Acetohexamide	IA1aiii		TB
Tablets	IIIB1	247	
Acetohydroxamic Acid	IIIA4	502	
Tablets	IIIA4	502	
Acetone	VA1	FID-P	
Acetylcholine Chloride	IA2b		Phth
for Ophthalmic Solution	VB1b	RI	
Acetylcysteine	VB1b	UV-214	(±)-phenylalanine
Solution	VB1b	UV-214	(±)-phenylalanine
and Isoproterenol Hydrochloride Inhalation Solution	VB1b	UV-214, 280	(±)-phenylalanine, acetaminophen
Acyclovir	VB1b	UV-254	
Capsules	VB1b	UV-254	
for Injection	VB1b	UV-254	
Ointment	VB1b	UV-254	
Oral Suspension	VB1b	UV-254	
Tablets	VB1b	UV-254	
Adenine	IAbii		Poten
Adensosine	IAbii		Poten
for Injection	VB1b	UV-254	
Air, Medical	VI		
Alanine	IA1bii		Poten

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Albendazole	IA1bii		OB
Oral Suspension	VB1b	UV-308	
Tablets	VB1b	UV-254	
Albuterol	IA1bii		CrV
Tablets	IA1bii		Nb
Albuterol Sulfate	IA1bii		OrB
Alcohol Rubbing	IIIA2, IA2bi	410	Phth
Alcohol in Dextrose Injection	VIJ, VIC		
Alfentanil Hydrochloride	IAbii		Nb
Injection	VB1b	UV-235	
Allopurinol	VB1b	UV-254	hypoxanthine
Tablets	IIIB1	250	
Allyl Isothiocyanate	IC11		FAS
Aloe	VIG		
Alprazlam	VB1a	UV-254	
Tablets	VB1a	UV-254	
Alprostadil	VB1b	UV-254	ethylparaben
Injection	VB1b	UV-254	ethylparaben
Alteplase	VIH		
for Injection	VIH		
Altretamine	VB1b	UV-227	
Capsules	VB1b	UV-227	
Alum	ID2a		DT
Ammonium	ID2a		DT
Potassium	ID2a		DT
Alumina and Magnesia Oral Suspension	ID2a, ID1a		DT, EBT
Tablets	ID2a, ID1a		DT, EBT
Alumina, Magnesia and Calcium Carbonate Oral Suspension Tablets	ID2a, ID1a, ID1a		DT, EBT, HNB
	ID2a, ID1a, ID1a		DT, EBT, HNB
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets	ID2b, IIIF1, ID1a	285.2	dithizone
Alumina Magnesia and Simethicone Oral Suspension	IC2b, ID1a, IIIC1		DT, EBT
Tablets	IC2b, ID1a, IIIC1		DT, EBT
Alumina and Magnesium Carbonate Tablets	IIIF1		
Oral Suspension	IIIF1		
and Magnesium Oxide Tablets	ID1a, IIB, ID2a		
Alumina and Magnesium Trisilicate Oral Suspension	ID2a, ID1a		DT, EBT
Tablets	ID2a, IIIF1		DT
Aluminum Acetate Topical Solution	ID2a, IA2b		DT, Phth
Aluminum Chloride	ID2a		DT
Aluminum Chlorohydrate	ID1a		DT
Solution	ID1a		DT
Aluminum Chlorohydrex Polyethylene Glycol	IC1a		DT
Aluminum Chlorohydrex Propylene Glycol	IC1a		DT
Aluminum Dichlorohydrate	ID1a		DT
Solution	ID1a		DT
Polyethylene Glycol	ID1a		DT
Propylene Glycol	ID1a		DT
Aluminum Hydroxide Gel	ID2a		DT
Dried	ID2a		DT
Dried, Capsules	ID2a		DT
Dried Tablets	ID2a		DT
Aluminum Monostearate	IIC		
Aluminum Phosphate Gel	IA2b		Phth
Aluminum Sesquichlorohydrate	ID1a		DT
Solution	ID1a		DT
Polyethylene Glycol	ID1a		DT
Propylene Glycol	ID1a		
Aluminum Subacetate Topical Solution	ID2a, IA2b		DT, Phth
Aluminum Sulfate	ID2a		DT
and Calcium Acetate Tablets for Topical Solution	ID1a		DT, EBT
Aluminum Zirconium Octachlorohydrate Solution	ID1a		DT
Aluminum Zirconium			
Octachlorohydrex Gly Solution	ID1a		DT
Pentachlorohyrate Solution	ID1a		DT
Pentachlorohyrate Gly Solution	ID1a		DT
Tetrachlorohydrate Solution	ID1a		DT
Tetrachlorohydrex Gly Solution	ID1a		DT
Trichlorohydrate Solution	ID1a		DT
Trichlorohydrex Gly Solution	ID1a		DT
Amantadine Hydrochloride	IA1biii		Poten
Capsules	VA1	FID	naphthalene
Syrup	VA1	FID	naphthalene
Amcinonide	VB1b	UV-254	
Cream	VB1b	UV-254	
Ointment	VB1b	UV-254	dibutyl phthalate
Amikacin	VB2b	UV-340	
Amikacin Sulfate	VB2b	UV-340	
Sulfate Injection	VB2b	UV-340	
Amiloride Hydrochloride	IA1biii		CrV
Tablets	VB1b	UV-286	
and Hydrochlorothiazide Tablets	VB1b	UV-286	
Aminobenzoate Potassium	IC1j		Poten
Capsules	IIIB1	270	
for Oral Solution	IC1j		Poten
Tablets	IIIB1	270	

Appendix B. Assay Index of Official USP-NF Drugs

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Aminobenzoate Sodium	IC1j		Poten
Aminobenzoic Acid	IC1j		Poten
Gel	VB1b		salicylic acid
Topical Solution	IC1j		Poten
Aminocaproic Acid	VB1b	UV-210	
Injection	VB1b	UV-210	
Syrup	IA1bii		CrV
Tablets	IA1bii		CrV
Aminoglutethimide	VB1b	UV-240	
Tablets	VB1b	UV-240	
Aminohippurate Sodium Injection	IC1j		Poten
Aminohippuric Acid	IA1a		Poten
Aminophylline	VB1b	UV-254	
Delayed-release Tablets	IB1bi		
Enema	IIIB1	270	
Injection	VB1b	UV-254	
Oral Solution	VB1b	UV-254	
Suppositories	IB1bi		FAS
Tablets	IB1bi		FAS
Aminosalicylate Sodium	VB1b	UV-254	sulfanilamide and acetaminophen
Tablets	VB1b	UV-254	sulfanilamide and acetaminophen
Aminosalicylic Acid	VB1b	UV-254	acetaminophen
Tablets	VB1b	UV-254	sulfanilamide and acetaminophen
Amitraz	VA1	FID	Squalene
Concentrate for Dip	VA1	FID	Squalene
Amitriptyline Hydrochloride	IA1biii		CrV
Injection	VB1b	UV-254	
Tablets	IIIB1	265	
Strong Ammonia Solution	IA2a		MeR
Aromatic Ammonia Spirit	IA2a, IA1b		MeR, MeO
Ammonio Methacrylate Copolymer	IA1aiii		Poten
Ammonium Carbonate	IA2a		MeO
Ammonium Chloride	IB1a		EY
Injection	IA1c		FAS
Tablets, Delayed Release	IA1c		FAS
Ammonium Molybdate	IIB		
Injection	IIIF1		
Ammonium Phosphate	IA1b		Poten
Amobarbital Sodium	IIA		
for Injection	IIA		
Amodiaquine	IIIB1	342	
Amodiaquine Hydrochloride	IIIB1	342	
Tablets	IIIB1	342	
Amoxapine	IA1bii		CV
Tablets	VB1b	UV-254	
Amoxicillin	VB1b	UV-230	
Boluses	VB1b	UV-230	
Capsules	VB1b	UV-230	
Intramammary Infusion	VIN1		
for Oral Suspension	VB1b	UV-230	
for Injectable Suspension	VB1b	UV-230	
Oral Suspension	VIN2		SPI
Tablets	VB1b	UV-230	
and Clavulanate Potassium for Oral Suspension	VB1b	UV-220	
and Clavulanate Potassium Tablets	VB1b	UV-220	
Amphetamine Sulfate	IIIB3	257, 280	
Tablets	IIIB3	257, 280	
Amphotericin B	VIN1		
Cream	VIN1		
Injection	VIN1		
Lotion	VIN1		
Ointment	VIN1		
Ampicillin	VB1b	UV-254	
Boluses	VIN2		SPI
Capsules	VIN2		SPI
for Oral Suspension	VIN2		SPI
Soluble Powder	VIN2		SPI
for Injection	VB1b	UV-254	
for Injectable Suspension	VIN2		SPI
Sodium	VB1b	UV-230	
Sodium and Sulbactam Sodium	VB1b	UV-230	
and Probenicid for Oral Suspension	VIN2, IIIB1	257	SPI
Amprolium	VB1b	UV-254	
Oral Solution	VB1b	UV-254	
Soluble Powder	VB1b	UV-254	
Amrinone	IA1b		Poten
Injection	VB1b	UV-313	
Amyl Nitrite	IIIG1		benzyl benzoate
Inhalant	IIIG1		benzyl benzoate
Amylene Hydrate	VA1	TC-I	
Anileridine	IA1bii		CrV
Injection	IIIA4	560	
Anileridine Hydrochloride	IA1biii		CrV
Tablets	IIIA4	560	
Antazoline Phosphate	IA1bii		Poten
Anthralin	VB1a	UV-354	*o*-nitroaniline
Cream	VB1a	UV-354	*o*-nitroanilinine
Ointment	VB1a	UV-354	*o*-nitroaniline
Anticoagulant Citrate Dextrose Solution	IIIA4, IA1a, VIC1	425	Phth
Anticoagulant Citrate Phosphate Dextrose Solution	IIIA4, IA1a, IIB	425, 660	Phth
Adenine Solution	IIIA4, IA1a, IIB, VB1b, 425, 660	UV-254	Phth

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Anticoagulant Heparin Solution	VIF, IB1a		PC
Anticoagulant Sodium Citrate Solution	IA1bii		Poten
Antimony Potassium Tartrate	IC1k		ST
Antimony Sodium Tartrate	IC1k		ST
Antipyrine	IC11		ST
and Benzocaine Otic Solution	VB1b	UV-280	
Antipyrine, Benzocaine and Phenylephrine Hydrochloride Otic Solution	VB1b	UV-272	
Apomorphine Hydrochloride	IA1biii		CrV
Tablets	IA2a		MeR
Apraclonidine Hydrochloride	IAibii		Poten
Ophthalmic Solution	VB1b	UV-254	
Arginine	IA1bii		Poten
Arginine Hydrochloride	IA1biii		Poten
Injection	IIIA4	520	
Arsanilic Acid	IC1b		
Ascorbic Acid	IC1k		ST
Injection	VB1b	UV-245	
Oral Solution	IC1c		
Tablets	IC1c		
Ascorbyl Palmitate	IC1k		
Aspartame	IA1aiii		TB
Aspirin	IA2b		Phth
Boluses	VB1b	UV-254	
Capsules	IIIB1	280	
Delayed Release Capsules	VB1b	UV-280	
Delayed Release Tablets	VB1b	UV-280	
Effervescent Tablets for Oral Solution	VB1b	UV-280	
Extended Release Tablets	VB1b	UV-280	
Suppositories	IIIB1	280	
Tablets	VB1b	UV-280	
Alumina and Magnesia Tablets	VB1b, ID2a	UV-280	phenacetin
Alumina and Magnesium Oxide Tablets	VB1b, ID2b, ID1a	UV-205	dithizone, EBT
Caffeine and Dihydrocodeine Bitartraic Capsules	VB1b	UV-215	
and Codeine Phosphate Tablets	VB1b	UV-280	phenacetin
and Codeine Phosphate, Alumina and Magnesia Tablets	VB1b, ID2b, ID1c		phenacetin, DT, EBT
Astemizole	VB1b	UV-220	
Tablets	VB1b	UV-220	
Atenolol	VB1b	UV-226	
Injection	VB1b	UV-275	
Tablets	VB1b	UV-226	
and Chlorthalidone Tablets	VB1b	UV-275	
Atropine	IA1bii		CrV
Atropine Sulfate	IA1bii		Poten
Injection	VB1b	UV-218	
Ophthalmic Ointment	VA1	TC-I	homatropine hydrobromide
Ophthalmic Solution	VA1	TC-I	homatropine hydrobromide
Tablets	VA1	TC-I	homatropine hydrobromide
Aurothioglucose	IIB		
Injectible Suspension	IIB		
Avobenzone	VA1	FID-P	
Azaperone	VB1b	UV-243	
Injection	VB1b	UV-230	
Azatadine Maleate	IA1bii		CrV
Tablets	III1	283	
Azathioprine	IA1aiii		TB
Tablets	VB1b	UV-254	TB
Azathioprine Sodium for Injection	IVA1		
Azithromycin	VB1b	EC	
Capsules	VB1b	EC	
for Oral Suspension	VB1b	EC	
Aztreonam	VB1b	UV-270	
Injection	VB1b	UV-206	
for Injection	VB1b	UV-206	
Bacampicillin Hydrochloride	VB1b	UV-254	
for Oral Suspension	VIN2		SPI
Tablets	VB1b	UV-254	
Bacitracin	None		
for Injection	None		
Ointment	VIN1		
Ophthalmic Ointment	None		
Soluble Methylene Disalicylate	VN1		DT
Soluble Powder	VN1		DT
and Polymyxin B Sulfates			
Topical Aerosol	VIN1		
for Injection	None		
Zinc	None		
Zinc Ointment	VIN1		
Sterile Zinc	None		
Zinc Soluble Powder	VIN1		
Zinc and Polymyxin B Sulfate Ophthalmic Ointment	None		
Zinc and Polymyxin B Sulfate Ointment	None		
Baclofen	IA1bii		Poten
Tablets	VB1b	UV-265	benzoic acid
Barium Hydroxide Lime	VIK		
Barium Sulfate	IIB		
Barium Sulfate Suspension	IIB		
for Suspension	IIB		
Beclomethasone Dipropionate	VB1b	UV-254	testosterone propionate
Belladonna Extract	VA1	TC-I	homatropine hydrobromide
Tablets	VA1	TC-I	homatropine hydrobromide

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Belladonna Leaf	VA1	TC-I	homatropine hydrobromide
Tincture	VA1	TC-I	homatropine hydrobromide
Bendroflumethiazide	IA1aiii		AV
Tablets	VB1b	UV-270	
Benoxinate Hydrochloride	IA1bii		Poten
Ophthalmic Solution	IIIB1	308	
Benzaldehyde	IA1ai		BpB
Benzalkonium Chloride	IC1n		
Solution	IC1n		
Benzethonium Chloride	IE1	BpB	
Tincture	IIB		
Topical Solution	IE1		BpB
Benzocaine	IC1j		SPI
Cream	IC1j		Poten
Gel	VB1b	UV-294	
Lozenges	VB1b	UV-280	
Ointment	IC1j		Poten
Otic Solution	IC1j		Poten
Topical Aerosol	IC1j		Poten
Topical Solution	IC1j		Poten
and Menthol Topical Aerosol	VA1	FID	n-hexane
and Butamben and Tetracaine Hydrochloride Gel	VB1b	UV-254	
and Butamben and Tetracaine Hydrochloride Ointment	VB1b	UV-254	
and Butamben, and Tetracaine Hydrochloride Topical Aerosol	VB1b	UV-254	
and Butamben and Tetracaine Hydrochloride Topical Solution	VB1b	UV-254	
Benzoic Acid	IA1a		Phth
and Salicylic Acid Ointment	IIIB1	311, 275	
Benzoin	VIG		
Benzonatate	IA2bi		Btb
Capsules	IIIA4	500	
Hydrous Benzoyl Peroxide	IC11ii		SPI
Gel	VB1b	UV-254	ethyl benzoate
Lotion	VB1b	UV-254	ethyl benzoate
Benztropine Mesylate	IA1bii		MeR
Injection	VB1b	UV-259	
Tablets	VB1b	UV-259	
Benzyl Alcohol	IA1a		Phth
Benzyl Benzoate	IA2bi		Phth
Lotion	IA2bi		Phth
Benzylpenicilloyl Polylysine	IIIB2	282	
Concentrate			
Injection	IIIB2	282	
Beta Carotene	IIIA3	455	
Capsules	IIIA4	452	
Betadex	VB1b	RI	
Betaine Hydrochloride	IA1biii		CrV
Betamethasone	VB1b	UV-240	propylparaben
Cream	VB1b	UV-240	propylparaben
Syrup	IIIA1	525	
Tablets	VB1b	UV-254	beclomethasone
Betamethasone Acetate	VB1b	UV-254	progesterone
Betamethasone Benzoate	VB1b	UV-254	betamethasone dipropionate
Gel	VB1b	UV-236	methyltestosterone
Betamethasone Dipropionate	VB1b	UV-254, 240	beclomethasone dipropionate
Topical Aerosol	VB1b	UV-254, 240	beclomethasone dipropionate
Cream	VB1b	UV-254, 240	beclomethasone dipropionate
Lotion	VB1b	UV-254, 240	beclomethasone dipropionate
Ointment	VB1b	UV-254, 240	beclomethasone dipropionate
Betamethasone Sodium Phosphate	VB1b	UV-254	
Injection	VB1b	UV-254	butylparaben
and Betamethasone Acetate Suspension	VB1b	UV-254	methyltestosterone
and Betamethasone Acetate Injectable Suspension	VB1b	UV-254	methyltestosterone
Betamethasone Valerate	VB1b	UV-254	beclomethasone dipropionate
Cream	VB1b	UV-254	beclomethasone dipropionate
Lotion	VB1b	UV-254	beclomethasone dipropionate
Ointment	VB1b	UV-254	beclomethasone dipropionate
Betaxolol Hydrochloride	IA1bii		Poten
Ophthalmic Solution	VB1b	UV-280	
Tablets	VB1b	UV-273	
Bethanechol Chloride	IA1biii		CrV
Injection	IIB		
Tablets	IIIA4	590	
Biotin	IA1b		Phth
Biperiden	IA1bii		CrV
Biperiden Hydrochloride	IA1biii		CrV
Tablets	IIIA2	408	
Biperiden Lactate Injection	IIIA2	408	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Bisacodyl	IA1bii		Nb
Rectal Suspension	VB1b	UV-254	
Suppositories	VB1b	UV-265	
Delayed Release Tablets	VB1b	UV-265	
Milk of Bismuth	IIC		
Bismuth Subcarbonate	D1a		XyO
Bismuth Subgallate	IIC		
Bismuth Subnitrate	ID1a		XyO
Bismuth Subsalicylate	ID1a, IIIA4	525	XyO
Bleomycin Sulfate	VIN1		
for Injection	VIN		
Boric Acid	IA1a		Phth
Bretylium Tosylate	IA1bii		CrV
Injection	VB1b	UV-220	
in Dextrose Injection	VB1B, IIIC	UV-220	
Bromocriptine Mesylate	IA1bii		Poten
Capsules	VB1b	UV-300	
Tablets	VB1b	UV-300	
Bromodiphenhydramine Hydrochloride	IA1biii		CrV
Elixir	IA2a		MeR
Brompheniramine Maleate	IA1bii		CrV
Elixir	IA1bii		CrV
Injection	IIIB1	262	
Tablets	IIIB1	264	
and Pseudoephedrine Sulfate Syrup	VB1b	UV-254	naphazoline IIC1
Bumetanide	IA1a		PhR
Injection	VB1b	UV-254	ethylbenzaldehyde
Tablets	VB1b	UV-254	
Bupivacaine Hydrochloride and Epinephrine Injection	VB1b	UV-263, EC	dibutyl phthalate
Bupivacaine Hydrochloride	IA1biii		CrV
in Dextrose Injection	VB1b	UV-263	dibutyl phthalate
Injection	VB1b	UV-263	dibutyl phthalate
Buprenorphine Hydrochloride	IA1bii		CrV
Buspirone Hydrochloride	VB1b	UV-254	propylparaben
Tablets	VB1b	UV-254	
Busulfan	IA1ai		Phth
Tablets	IA1ai		Phth
Butabarbital	IIIB1	240	
Butabarbital Sodium	IIIB1	240	
Elixir	VA1	FID-I	secobarbital
Tablets	VA1	FID-I	secobarbital
Butalbital	VA1	FID-I	tetracosane
Acetaminophen, and Caffeine Capsules	VB1b	UV-254	
Acetaminophen, and Caffeine Tablets	VB1b	UV-216	phenacetin
Aspirin, and Caffeine Capsules	VB1b	UV-277, 210	
Aspirin Tablets	VB1b	UV-214	
Aspirin, and Caffeine Tablets	VB1b	UV-277, 210	
Aspirin, Caffeine, and Codeine Phosphate Capsules	VB1b	UV-277, 210	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Butamben	IC1j		SPI
Butane	VA1	TC-I	
Butoconazole Nitrate	VB1b	UV-229	
Nitrate Cream	VB1b	UV-225	1-benzylimidazole
Butorphanol Tartrate	IA1bii		CrV
Injection	VB1b	UV-280	propylparaben
Butylated Hydroxyanisole	VA1	FID-I	4-*tert*-butylphenol
Butylparaben	IA2b		Poten
Caffeine	VB1b	UV-275	
and Sodium Benzoate Injection	IIA, IA1b		MeO
Calamine	IA2a		MeO
Calcifediol	VB1a	UV-254	testosterone
Capsules	VB1a	UV-254	testosterone
Calcium Acetate	ID1a		HNB
Tablets	ID1a		HNB
Calcium Ascorbate	ID1a		HNB
Calcium Carbonate	ID1a		HNB
Lozenges	IIIF		
Tablets	ID1a		HNB
Oral Suspension	ID1a		HNB
and Magnesia Tablets	ID1a		HNB, EBT
and Magnesia and Simethicone Tablets	IIIF1	251.6, 422.7, 285.2	HNB
and Magnesium Carbonates Oral Suspension	ID1a		HNB, EBT
and Magnesium Carbonates Tablets	ID1a		HNB, EBT
Calcium with Vitamin D Tablets	VB1a	UV-265	
Calcium Chloride	ID1a		HNB
Calcium Citrate	ID1a		HNB
Calcium Glubionate Syrup	ID1a		HNB
Calcium Gluceptate	ID1a		HNB
Injection	ID1a		HNB
Calcium Gluconate	ID1a		HNB
Injection	ID1a		HNB
Tablets	ID1a		HNB
Calcium Hydroxide	ID1a		HNB
Topical Solution	IA1b		Phth
Calcium Lactate	ID1a		HNB
Tablets	ID1a		HNB
Calcium Lactobionate	ID1a		HNB
Calcium Levulinate	ID1a		HNB
Injection	ID1a		HNB
Calcium Pantothenate			
Tablets	VIII		
Dibasic Calcium Phosphate	ID1a		HNB
Tablets	ID1a		HNB
Tribasic Calcium Phosphate	ID1a		HNB
Calcium Saccharate	ID1a		HNB
Calcium Silicate	ID1a, IIC		HNB
Calcium Stearate	ID1a		HNB
Calcium Sulfate	ID1a		HNB
Calcium Undecylenate	IA2a		MeO
Camphor Spirit	iiB		

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Capreomycin Sulfate	VIN		
for Injection	VIN		
Capsaicin	VB1b	UV-281	
Capsicum Oleoresin	VB1b	UV-280	
Captopril	IC1n		ST
Tablets	Vb1b	UV-220	
and Hydrochlorothiazide Tablets	VB1b	UV-210	
Carbachol	IA1bii		CV
Intraocular Solution	IIIA5	590	
Ophthalmic Solution	IIIA5	590	
Carbachol	IA1biii		CrV
Intraocular Solution	IIIA5	590	
Ophthalamic Solution	IIIA5	590	
Carbamazepine	VB1b	UV-230	
Oral Suspension	VB1b	UV-254	
Tablets	IIIB1	285	
Carbamide Peroxide	IC2c		AM
Topical Solution	IC1lii		ST
Carbenicillin Disodium	VIN1		
for Injection	VIN1		
Carbenicillin Indanyl Sodium	VB1b	UV-210	
Tablets	VB1b	UV-210	
Carbidopa	VB1b	UV-280	
and Levodopa Tablets	VB1b	UV-280	
Carbinoxamine Maleate	IA1bii		CrV
Tablets	IA1bii		CrV
Carbomer 934P	IA1a		Poten
Carbon Dioxide	VIA		
Carbon Monoxide C 11	VIE		
Carboplatin	VB1b	UV-230	
Injection	VB1b	UV-230	
Carboxymethylcellulose Sodium	IA1bii		Poten
Paste	IA1bii		Poten
Tablets	IA1bii		Poten
Carisoprodol	IA2b		Phth
Tablets	VB1b	RI	
and Aspirin Tablets	VB1b	RI	
Aspirin and Codeine Phosphate Tablets	VB1b	RI, UV-254	
Carrageenan	None		
Carteolol Hydrochloride	VB1b	UV-252	
Ophthalmic Solution	VB1b	UV-252	
Tablets	VB1b	UV-252	
Casanthranol	IC1g, IIIA	515	
Cascara Sagrada	IIIA4	515	
Extract	IIIA4	515	
Cascara Sagrada			
Aromatic Fluidextract	IIA		
Tablets	IIIA4	515	
Castor Oil			
Aromatic	VA1	FID-I	bis(2-ethyl hexyl)-phthalate
Emulsion	VA1	FID-I	bis(2-ethyl hexyl)-phthalate
Cefaclor	VB1b	UV-265	
Capsules	VB1b	UV-265	
for Oral Suspension	VB1b	UV-265	
Cefadroxil	VB1b	UV-230	
Capsules	VB1b	UV-230	
for Oral Suspension	VB1b	UV-230	
Tablets	VB1b	UV-230	
Cefamandole Nafate	IVA2		
for Injection	IVA2		
Cefazolin Sodium	VB1b	UV-254	salicylic acid
Injection	VB1b	UV-254	salicylic acid
for Injection	VB1b	UV-254	salicylic acid
Cefixime	VB1b	UV-254	
for Oral Suspension	VB1b	UV-254	
Tablets	VB1b	UV-254	
Cefmenoxime for Injection	VB1b	UV-254	phthalimide
Hydrochloride	VB1b	UV-254	phthalimide
Cefmetazole	VB1b	UV-214	
Injection	VB1b	UV-214	
Cefmetazole Sodium	VB1b	UV-214	
for Injection	VB1b	UV-214	
Cefonicid Sodium	VB1b	UV-254	
for Injection	VB1b	UV-254	
Cefoperazone Sodium	VB1b	UV-254	
Injection	VB1b	UV-254	
for Injection	VB1b	UV-254	
Ceforanide	VB1b	UV-254	
for Injection	VB1b	UV-254	
Cefotaxime Sodium	VB1b	UV-235	
Injection	VB1b	UV-235	
for Injection	VB1b	UV-235	
Cefotiam Hydrochloride	VB1b	UV-254	
Injection	VB1b	UV-254	
for Injection	VB1b	UV-254	
Cefotetan	VB1b	UV-254	
Injection	VB1b	UV-254	
for Injection	VB1b	UV-254	
Cefotetan Disodium	VB1b	UV-254	
Cefoxitin	VB1b	UV-254	
Injection	VB1b	UV-254	
for Injection	VIN3	480	
Cefpiramide	VB1b	UV-254	
for Injection	VB1b	UV-254	
Cefprozil	VB1b	UV-280	
for Oral Suspension	VB1b	UV-280	
Tablets	VB1b	UV-280	

DRUG	ASSAY CATEGORY	AND/OR DETECTOR	ANALYTICAL WAVELENGTH INDICATOR OR INTERNAL STANDARD
Ceftazidime	VB1b	UV-254	
for Injection	VB1b	UV-254	
Injection	VB1b	UV-254	
Ceftizoxime Sodium	VB1b	UV-254	salicylic acid
Injection	VB1b	UV-254	salicylic acid
for Injection	VB1b	UV-254	salicylic acid
Ceftriaxone	VB1b	UV-270	
Injection	VB1b	UV-270	
for Injection	VB1b	UV-270	
Cefuroxime Injection	VB1b	UV-254	orcinol
for Injection	VB1b	UV-254	orcinol
Cefuroxime Axetil	VB1b	UV-278	acetanilide
Tablets	VB1b	UV-278	acetanilide
Cefuroxime Sodium	VB1b	UV-254	orcinol
Injection	VB1b	UV-254	orcinol
for Injection	VB1b	UV-254	orcinol
Microcrystalline Cellulose and Carboxymethylcellulose Sodium	IC1e IA1bii		Poten
Oxidized Cellulose	IA1ai		Phth
Regenerated	IA2b		Phth
Powdered Cellulose	IC1e		OP
Cephalexin	VB1b	UV-254	1-hydroxy-benzotriazole
Capsules	VB1b	UV-254	1-hydroxy-benzotriazole
for Oral Suspension	VB1b	UV-254	1-hydroxy-benzotriazole
Tablets	VB1b	UV-254	1-hydroxy-benzotriazole
Cephalexin Hydrochloride	VB1b	UV-254	1-hydroxy-benzotriazole
Cephalothin Sodium	VB1b	UV-254	
for Injection	VB1b	UV-254	
Injection	VB1b	UV-254	
Cephapirin Benzathine Intramammary Infusion	VIN VIN		
Cephapirin Sodium	VB1b	UV-254	
for Injection	VB1b	UV-254	
Cephapirin Sodium Intramammary Infusion	VIN		
Cephradine	VB1b	UV-254	
Capsules	VB1b	UV-254	
for Injection	VB1b	UV-254	
for Oral Suspension	VB1b	UV-254	
Tablets	VB1b	UV-254	
Cetostearyl Alcohol	VA1	FID-I	
Cetyl Alcohol	VA1	FID-I	
Cetylpyridinium Chloride	IE1		BpB
Lozenges	IE2		MeY
Topical Solution	IE1		BpB
Activated Charcoal	VIK		
Chloral Hydrate	IA2b		Phth
Capsules	IA2b		Phth
Syrup	IA2b		Phth
Chlorambucil	IA1a		Phth
Tablets	VB1b	UV-254	propylparaben

DRUG	ASSAY CATEGORY	WAVELENGTH AND/OR DETECTOR	ANALYTICAL INDICATOR OR INTERNAL STANDARD
Chloramphenicol	VB1b	UV-280	
Capsules	VB1b	UV-280	
Cream	VB1b	UV-280	
Injection	VB1b	UV-280	
Oral Solution	VIN1		
Ophthalmic Ointment	VB1b	UV-280	
Ophthalmic Solution	VB1b	UV-280	
for Ophthalmic Solution	VB1b	UV-280	
Otic Solution	VB1b	UV-280	
Tablets	VB1b	UV-280	
and Hydrocortisone Acetate for Ophthalmic Suspension	VB1b	UV-280	
and Polymyxin B Sulfate Ophthalmic Ointment	VB1b	UV-280	
Polymyxin B Sulfate and Hydrocortisone Acetate Ophthalmic Ointment	VB1b	UV-280	
and Prednisolone Ophthalmic Ointment	VB1b	UV-280	
Chloramphenicol Palmitate	VB1b	UV-280	
Oral Suspension	VB1b	UV-280	
Chloramphenicol Sodium Succinate	IIIB1	276	
for Injection	VB1b	UV-275	
Chlordiazepoxide	VB1b	UV-254	sulfanilamide
Tablets	VB1b	UV-254	sulfanilamide
and Amitriptyline Hydrochloride Tablets	VB1b	UV-254	sulfanilamide
Chlordiazepoxide Hydrochloride	VB1b	UV-254	sulfanilamide
Capsules	IIIB1	245	
for Injection	IA1biii		CrV
and Clindinium Bromide Capsules	VB1b	UV-212	
Chlorobutanol	IB2aii		Poten
Chlorocresol	IC2f		ST
Chloroprocaine Hydrochloride	VB1b	UV-278	
Injection	VB1b	UV-278	
Chloroquine	IA1bii		CrV
Chloroquine Hydrochloride Injection	IIIB1	343	
Chloroquine Phosphate	IIIB1	343	
Tablets	IIIB1	343	
Chlorothiazide	VB1b	UV-254	
Oral Suspension	IIIB1	292	
Tablets	VB1b	UV-254	
Chlorothiazide Sodium for Injection	IIIB1	292	
Chloroxylenol	VA1	FID-I	p-chlorophenol
Chlorpheniramine Maleate	IA1bii		CrV
Extended-release Capsules	VB1b	UV-261	
Injection	IIIB1	264	
Syrup	IIIB1	264	
Tablets	IIIB1	264	
and Pseudoephedrine Hydrochloride Oral Solution	VB1b	UV-261	

Appendix B. Assay Index of Official USP-NF Drugs

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Chlorpromazine	IA1bii		CrV
Suppositories	IIIB1	254, 277	
Chlorpromazine Hydrochloride	IA1bii		Poten
Injection	IIIB1	254, 277	
Oral Concentrate	IIIB1	277, 254	
Syrup	IIIB1	254, 277	
Tablets	IIIB1	254, 277	
Chlorpropamide	VB1b	UV-240	
Tablets	VB1b	UV-240	
Chlortetracycline Bisulfate and Sulfamethazine	VIN1		
Bisulfates Soluble Powder	VIN1, IC1j		
Chlortetracycline Hydrochloride	VIN1		
Ointment	VIN1		
Ophthalmic Ointment	VIN1		
Soluble Powder	VIN1		
Tablets	VIN1		
Chlorthalidone	VB1b	UV-254	2,7-naphthalenediol
Tablets	VB1b	UV-254	2,7-naphthalenediol
Chlorzoxazone	IIIB1	282	
Tablets	VB1b	UV-280	phenacetin
Cholecalciferol	VB1a	UV-254	
Solution	VB1b	UV-254	
Cholestyramine for Oral Suspension	IIIB2	318	
Sodium Chromate Cr51 Injection	IIIB1, VIE	370	
Chromic Chloride	IC1lii		ST
Injection	IIIF1	357.9	
Chymotrypsin	VIF		
for Ophthalmic Suspension	VIF		
Ciclopirox Olamine	IIIA4	440	
Cream	IIIA4	440	
Topical Suspension	IIIA4		
Cilastatin Sodium	IA1a		Poten
Cimetidine	VB1b	UV-220	
Tablets	VB1b	UV-220	
Injection	VB1b	UV-220	
in Sodium Chloride Injection	VB1b	UV-220	
Cimetidine Hydrochloride	VB1b	UV-220	
Cinoxacin	VB1b	UV-254	sulfanilic acid
Capsules	IIIB1	352	
Cinoxate	IA2b		Phth
Lotion	IIIB1	308	
Ciprofloxacin	VB1b	UV-278	
Injection	VB1b	UV-278	
Ophthalmic Solution	VB1b	UV-280	
Tablets	VB1b	UV-278	
Ciprofloxacin Hydrochloride	VB1b	UV-278	
Cisplatin	VB1b	UV-310	
for Injection	VB1b	UV-310	
Citric Acid	IA1a		Phth
Magnesium Oxide and Sodium Carbonate Irrigation	VB1b, IIB, IIARI		
Clarithromycin	VB1b	UV-210	
for Oral Suspension	VB1b	UV-210	
Tablets	VB1b	UV-210	
Clavulanate Potassium	VB1b	UV-220	
Clemastrine Fumarate	IA1bii		Poten
Tablets	VB1b	UV-220	
Clidinium Bromide	IA1biii		Poten
Clindamycin Injection	VB1b	UV-210	
for Injection	VB1b	UV-210	
Clindamycin Hydrochloride	VB1b	UV-210	
Capsules	VB1b	UV-210	
Oral Solution	VB1b	UV-210	
Clindamycin Palmitate Hydrochloride	VA1	FID-I	cholesteryl benzoate
for Oral Solution	VA1	FID-I	cholesteryl benzoate
Clindamycin Phosphate	VB1b	UV-210	hydroxy acetophenone
Gel	VB1b	UV-210	
Injection	VB1b	UV-210	
for Injection	VA2	FID-I	hexacosane
Topical Solution	VA2	FID-I	hexacosane
Topical Suspension	VB1b	UV-210	
Vaginal Cream	VB1b	UV-210	
Clioquinol	VA1	FID-I	pyrene
Cream	VA1	FID-I	pyrene
Ointment	VA1	FID-I	pyrene
Compound Topical Powder	IIIB1	267	
and Hydrocortisone Cream	VA1, VB1b	FID, UV-254	pyrene
and Hydrocortisone Ointment	VA1, VB1b	FID, UV-254	pyrene
Clobetazole Propionate	VB1b	UV-240	beclomethasone diproprionate
Cream	VB1b	UV-240	beclomethasone diproprionate
Ointment	VB1b	UV-240	beclomethasone diproprionate
Topical Solution	VB1b	UV-240	beclomethasone diproprionate
Clocortolone Pivalate	IIIA4	405	
Cream	IIIA4	390	
Clofazimine	IA1b		Poten
Capsules	IIIA1	491	
Clofibrate	IIIB1	226	
Capsules	IIIB1	226	
Clomiphene Citrate	VB1b	UV-233	
Tablets	VB1b	UV-233	
Clonazepam	VB1b	UV-254	
Tablets	VB1b	UV-254	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Clonidine Hydrochloride	IA1biii		Poten
Tablets	VB1b	UV-220	
and Chlorthalidone Tablets	VB1b	UV-220	
Clorazepate Dipotassium	IA1bii		Poten
Tablets	VB1b	UV-232	
Clorsulon	VB1b	UV-254	
Clotrimazole	VB1b	UV-254	testosterone propionate
Cream	VB1b	UV-254	testosterone propionate
and Betamethasone Dipropionate Cream	VB1b	UV-254	progesterone
Lotion	VB1b	UV-254	testosterone
Lozenges	VB1b	UV-215	triphenylmethane
Topical Solution	VB1b	UV-254	testosterone propionate
Vaginal Tablets	VB1b	UV-254	testosterone propionate
Cloxacillin Benathine	VIN1		
Intramammary Infusion	VIN1		
Cloxacillin Sodium	VB1b	UV-225	
Capsules	VB1b	UV-225	
for Oral Solution	VB1b	UV-225	
Intramammary Infusion	VIN1		
Cyanocobalamin Co 57 Capsules	VIE		
Oral Solution	VIE		
Cocaine	IA1bii		CrV
Cocaine Hydrochloride	IA1biii		QR
Tablets for Topical Solution	IA2a		MeR
Cod Liver Oil	VIL		
Codeine	IA2a		MeR
Codeine Phosphate	IA1bii		Poten
Injection	IA1b		MeR
Tablets	IA1b		MeR
Codeine Sulfate	IA1bii		Poten
Tablets	IA2a		MeR
Colchicine	VB1b	UV-254	
Injection	VB1b	UV-254	
Tablets	VB1b	UV-254	
Colistimethate Sodium	VIN1		
for Injection	VIN1		
Colistin Sulfate	VIN1		
for Oral Suspension	VIN1		
and Neomycin Sulfate and Hydrocortisone Acetate Otic Suspension	VIN1, IIIA4	410	
Collodion	IIA		
Copper Gluconate	IC2f		ST
Corticotropin Injection	VIII		
for Injection	VIII		
Corticotropin Zinc Hydroxide Injectable Suspension	VIII		
Cortisone Acetate	VB1b	UV-254	methylparaben
Injectable Suspension	VB1b	UV-254	prednisone
Tablets	VB1b	UV-254	methylparaben
Creatinine	IA1c		

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Cromolyn Sodium	IIIB1	326	
for Inhalation	IIIB1	326	
Inhalation Solution	IIIB1	326	
Nasal Solution	IIIb1	326	
Crotamiton	IIIB1	242	
Cream	VB1b	UV-254	butyl benzoate
Cupric Chloride	IC1lii		ST
Injection	IIIF1	324.8	
Cupric Sulfate	IC1lii		ST
Injection	IIIF1	324.8	
Cyanocobalamin	IIIB1	361	
Injection	IIIB1	361	
Cyclizine Hydrochloride	IA1biii		Poten
Tablets	IIIB1	264	
Cyclobenzaprine Hydrochloride	IA1biii		Poten
Tablets	VB1b	UV-290	
Cyclomethicone	VA1	TC	
Cyclopentolate Hydrochloride	VB1b	UV-220	
Ophthalmic Solution	VB1b	UV-220	
Cyclophosphamide	VB1b	UV-195	ethylparaben
for Injection	VB1b	UV-195	ethylparaben
Tablets	VB1b	UV-195	ethylparaben
Cyclopropane	VIA		
Cycloserine	VIN1		
Capsules	VIN1		
Cyclosporine	VB1b	UV-210	
Capsules	VB1b	UV-210	
Injection	VB1b	UV-210	
Oral Solution	VB1b	UV-210	
Cyproheptadine Hydrochloride	IA1biii		CrV
Syrup	VB1b	UV-285	
Tablets	VB1b	UV-285	
Cysteine Hydrochloride	IC1lii		ST
Injection	IVA1		
Cytarabine	VB1b	UV-254	
for Injection	VB1b	UV-254	
Dacarbazine	IIIB1	323, 329	
for Injection	IIIB1	323	
Dactinomycin	VB1b	UV-254	
for Injection	VB1b	UV-254	
Danazol	IIIB1	285	
Capsules	VB1b	UV-270	
Dapsone	VB1a	UV-254	
Tablets	VB1a	UV-254	
Daunorubicin Hydrochloride	VB1b	UV-254	2-naphthalene-sulfonic acid
for Injection	VB1b	UV-254	2-naphthalene-sulfonic acid
Decoquinate	IAbii		CrV
Premix	IIIB1	265	
Deferoxamine Mesylate	IIIA4	485	
for Injection	IIIA4	485	

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Dehydrocholic Acid	IA1a		Phth
Tablets	IA1a		Phth
Demecarium Bromide	IA1biii		CrV
Ophthalmic Solution	IIIB1	292	
Demeclocycline	VIN1		
Oral Suspension	VIN1		
Demeclocycline Hydrochloride	VIN1		
Capsules	VIN1		
Tablets	VIN1		
Denatonium Benzoate	IA1bii		CrV
Desflurane	VA1	FID	halothane
Desipramine Hydrochloride	IA1biii		Poten
Tablets	IIIB1	255	
Deslanoside	IIIA1		FC
Injection	IIIA1		FC
Desoximetasone	VB1b	UV-254	
Cream	VB1b	UV-254	ethylparaben
Gel	VB1b	UV-254	
Ointment	VB1b	UV-254	
Desoxycorticosterone Acetate	IIIA1	525	
Injection	IIIA1	525	
Pellets	IIIA1	525	
Desoxycorticosterone Pivalate	VB1b	UV-254	desoxycorticosterone
Injectable Suspension	VB1b	UV-254	desoxycorticosterone
Dexamethasone	VB1b	UV-254	
Topical Aerosol	IIIA1	525	
Elixir	VB1b	UV-254	
Gel	IIIA1	525	
Ophthalmic Suspension	VB1b	UV-254	
Oral Solution	VB1b	UV-254	
Tablets	VB1b	UV-254	
Dexamethasone Acetate	VB1b	UV-254	
Injectable Suspension	VB1b	UV-254	
Dexamethasone Sodium Phosphate	VB1b	UV-254	
Inhalation Aerosol	IIIB1	239	
Cream	VB1b	UV-254	
Injection	VB1b	UV-254	
Ophthalmic Ointment	VB1b	UV-254	
Ophthalmic Solution	VB1b	UV-254	
Dexbrompheniramine Maleate	IA1bii		CrV
and Pseudoephedrine Sulfate Oral Solution	VB1b	UV-254	
Dexchlorpheniramine Maleate	IA1bii		CrV
Syrup	IIIB1	264	
Tablets	IIIB1	264	
Dexpanthenol	IA2aiv		CrV
Preparation	IA2aiv		CrV
Dextroamphetamine Sulfate	IA1bii		Poten
Capsules	VB1b	UV-254	
Elixir	IIIB1	257, 280	
Tablets	VB1b	UV-254	
Dextromethorphan	IA1bii		CrV
Dextromethorphan Hydrobromide	VB1b	UV-280	
Syrup	VB1b	UV-280	
Dextrose Injection	VIC1		
and Sodium Chloride Injection	VIC1, IB1a		DCF
Diatrizoate Meglumine	IB1a		TBP
Injection	IB1a		TBP
and Diatrizoate Sodium Injection	VIC1, IB1a		TBP
and Diatrizoate Sodium Solution	IC1liii, IB1a		ST, TBP
Diatrizoate Sodium	IB1a		TBP
Injection	IB1a		TBP
Solution	IB1a		TBP
Diatrizoic Acid	IB1a		TBP
Diazepam	IA1bii		Poten
Capsules	VB1b	UV-254	ethylparaben
Capsules, Extended-Release	VB1b	UV-254	ethylparaben
Injection	VB1b	UV-254	tolualdehyde
Tablets	VB1b	UV-254	ethylparaben
Diazoxide	VB1b	UV-254	hydrochlorothiazide
Capsules	VB1b	UV-254	hydrochlorothiazide
Injection	VB1b	UV-254	hydrochlorothiazide
Oral Suspension	VB1b	UV-254	hydrochlorothiazide
Dibucaine	IA1bii		CrV
Cream	IIIB1	247	
Ointment	IIIB1	247	
Dibucaine Hydrochloride	IA1biii		CrV
Injection	IIIB1	247	
Dibutyl Sebacate	VA1	FID-NI	
Dichloralphenazone	IAb, IC2a		ST
Dichlorodifluoromethane	VA1	FID	
Dichlorotetrafluoroethane	VA1	FID	
Dichlorphenamide	VB1b	UV-280	
Tablets	IVA1		
Diclofenac Sodium	IA1bii		Poten
Delayed-release Tablets	VB1b	UV-254	
Dicloxacillin Sodium	VB1b	UV-225	
Capsules	VB1b	UV-225	
for Oral Suspension	VIN1		
Dicyclomine Hydrochloride	IA1biii		CrV
Capsules	VA1	FID	phenacetin
Injection	VA1	FID	phenacetin
Syrup	VA1	FID	phenacetin
Tablets	VA1	FID	phenacetin
Dienestrol	VB1b	UV-254	methyltestosterone
Cream	VB1b	UV-254	methyltestosterone
Diethanolamine	IA1b		BcG

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Diethylcarbamazine Citrate	IA1bii		Nb
Tablets	IA1bii		TB
Diethylphthalate	IA2b		Phth
Diethylpropion Hydrochloride	VB1b	UV-254	
Tablets	VB1b	UV-254	
Diethylstilbestrol	VB1b	UV-254	
Injection	IIIA4	418	
Tablets	VB1b	UV-254	
Diethylstilbestrol Diphosphate	IIIB1	241	
Injection	IIIB1	241	
Diethyltoluamide	IIIC1	14.1	
Topical Solution	IIIC1	14.1	
Diflorasone Diacetate	VB1b	UV-254	isoflupredone acetate
Cream	VB1b	UV-254	isoflupredone acetate
Ointment	VB1b	UV-254	isoflupredone acetate
Diflunisal	VB1b	UV-254	
Tablets	VB1b	UV-254	
Digitalis	VIH		
Powdered	VIH		
Capsules	VIH		
Tablets	VIH		
Digitoxin	VB1b	UV-218	
Injection	VB1b	UV-218	
Tablets	VB1b	UV-218	
Digoxin	VB1b	UV-218	
Elixir	VB1b	UV-218	
Injection	VB1b	UV-218	
Tablets	VB1b	UV-218	
Dihydrocodeine Bitartrate	VB1b	UV-280	
Dihydroergotamine Mesylate	IIIA4	585	
Injection	IIIA4	585	
Dihydrostreptomycin Sulfate	VIN1		
Boluses	VIN1		
Injection	VIN1		
Dihydrotachysterol	VB1b	UV-254	
Capsules	VB1b	UV-254	
Oral Solution	VB1b	UV-254	
Tablets	VB1b	UV-254	
Dihydroxyacetone	IC1M		ST
Dihydroxyaluminum Aminoacetate	ID2a		DT
Magma	ID2a		DT
Dihydroxyaluminum Sodium Carbonate	ID2a		DT
Tablets	ID2a		DT
Diltiazem Hydrochloride	VB1b	UV-240	
Extended-release Capsules	VB1b	UV-240	
Tablets	VB1b	UV-240	
Dimenhydrinate	IA1bii, IB2aii		Poten, FAS
Injection	VB1b	UV-254	2-hydroxy benzyl alcohol
Syrup	VB1b	UV-254	2-hydroxy benzyl alcohol
Tablets	VB1b	UV-254	2-hydroxy benzyl alcohol
Dimercaprol	IC1k		
Injection	IC1k		
Dimethicone	IIIC1		
Dimethyl Sulfoxide	None		
Gel	VA1	FID	dimethylformamide
Irrigation	VA1	FID-P	
Topical Solution	VA1	FID	dimethylformamide
Dioxybenzone and Oxybenzone Cream	IIIA3 VC1b	325	
Diphenhydramine Citrate	IA1bii		Poten
Diphenhydramine Hydrochloride	VB1b	UV-254	
Capsules	VB1b	UV-254	
Elixir	VB1b	UV-254	
Injection	VB1b	UV-254	
and Pseudoephedrine Capsules	VB1b	UV-254	
Diphenoxylate Hydrochloride	IA1biii		Poten
and Atropine Sulfate Oral Solution	IA1biii, VA1	FID-I	Poten, homatropine hydrobromide
and Atropine Sulfate Tablets	VB1b	UV-206, 254	
Dipivefrin Hydrochloride	VB1b	UV-254	
Ophthalmic Solution	VB1b	UV-254	
Dipyridamole	IA1bii		Poten
Tablets	VB1b	UV-288	
Dirithromycin	VB1b	UV-205	
Delayed-Release Tablets	VB1b	UV-205	
Disopyramide Phosphate	IA1bii		Poten
Capsules	IIIB1	268	
Capsules, Extended-Release	IIIB2	261	
Disulfiram	VB1b	UV-250	
Tablets	VB1b	UV-250	
Dobutamine Hydrochloride	VB1b	UV-280	
Injection	VA2	FID-I	n-tricontance
for Injection	VB1b	UV-280	
Docusate Calcium	IE3		BpB
Capsules	IIIA2	545	
Docusate Potassium	IE3		BpB
Capsules	VB1b	RI	
Docusate Sodium	IE3		BpB
Capsules	VB1b	UV-214	
Solution	VB1b	UV-214	
Syrup	IIIA2	650	
Tablets	VB1b	UV-210	
Dopamine Hydrochloride	IA1biii		Poten
Injection	VB1b	UV-280	
and Dextrose Injection	VB1b	UV-280, RI	
Doxapram Hydrochloride	IA1biii		CrV
Injection	VB1b	UV-225	diphenylhydramine
Doxepin Hydrochloride	VB1b	UV-254	
Capsules	VB1b	UV-254	
Oral Solution	IIIB1	292	
Doxorubicin Hydrochloride	VB1b	UV-254	2-naphthalene-sulfonic acid
Injection	VB1b	UV-280	
for Injection	VB1b	UV-254	2-naphthalene-sulfonic acid

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Doxycycline	VB1b	UV-270	
Capsules	VB1b	UV-270	
for Injection	VB1b	UV-270	
for Oral Suspension	VB1b	UV-270	
Doxycycline Calcium Oral Suspension	VB1b	UV-270	
Doxycycline Hyclate	VB1b	UV-270	
Capsules	VB1b	UV-270	
Capsules, Delayed-Release	VB1b	UV-280	
for Injection	VB1b	UV-280	
Tablets	VB1b	UV-280	
Doxylamine Succinate	IA1bii		CrV
Syrup	IIIB1	262	
Tablets	VB1b	UV-262	
Dronabinol	VB1b	UV-228	
Capsules	VB1b	UV-228	
Droperidol	IA1bii		Nb
Injection	VB1b	UV-280	
Absorbable Dusting Powder	ID1a		EBT
Dyclonine Hydrochloride	VB1b	UV-254	
Gel	VB1b	UV-254	
Topical Solution	VB1b	UV-254	
Dydrogesterone	VB1b	UV-280	
Tablets	VB1b	UV-280	
Dyphylline	IA1bii		SD
Elixir	VB1b	UV-254	
Injection	VB1b	UV-254	
Tablets	VB1b	UV-254	
and Guaifenesin Elixir	VB1b	UV-230	
and Guaifenesin Tablets	VB1b	UV-230	
Echothiophate Iodide	IC1k		Poten
for Ophthalmic Solution	IC1k		Poten
Econazole Nitrate	IA1bii		Poten
Edetate Calcium Disodium	ID1b		DC
Injection	ID1b		DC
Edetate Disodium	ID1a		HNB
Injection	ID1a		HNB
Edetic Acid	ID1a		HNB
Edrophonium Chloride	IA1biii		CrV
Injection	IIIB1	273	
Multiple Electrolytes Injection Type 1	VIO		
Multiple Electrolytes Injection Type 2	VIO		
Multiple Electrolytes and Dextrose Injection Type 1	VIO		
Multiple Electrolytes and Dextrose Injection Type 2	VIO		
Multiple Electrolytes and Dextrose Injection Type 3	VIO		
Multiple Electrolytes and Dextrose Injection Type 4	VIO		
Multiple Electrolytes and Invert Sugar Injection Type 1	VIO		
Multiple Electrolytes and Invert Sugar Injection Type 2	VIO		
Multiple Electrolytes and Invert Sugar Injection Type 3	VIO		
Trace Elements Injection	IIIF1, IC1lii, VB1b 213.8, 357.9, 279, ST	UV-226	
Emetine Hydrochloride	IA1biii		CrV
Injection	IA2a		MeR
Enalapril Maleate	VB1b	UV-210	
Tablets	VB1b	UV-215	
and Hydrochlorothiazide Tablets	VB1b	UV 215, 310	
Enalaprilat	VB1b	UV-210	
Enflurane	VA1	TC-P	
Ephedrine	IA2a		MeR
Ephedrine Hydrochloride	IA1biii		CrV
Ephedrine Sulfate	IA1bii		MeR
Capsules	IIIB2	242	
Injection	IA1bii		MeR
Nasal Solution	IIIB2	242	
Syrup	IIIB2	242	
Epinephrine	IA1bii		CrV
Inhalation Solution	VIC2		
Inhalation Aerosol	VIC2		
Injection	VB1b	UV-280	
Nasal Solution	VIC2		
Ophthalmic Solution	IIIB1	280	
Epinephrine Bitartrate	IA1bii		CrV
Inhalation Aerosol	IIIA4	530	
for Ophthalmic Solution	VIC2		
Ophthalmic Solution	VB1b	UV-280	
Epinephryl Borate Ophthalmic Solution	VIC2		
Epitetracycline Hydrochloride	VIN1		
Equilin	VB1b	UV-280	phenol
Ergocalciferol	VB1a	UV-254	
Capsules	VB1a	UV-254	
Oral Solution	VB1a	UV-254	
Tablets	VIL		
Ergoloid Mesylates	VB1b	UV-280	
Capsules	VB1b	UV-280	m-chloroacetamilide
Oral Solution	VB1b	UV-280	
Tablets	VB1b	UV-280	papaverine HCl

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Ergonovine Maleate	IIIA4	550	
Injection	VB1b	UV-312	
Tablets	VB1b	UV-312	
Ergotamine Tartrate	IA1bii		CrV
Inhalation Aerosol	IIIA4	546	
Injection	IIIA4	545	
Tablets	VB1b	UV-254	ergonovine maleate
and Caffeine Suppositories	VB1b	UV-244, F-239	
and Caffeine Tablets	VB1b	UV-254, F-325	
Erythromycin	VB1b	UV-215	
Capsules, Delayed-Release	VIN1		
Intramammary Infusion	VIN1		
Injection	VIN1		
Ointment	VIN1		
Ophthalmic Ointment	VIN1		
Pledgets	VIN1		
Tablets	VIN1		
Tablets, Delayed-Release	VIN1		
Topical Gel	VIN1		
Topical Solution	VIN1		
Sterile Lactobionate	VIN1		
and Benzoyl Peroxide Topical Gel	VIN1, VB1b	UV-254	ethyl benzoate
Erythromycin Estolate	VIN1		
Capsules	VIN1		
Oral Suspension	VIN1		
Tablets	VIN1		
and Sulfisoxazole Acetyl Oral Suspension	VIN1, VB1b	UV-254	benzanilide
Erythromycin Ethylsuccinate	VIN1		
Injection	VIN1		
Sterile	VIN1		
Oral Suspension	VIN1		
for Oral Suspension	VIN1		
Tablets	VIN1		
and Sulfisoxazoleacetyl for Oral Suspension	VIN1, VB1b	UV-254	benzanilide
Sterile Erythromycin Gluceptate	VIN1		
Erythromycin Lactobionate for Injection	VIN1		
Sterile Erythromycin Lactobionate	VIN1		
Erythromycin Stearate	VIN1		
Tablets	VIN1		
Estradiol	VB1b	UV-205	ethylparaben
Pellets	VA2	FID-I	dotriacontane
Injectable Suspension	IIIA4	520	
Tablets	VB1b	UV-205	ethylparaben
Vaginal Cream	VB1b	UV-280	dydrogesterone
Estradiol Cypionate	VB1b	UV-280	testosterone benzoate
Injection	VB1b	UV-280	testosterone benzoate
Estradiol Valerate	VB1b	UV-280	testosterone benzoate
Injection	VB1b	UV-280	testosterone benzoate
Estriol	IIIB1	281	
Conjugated Estrogens	VA2	FID-I	3-*o*-methylestrone
Tablets	VA2	FID-I	testosterone
Esterified Estrogens	IIIA4	635, 515	
Tablets	IIIA4	635, 515	
Estrone	VB1b	UV-280	
Injection	IIA		
Injectable Suspension	VB1b	UV-268	
Estropipate	VB1b	UV-213	*p*-nitroacetophenone
Tablets	VB1b	UV-213	*p*-nitroacetophenone
Vaginal Cream	VB1b	UV-213	*p*-nitroacetophenone
Ethacrynate Sodium for Injection	VB1b	UV-254	
Ethacrynic Acid	VB1b	UV-254	
Tablets	IVA1		
Ethambutol Hydrochloride	IA1biii		CrV
Tablets	IA1biii		CrV
Ethchlorvynol	VA1	TC-I	
Capsules	IA1ai		MRB
Ethinyl Estradiol	VB1b	UV-280	ethylparaben
Tablets	VB1b	UV-280	ethylparaben
Ethiodized Oil Injection	IC1lii		ST
Ethionamide	IIIB1	290	
Tablets	IIIB1	290	
Ethopabate	VB1b	UV-268	
Ethosuximide	IA1aiii		AV
Capsules	VB1b	UV-225	
Ethotoin	VB1b	UV-210	
Tablets	VB1b	UV-254	ethylparaben
Ethyl Acetate	IA2b		Phth
Ethyl Chloride	IA2b		Phth
Ethyl Oleate	None		
Ethyl Vanillin	IA1aiii		TB
Ethylcellulose	IC1lii		ST
Aqueous Dispersion	IC11		
Ethylenediamine	IA1b		BpB
Ethylparaben	IA2b		BtB
Ethynodiol Diacetate	VB1b	UV-200	
and Ethinyl Estradiol Tablets	VB1b	UV-210	
and Mestranol Tablets	VB1b	UV-204	
Etidronate Disodium	ID1b		XyO
Tablets	ID1b		XyO
Etodolac	IA1aiii		Poten
Tablets	VB1b	UV-274	
Etoposide	VB1b	UV-254	
Capsules	VB1b	UV-254	
Injection	VB1b	UV-254	
Eucalyptol	VA1	FID	
Eucatropine Hydrochloride	IA2a		MeR
Ophthalmic Solution	IIIB2	242	
Eugenol	None		
Famotidine	IAbii		Poten
Tablets	VB1b	UV-254	
Fenoprofen Calcium	VB1b	UV-272	
Capsules	VB1b	UV-272	
Tablets	VB1b	UV-272	

Appendix B. Assay Index of Official USP-NF Drugs

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Fentanyl Citrate	IA1bii		Nb
Injection	VB1b	UV-230	
Ferric Oxide	IIC		
Ferrous Fumarate	IC1a		Op
Tablets	IC1lii		ST
and Docusate Sodium Extended-release Tablets	IIIF1, VB1b	248.3, UV-214	
Ferrous Gluconate	IC1a		Op
Capsules	IIIA4	522	
Elixir	IC1a		Op
Tablets	IIIA4	522	
Ferrous Sulfate	IC1a		Op
Oral Solution	IC1a		Op
Syrup	IC1a		Op
Tablets	IC1a		Op
Dried	IC1a		Op
Flecainide Acetate	IA1aiii		Poten
Tablets	VB1b	UV-254	
Floxuridine	IA1a		Poten
for Injection	IIIB1	268	
Flucytosine	IA1bii		Poten
Capsules	IIIB1	285	
Fludrocortisone Acetate	IIIA1	525	
Tablets	VB1b	UV-254	norethindrone
Flumethasone Pivalate	IIIA1	520	
Cream	IIIB2	390	
Flunisolide	VB1b	UV-254	
Nasal Solution	VB1b	UV-254	norethindrone
Flunixin Meglumine	IAbii		Poten
Granules	IIIA3	283	
Injection	IIIA3	327	
Paste	VB1b	UV-254	sodium benzoate
Fluocinolone Acetonide	VB1b	UV-254	
Cream	VB1b	UV-254	
Ointment	VB1b	UV-254	norethindrone
Topical Solution	VB1b	UV-254	norethindrone
Fluocinonide	VB1b	UV-254	norethidrone
Cream	VB1b	UV-254	norethindrone
Gel	VB1b	UV-254	norethindrone
Ointment	VB1b	UV-254	norethindrone
Topical Solution	VA1	FID-P	isopropyl alcohol
Fluorescein	IIIE1	515	
Injection	IIIE1	515	
Fluorescein Sodium	IIIE1	515	
Ophthalmic Strips	IIIE1	515	
and Benoxinate Hydrochloride Ophthalmic Solution	VB1b	UV-254	
and Proparacaine Hydrochloride Ophthalmic Solution	IIIE1, VB1b	515, UV-270	
Fluorodopa F 18 Injection	VIE		
Fluorometholone	VB1b	UV-254	
Cream	VB1b	UV-254	fluoxymesterone
Ophthalmic Suspension	VB1b	UV-254	
Fluorouracil	VB1b	UV-254	TB
Cream	VB1b	UV-254	
Injection	VB1b	UV-254	
Topical Solution	VB1b	UV-254	
Fluoxetine Hydrochloride	VB1b	UV-227	
Capsules	VB1b	UV-227	
Fluoxymesterone	VB1b	UV-254	methylprednisolone
Tablets	VB1b	UV-254	methylprednisolone
Fluphenazine Decanoate	IAbiii		CV
Injection	VB1b	UV-254	
Fluphenazine Enanthate	IA1bii		CrV
Injection	IA1bii		CrV
Fluphenazine Hydrochloride	VB1b	UV-254	
Elixir	VB1b	UV-254	
Injection	IIIA4	485	
Oral Solution	IIIA4	485	
Tablets	VB1b	UV-254	
Flurandrenolide	VB1b	UV-240	prednisone
Lotion	VB1b	UV-240	testosterone
Tape	VB1b	UV-240	testosterone
Flurazepam Hydrochloride	IA1biii		Poten
Capsules	VB1b	UV-239	
Flurbiprofen	IA1a		Phth
Tablets	VB1b	UV-254	
Flurbiprofen Sodium	VB1b	UV-280	
Ophthalmic Solution	VB1b	UV-280	
Flutamide	VB1b	UV-240	
Capsules	VB1b	UV-254	testosterone
Folic Acid	VB1b	UV-280	
Injection	VIL		
Tablets	VIL		
Formaldehyde Solution	IA2b		BtB
Fructose	VIC1		
Injection	VIC1		
and Sodium Chloride Injection	VIC1, IB1a		DCF
Basic Fuchsin	IC1f		
Fumaric Acid	IA1a		Phth
Furazolidone	IIIB1	367	
Oral Suspension	IIIB1	367	
Tablets	IIIB1	367	
Furosemide	IA1a		
Injection	VB1b	UV-254	
Tablets	VB1b	UV-254	
Gadopentetate Dimeglumine Injection	VB1b	UV-195	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Gallamine Triethiodide	VB1b	UV-200	
Injection	VB1b	UV-200	
Gallamine Citrate Ga 67 Injection	VIE		
Absorbent Gauze	None		
Petrolatum Gauze	None		
Gelatin	None		
Absorbable Film	None		
Absorbable Sponge	None		
Gemfibrozil	VB1b	UV-276	
Capsules	VB1b	UV-276	
Tablets	VB1b	UV-276	
Gentamicin Uterine Infusion	VIN1		
Gentamicin Sulfate	VIN1		
Cream	VIN1		
Injection	VIN1		
Ointment	VIN1		
Ophthalmic Ointment	VIN1		
Ophthalmic Solution	VIN1		
and Betamethasone Acetate Ophthalmic Solution	VIN1, VB1b	UV-254	o-phenylphenol
and Betamethasone Valerate Ointment	VIN1, VB1b	UV-254	beclomethasone diproprionate
and Betamethasone Valerate Otic Solution	VIN1, VB1b	UV-254	beclomethasone diproprionate
and Betamethasone Valerate Topical Solution	VIN1, VB1b	UV-254	beclomethasone diproprionate
and Prednisolone Acetate Ophthalmic Suspension	VIN1, VB1b	UV-254	
and Prednisolone Acetate Ophthalmic Ointment	VIN1, VB1b	UV-254	fluorometholone acetate
Gentian Violet	IC2d		FAS
Cream	IIIA3	435	
Topical Solution	IC2d		FAS
Pharmaceutical Glaze	IIA		
Glipizide	VB1b	UV-225	
Tablets	VB1b	UV-225	
Glucagon for Injection	VIH		
Gluconalactone	IA2bii		Phth
Glutaral Concentrate	IA2b		BpB
Glyburide	VB1b	UV-254	progesterone
Tablets	VB1b	UV-254	
Glycerin	IC1liii		ST
Ophthalmic Solution	IC1m		ST
Oral Solution	IC1m		ST
Suppositories	None		
Glyceryl Behenate	None		
Glyceryl Monostearate	VA2	FID-I	hexadecyl hexadecanoate
Glycine	IA1bii		CrV
Irrigation	IA1a		Phth, TB
Glycopyrrolate	IA1biii		CrV
Injection	VB1b	UV-222	
Tablets	IIIA2	410	
Gold Sodium Thiomalate	IIC		
Injection	IIC		
Gonadorelin Hydrochloride	VB1b, Ib1a	UV-220	Poten
Gonadorelin for Injection	VB1b	UV-220	
Chorionic Gonadotropin for Injection	VIH		
	VIH		
Gramicidin	VIN1		
Griseofalvin	VB1b	UV-254	3-phenylphenol
Capsules	VB1b	UV-254	3-phenylphenol
Oral Suspension	VB1b	UV-254	3-phenylphenol
Tablets	VB1b	UV-254	3-phenylphenol
Ultramicrosize Tablets	VB1b	UV-254	3-phenylphenol
Guaifenesin	VB1b	UV-276	
Capsules	VB1b	UV-276	
for Injection	IIIA1	276	
Syrup	VB1b	UV-276	
Tablets	VB1b	UV-276	benzoic acid
and Codeine Phosphate Syrup	VA1	FID-I	hydrocodone bitartrate
and Pseudoephedrine Hydrochloride Capsules	VB1b	UV-263, 276	benzoic acid, dextromethorphan HCl
Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules	VB1b	UV-263, 276	benzoic acid, dextromethorphan HCl
Guanabenz Acetate	IAbii		Poten
Tablets	VB1b	UV-254	
Guanadrel Sulfate	VB1b	RI	ethylparaben
Tablets	VB1b	Ri	ethylparaben
Guanethidine Monosulfate	IIIA4	500	
Tablets	IIIA4	412	
Guanfacine Hydrochloride	VB1b	UV-220	
Tablets	VB1b	UV-220	butylparaben
Halazone	IC1lii		ST
Tablets for Solution	IC1lii		ST
Halicinonide	IIIB1	239	
Cream	VB1b	UV-254	progesterone
Ointment	VB1b	UV-254	butylparaben
Topical Solution	VB1b	UV-254	progesterone
Haloperidol	IA1bii		Nb
Injection	IIIB1	245	
Oral Solution	IIIB1	245	
Tablets	VB1b	UV-254	
Helium	VA1	TC-I	
Heparin Lock Flush Solution	VIH, IB1a		PC
Heparin Calcium	VIH		
Injection	VIH		
Heparin Sodium	VIH		
Injection	VIH		
Hexachlorophene	IA1a		Poten
Cleansing Emulsion	IIIB1	299	
Liquid Soap	IIIB1	299	
Hexylresorcinol	IC2c		ST
Lozenges	VB1b	UV-280	hexaphenone
Histamine Phosphate	IA1a		TP
Injection	IIIA4	460	

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Histidine	IA1bii		Poten
Homatropine Hydrobromide	IC1a		Np
Ophthalmic Solution	IIIB2	242	
Homatropine Methylbromide	IA1biii		CrV
Tablets	IIIA4	525	
Homosalate	VA1	FID-P	
Hyaluronidase Injection	VIF		
for Injection	VIF		
Hydralazine Hydrochloride	VB1b	UV-230	
Injection	IC1n		
Tablets	VB1b	UV-230	
Hydrochloric Acid	IA1a		MeR
Diluted	IA1a		MeR
Hydrochlorothiazide	VB1b	UV-254	
Tablets	VB1b	UV-254	
Hydrocodone Bitartrate	VB1b	UV-280	
Tablets	IA1bii		Poten
and Acetaminophen Tablets	VB1b	UV-280	
Hydrocortisone	VB1b	UV-254	prednisone
Cream	VB1b	UV-254	
Enema	VB1b	UV-254	acetaminophen
Gel	VB1b	UV-254	
Lotion	VB1b	UV-254	
Ointment	VB1b	UV-254	
Injectable Suspension	IIIA1	525	
Tablets	VB1b	UV-254	prednisone
and Acetic Acid Otic Solution	VB1b, VA1	UV-254, FID-P	anisole
Hydrocortisone Acetate	VB1b	UV-254	
Cream	VB1b	UV-254	
Lotion	VB1b	UV-254	fluoxymesterone
Ointment	VB1b	UV-254	fluoxymesterone
Ophthalmic Ointment	IIIA1	525	
Ophthalmic Suspension	IIIA1	525	
Injectable Suspension	IIIA1	525	
Hydrocortisone Butyrate	VB1b	UV-254	
Cream	VB1b	UV-254	
Hydrocortisone Hemisuccinate	VB1b	UV-254	fluorometholone
Hydrocortisone Sodium Phosphate	IIIB2	239	
Injection	IIIA4	410	
Hydrocortisone Sodium Succinate	IIIA1	525	
for Injection	VB1b	UV-254	fluorometholone
Hydrocortisone Valerate	VB1b	UV-254	ethyl benzoate
Cream	VB1b	UV-254	ethyl benzoate
Hydroflumethiazide	IIIB1	273	
Tablets	IIIB1	273	
Hydrogen Peroxide Concentrate	IC1b		
Topical Solution	IC1b		
Hydromorphone Hydrochloride	IA1biii		CrV
Injection	IIIA4	440	
Tablets	IIIA4	440	
Hydroquinone	IC1a		DP
Cream	IIIB1	293	
Topical Solution	VB1b	UV-280	
Hydroxocobalamin	VIE, IIIB2	361	
Injection	IIIB2	361	
Hydroxyamphetamine	IA1biii		CrV
Hydrobromide			
Ophthalmic Solution	IIB		
Hydroxychloroquine Sulfate	IIIB1	343	
Tablets	VB1b	UV-254	
Hydroxyprogesterone	IIIB1	240	
Caproate			
Injection	IIIB2	380	
Hydroxypropyl Cellulose	IC11		ST
Low-Substituted	VA2	TC-I	toluene
Ocular System	IIIa2	620	
Hydroxypropyl Methylcellulose	VA2	TC-I	toluene
Ophthalmic Solution	IIIA4	635	
Hydroxyurea	VB1b	UV-214	uracil
Capsules	VB1b	UV-214	uracil
Hydroxyzine Hydrochloride	IA1biii		Poten
Injection	VB1b	UV-254	
Syrup	VB1b	UV-232	
Tablets	VB1b	UV-232	
Hydroxyzine Pamoate	VB1b	UV-230	
Capsules	VB1b	UV-232	
Oral Suspension	VB1b	UV-232	
Hyoscyamine	IA1biii		CrV
Tablets	VA1	TC-I	homatropine hydrobromide
Hyoscyamine Hydrobromide	IA1biii		CrV
Hyoscyamine Sulfate	IA1bii		Poten
Elixir	VA1	TC-I	homatropine hydrobromide
Injection	VA1	TC-I	homatropine hydrobromide
Oral Solution	VA1	TC-I	homatropine hydrobromide
Tablets	VA1	TC-I	homatropine hydrobromide
Hypophosphorous Acid	IA1a		Phth
Ibuprofen	VB1b	UV-254	valerophenone
Oral Suspension	VB1b	UV-220	
Tablets	VB1b	UV-254	valerophenone
and Pseudoephedrine Hydrochloride Tablets	VB1b	UV-254	butylparaben
Ichthammol	IA2a, IIB		MeR
Ointment	IA2a		MeR
Idarubicin Hydrochloride	VB1b	UV-254	
for Injection	VB1b	UV-254	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Idoxuridine	IA1aiii		TB
Ophthalmic Ointment	IIIB1	320, 283	
Ophthalmic Solution	IIIB1	320, 283	
Ifosfamide	VB1b	UV-195	ethylparaben
for Injection	VB1b	UV-195	ethylparaben
Imidurea	None		
Imipenem	VB1b	UV-300	
Imipenem and Cilastatin	VB1b	UV-254	
for Injection	VB1b	UV-254	
for Injectable Suspension	VB1b	UV-254	
Imipramine Hydrochloride	IA1biii		CrV
Injection	IIIB1	250	
Tablets	IIIB1	250	
Indapamide	VB1b	UV-254	p-chloro- acetanilide
Tablets	VB1b	UV-242	2-chloro-acetophenone
Indigotinsulfonate Sodium	IIIA3	610	
Injection	IIIA3	610	
Indium In 111 Chloride Solution	VIE		
Capromab Pendetide Injection	VIE		
Oxyquinoline Solution	VIE		
Pentetate Injection Solution	VIE		
Pentetreotide Injection	VIE		
Satumomab Pendetide Injection	VIE		
Indocyanine Green	IIIA3	785	
for Injection	IIIA3	785	
Indomethacin	VB1b	UV-254	
Capsules	IIIB1	318	
Capsules, Extended-Release	VB1b	UV-240	
Oral Suspension	VB1b	UV-240	
Suppositories	IIIB1	320	
Indomethacin Sodium	VB1b	UV-254	
for Injection	VB1b	UV-240	
Influenza Virus Vaccine	None		
Insulin	VB1b	UV-214	
Injection	VB1b	UV-214	
Human	VB1b	UV-214	
Human Injection	VB1b	UV-214	
Isophane Suspension	VB1b	UV-214	
Isophane Human Suspension	VB1b	UV-214	
Zinc Suspension	VB1b	UV-214	
Extended Zinc Suspension	VB1b	UV-214	
Prompt Zinc Suspension	VIH		
Human Zinc Suspension	VB1b	UV-214	
Extended Human Zinc Suspension	VB1b	UV-214	
Inulin	IIIA4	435	
in Sodium Chloride Injection	IIIA4, IB1a	435	DCF
Iobenguane I 123 Injection	VIE		
131 Injection	VIE		
Iodine	IC11		ST
Topical Solution	IC1l		ST
Strong Solution	IC1l		ST
Tincture	IC1l		ST
Strong Tincture	IC1l		ST
Sodium Iodide I123 Capsules	VIE		
Solution	VIE		
Iodinated I125 Albumin Injection	VIE		
Iodinated I131 Albumin Injection	VIE		
Aggregated	VIE		
Iodohippurate Sodium I123 Injection	VIE		
Iodohippurate Sodium I131 Injection	VIE		
Rose Bengal Sodium I131 Injection	IIIA3, VIE	550	
Sodium Iodide I131 Capsules	VIE		
Solution	VIE		
Iodipamide	IB1a		TBPE
Meglumine Injection	IB1a		TBPE
Iodohippurate Sodium I123 Injection	VIE		
Iodoquinol	IC1lii		ST
Tablets	IC1lii		ST
Iohexol	IBk		TBPh
Injection	IBk		TBPh
Iopamidol	IA1b		Poten
Injection	IIb1	240	
Iopanoic Acid	IB1a		TBP
Tablets	IA1a		TB
Iophendylate	IC11ii		ST
Injection	IC1lii		ST
Iopromide	VB1b	UV-254	
Iothalamate Meglumine Injection	IBIa		Poten
and Iothalamate Sodium Injection	VIC1, IBIa		Poten
Iothalamate Sodium Injection	IBIa		Poten
Iothalamic Acid	IB1a		Poten
Ioversol	IA2ai		Poten
Injection	IA2ai		Poten
Ioxaglate Meglumine and Ioxaglate Sodium Injection	VIC1		
Ioxaglic Acid	IC1k		Poten
Ioxilan	IB1a		TBP
Injection	VB1b	UV-245	
Ipecac	VIG1, IIIB1	283, 350	MeR
Powdered	VIG1, IIIB1	283, 350	MeR
Syrup	VIG1, IIIB1	283, 350	MeR
Ipodate Sodium	IB1a		EY
Capsules	IB1a		EY
Iron Dextran Injection	IIIA4	510	
Iron Sorbitex Injection	IIIA4	510	
Isoamyl Methoxycinnamate	VA1	FID-P	
Isobutane	VA1	TC-I	
Isoetharine Hydrochloride	VB1b	UV-278	
Inhalation Solution	VB1b	UV-278	
Isoetharine Mesylate	VB1b	UV-254	
Inhalation Aerosol	VB1b	UV-254	
Isoflurane	VA1	TC-P	
Isoflurophate	VA1	FID-I	cyclohexanone
Ophthalmic Ointment	VA1	FID-I	cyclohexane
Isoleucine	IA1bii		Poten

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Isometheptene Mucate	IC1lii		ST
Dichloralphenazone, and Acetaminophen Capsules	VB1b	UV-280	
Isoniazid	IC1j		Poten
Injection	IC1j		Poten
Syrup	IC1j		Poten
Tablets	VB1b	UV-254	
Isopropamide Iodide	IA1biii		CrV
Tablets	IIIB1	280, 258	
Isopropyl Alcohol	VA1	TC-I	
Rubbing	VID		
Isopropyl Myristate	VA1	FID-P	
Isopropyl Palmitate	VA1	FID-P	
Isoproterenol Hydrochloride	VB1b	UV-278	
Inhalation Aerosol	IIIA4	530	
Inhalation Solution	VB1b	UV-278	
Injection	VB1b	UV-280	
Tablets	VB1b	UV-280	
and Phenylephrine Bitartrate Inhalation Aerosol	IIIA4	495, 530	
Isoproternol Sulfate	VB1b	UV-278	
Inhalation Aerosol	IIIA4	530	
Inhalation Solution	VB1b	UV-278	
Isosorbide Concentrate	VA1	TC-I	triethyleneglycol
Oral Solution	VA1	TC-I	triethyleneglycol
Isosorbide Dinitrate, Diluted	VB1b	UV-220	nitroglycerin
Capsules, Extended-Release	VB1b	UV-220	nitroglycerin
Tablets	VB1b	UV-220	nitroglycerin
Tablets, Chewable	VB1b	UV-220	nitroglycerin
Tablets, Extended-Release	VB1b	UV-220	nitroglycerin
Tablets, Sublingual	VB1b	UV-220	nitroglycerin
Isotretinoin	IA1iii		TB
Capsules	VB1a	UV-365	
Isoxuprine Hydrochloride	IIIB1	269, 300	
Injection	IIIB1	275	
Tablets	IIIB1	275	
Isradipine	VB1b	UV-326	
Kanamycin	VIN1		
Capsules	VIN1		
Injection	VIN1		
Sulfate	VIN1		
Ketamine Hydrochloride	IA1biii		CrV
Injection	IIIB1	269	
Ketoconazole	IA1bii		Poten
Tablets	VB1b	UV-225	terconazole
Ketoprofen	VB1b	UV-215	
Ketorolac Tromethamine	VB1b	UV-313	
Injection	VB1b	UV-254	naproxen
Tablets	VB1b	UV-254	naproxen
Krypton Kr 81m	VIE		
Labetalol Hydrochloride	VB1b	UV-230	
Injection	VB1b	UV-254	
Tablets	VB1b	UV-230	
Lactic Acid	IA2b		Phth
Lactitol	VB1b	RI	
Lactulose Concentrate	VB1b	RI	
Solution	VIF		
Lanolin Alcohols	IIB		
Leucine	IA1bii		Poten
Leucovorin Calcium	VB1b	UV-254	
Injection	IIIB1	284	
Tablets	VB1b	UV-254	
Levamisole Hydrochloride	IA1a		Poten
Tablets	VB1b	UV-215	
Levmetamfetamine	IA1bii		CrV
Levobunolol Hydrochloride	VB1b	UV-254	
Ophthalmic Solution	VB1b	UV-254	
Levocarnitine	IA1bii		CrV
Injection	VB1b	UV-205	
Oral Solution	VB1b	UV-225	*p*-aminobenzoic acid
Levodopa	IA1bii		Poten
Capsules	IIIB1	280	
Tablets	IIIB1	280	
Levonordefrin	IA1bii		CrV
Levonorgestrel	IIIB1	241	
and Ethinyl Estradiol Tablets	VB1b	UV-215	
Levorphanol Tartrate	IA1bii		MeR
Injection	IA1bii		MeR
Tablets	IA1bii		MeR
Levothyroxin Sodium	VB1b	UV-225	
Oral Powder	VB1b	UV-225	
Tablets	VB1b	UV-225	
Lidocaine	VB1b	UV-254	
Topical Aerosol	IA1bii		CrV
Ointment	IA2a		Poten
Oral Topical Solution	IA1bii		CrV
Lidocaine Hydrochloride	VB1b	UV-254	
Injection	VB1b	UV-246	
Jelly	IA2a		Poten
Topical Solution	VB1b	UV-254	norepinephrine bitartrate
Topical Solution, Oral	VB1b	UV-254 EC	norepinephrine bitartrate
and Dextrose Injection	VB1b, VIC1	UV-261	
and Epinephrine Injection	VB1b	UV-254, EC	norepinephrine bitartrate
and Epinephrine Bitartrate Injection	VB1b	UV-261, EC	norepinephrine bitartrate
Lime	ID1a		HNB

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Lincomycin Injection	VB1b	UV-210	
Lincomycin Hydrochloride	VB1b	UV-210	
Capsules	VB1b	UV-210	
Syrup	VB1b	UV-210	
Soluble Powder	VB1b	UV-210	
Lindane	IB2aii		FAS
Cream	VA1	FID-I	methylene chloride
Lotion	VA1	FID-I	methylene chloride
Shampoo	VA1	FID-I	methylene chloride
Liothyronine Sodium	VB1b	UV-225	
Tablets	VB1b	UV-225	
Liotrix Tablets	VB1b	UV-225	
Lisinopril	VB1b	UV-210	
Tablets	VB1b	UV-215	
Lithium Carbonate	IA2a		MeO
Capsules	IIID	671	
Extended-release Tablets	IIIF1	671	
Tablets	IIID	671	
Lithium Citrate	IIID	671	
Syrup	IIID	671	
Lithium Hydroxide	IA1b		Phth
Loperamide Hydrochloride	IA1biii		Nb
Capsules	IIIA4	410	
Tablets	VB1b	UV-214	
Loracarbef	VB1b	UV-265	
Capsules	VB1b	UV-265	
for Oral Suspension	VB1b	UV-265	
Lorazepam	IA1biii		Poten
Injection	VB1b	UV-240	
Oral Concentrate	VB1a	UV-240	
Tablets	VB1b	UV-240	
Lovastatin	VB1b	UV-238	
Tablets	VB1b	UV-238	
Loxapine Succinate	IA1bii		Poten
Capsules	VB1b	UV-254	
Lypression Nasal Solution	VB1b	UV-220	
Lysine Acetate	IA1bii		Poten
Lysine Hydrochloride	IA1biii		Poten
Mafenide Acetate	IIIB1	267	
Cream	IIIB1	267	
Magaldrate	IA2a		Poten
Oral Suspension	IA2a		Poten
Tablets	IA2a		Poten
and Simethicone Oral Suspension	IA2a, IIIC1		Poten
and Simethicone Tablets	IA2a, IIIC1		Poten
Milk of Magnesia	ID1a		EBT
Magnesia Tablets	ID1a		EBT
Magnesium Aluminum Silicate	IIIF1	309, 285	
Magnesium Carbonate	IA2a		MeO
and Citric Acid for Oral Solution	ID1a		EBT
and Sodium Bicarbonate for Oral Suspension	ID1a, IIIF1	589	EBT
Magnesium Chloride	ID1a		EBT
Magnesium Citrate	ID1a		EBT
Oral Solution	IA2a, IIB		Phth
for Oral Solution	ID1a		EBT
Magnesium Gluconate	ID1a		EBT
Tablets	ID1a		EBT
Magnesium Hydroxide	IA2a		MeR
Paste	ID1a		EBT
Magnesium Oxide	IA2a		MeO
Capsules	ID1a		EBT
Tablets	ID1a		EBT
Magnesium Phosphate	IA2b		Phth
Magnesium Salicylate	IIIB1	296	
Tablets	IIIB1	296	
Magnesium Silicate	IA2a, IIC		MeO
Magnesium Stearate	ID2a		EBT
Magnesium Sulfate	ID1a		EBT
Injection	ID1a		EBT
in Dextrose Injection	ID1a, VIC		EBT
Magnesium Trisilicate	IA2a		MeO
Tablets	ID1a		EBT
Malathion	VB1b	UV-254	
Lotion	VA1	FID-I	parathion
Malic Acid	IA1a		Phth
Maltitol Solution	VB1b	RI	
Mandelic Acid	IA1a		Poten
Manganese Chloride	ID1a		EBT
Injection	IIIF1	279	
Manganese Gluconate	ID1a		EBT
Manganese Sulfate	ID1a		EBT
Injection	IIIF1	279	
Mannitol	VB1b	RI	
Injection	VB1b	RI	
in Sodium Chloride Injection	IC1liii		ST, FAS
Maprotiline Hydrochloride	IA1biii		Poten
Tablets	VB1b	UV-272	
Mazindol	IA1bii		CrV
Tablets	VB1b	UV-254	amitriptyline hydrochloride
Mebendazole	IA1bii		Poten
Oral Suspension	IIIB1	247	
Tablets	VB1b	UV-247	
Mebrofenin	IA1a		TB
Mecamylamine Hydrochloride	VIM		
Tablets	IA2a		MR
Mechlorethamine Hydrochloride	IC2b		ST
for Injection	IC2b		ST
Meclizine Hydrochloride	IA1biii		Poten
Tablets	VB1b	UV-340	
Meclocycline Sulfosalicylate	VB1b	UV-340	
Cream	VB1b	UV-340	
Meclofenamate Sodium	IA1a		Phth
Capsules	IIIB1	336	

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Medroxyprogesterone Acetate	VB1a	UV-254	progesterone
Injectable Suspension	VB1a	UV-254	progesterone
Tablets	VB1a	UV-254	progesterone
Mefenamic Acid	VB1b	UV-279	
Capsules	VB1b	UV-279	
Megestrol Acetate	VB1b	UV-280	propylparaben
Tablets	VB1b	UV-280	propylparaben
Meglumine	IA1a		MeR
Melphalan	IB1a		Poten
Tablets	VB1b	UV-254	
Menadiol Sodium Diphosphate	IC1a		Poten
Injection	IC1a		Poten
Tablets	IC1a		Poten
Menadione	IC1a		Op
Injection	IIIA4	635	
Meningococcal Polysaccharide Vaccine			
Group A	None		
Group C	None		
Groups A and C Combined	None		
Menotropins	VIH		
for Injection	VIH		
Menthol Lozenges	VA1	FID	anethole
Menthyl Anthranilate	VA1	FID-P	
Meperidine Hydrochloride	VB1b	UV-230	
Injection	VB1b	UV-230	
Syrup	IA1bii		CrV
Tablets	VB1b	UV-230	
Mepivacaine Hydrochloride	IA1biii		CrV
Injection	IA1bii		MeR
and Levonordefrin Injection	IA1bii, IIIA4	530	MeR
Meprednisone	IIIB1	238	
Meprobamate	IA1aii		Phth
Oral Suspension	IA1aii		Phth
Tablets	VB1b	UV-200	
Mercaptopurine	IA1aiii		TB
Tablets	IIIB1	325	
Ammoniated Mercury	IA1bi		MeR
Mesalamine	VB1b	UV-254	
Extended-release Capsules	VB1b	UV-240	sodium benzoate
Rectal Suspension	VB1b	UV-254	
Mesoridazine Besylate	IA1bii		Poten
Injection	IIIB1	262	
Oral Solution	IIIB1	267	
Tablets	VB1b	UV-265	
Mestranol	IIIA4	547	
Metacresol	IC2c		ST
Metaproterenol Sulfate	VB1b	UV-278	
Inhalation Aerosol	IIIB1	276	
Inhalation Solution	VB1b	UV-278	
Syrup	VB1b	UV-278	
Tablets	VB1b	UV-278	
Metaraminol Bitartrate	IA1bii		CV
Injection	VB1b	UV-264	
Methacholine Chloride	IA1biii		CrV
Methacrylic Acid Copolymer	IA1a		Phth
Dispersion	IA1A		Phth
Methacycline Hydrochloride	VIN1		
Capsules	VIN1		
Oral Suspension	VIN1		
Methadone Hydrochloride	IA1biii		CrV
Injection	VA1	FID-I	procaine
Oral Concentrate	VB1b	UV-254	
Oral Solution	VB1b	UV-254	pyrilamine maleate
Tablets	VB1b	UV-254	
Methamphetamine Hydrochloride	VB1b	UV-254	
Tablets	VB1b	UV-257	
Methazolamide	VB1b	UV-265	
Tablets	VB1b	UV-252	
Methdilazine Hydrochloride	IIIB1	252, 275	
Syrup	IIIA4	460	
Tablets	IIIA4	460	
Methenamine	IA2a		MeR
Elixir	IIIA4	570	
Tablets	IIIA4	570	
Methenamine Hippurate	IA1bii		Poten
Tablets	IA1a		TP
Methenamine Mandelate	IB1a		Poten
Delayed-release Tablets	IB1A		Poten
for Oral Solution	IB1a		Poten
Oral Suspension	IB1a		Poten
Tablets	IB1a		Poten
Methicillin for Injection	VB1b	UV-225	
Sodium	VB1b	UV-225	
Methimazole	IA1a		BtB
Tablets	IA1a		BtB
Methionine	IA1bii		Poten
Methocarbamol	IIIB1	274	
Injection	VB1b	UV-274	caffeine
Tablets	VB1b	UV-274	caffeine
Methohexital	IIIC1	5.93	
Sodium for Injection	VA1	FID-I	aprobarbital
Methotrexate	VB1b	UV-302	
Tablets	VB1b	UV-302	
Injection	VB1b	UV-302	
for Injection	VB1b	UV-302	
Methotrimeprazine	IA1bii		CrV
Injection	VB1b	UV-254	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Methoxsalen	VB1b	UV-254	trioxsalen
Capsules	VB1b	UV-254	trioxsalen
Topical Solution	VB1b	UV-254	trioxsalen
Methoxyflurane	VA1	TC-I	
Methsuximide	IIIB1	247	
Capsules	VB1b	UV-254	
Methyclothiazide	IB1a		EY
Tablets	IIIB1	268	
Methyl Alcohol	VA1	FID-I	
Methyl Salicylate	IA2b		Phth
Methyl Benzylidene Camphor	VA1	FID-P	
Methylbenzethonium Chloride	IC1n		
Lotion	IE4		SaO
Ointment	IE4		SaO
Topical Powder	IE4		SaO
Methylcellulose	VA2	TC-I	toluene
Ophthalmic Solution	IC1lii		ST
Oral Solution	IC1lii		ST
Tablets	IIA		
Methyldopa	IA1bii		CrV
Oral Suspension	VB1b	UV-280	
Tablets	IIIA4	520	
and Chlorothiazide Tablets	VB1b	UV-280	
and Hydrochlorothiazide Tablets	VB1b	UV-270	
Methyldopate Hydrochloride	VB1b	UV-280	
Injection	IIIB1	283	
Methylene Blue	IIIA3	663	
Injection	IIIA3	663	
Methylene Chloride	VA1	TC-I	
Methylergonovine Maleate	VB1b	FI	
Injection	VB1b	UV-240	
Tablets	VB1b	FI	
Methylparaben	IA2b		Poten
Sodium	IC2f		ST
Methylphenidate Hydrochloride	IA1biii		Nb
Tablets	VB1b	UV-210	
Tablets, Extended-Release	VB1b	UV-210	
Methylprednisolone	VB1b	UV-254	prednisone
Tablets	VB1b	UV-254	prednisone
Methylprednisolone Acetate	VB1b	UV-254	prednisone
Cream	IIIA1	525	
for Enema	VB1b	UV-254	prednisone
Injectable Suspension	VB1b	UV-254	prednisone
Methylprednisolone Hemisuccinate	VB1a	UV-254	fluorometholone
Methylprednisolone Sodium Succinate	IIIA1	525	
for Injection	VB1a	UV-254	fluorometholone
Methyltestosterone	VB1b	UV-241	
Capsules	IIIB1	241	
Tablets	IIIB1	241	
Methysergide Maleate	IA1bii		CrV
Tablets	VB1b	UV-318	
Metoclopramide Hydrochloride	IA1bii		Poten
Metoclopramide Injection	VB1b	UV-215	
Oral Solution	VB1b	UV-215	
Tablets	VB1b	UV-215	
Metolazone	IIIB1	343	
Tablets	IIIB1	343	
Metoprolol Fumarate	IA1bii		Poten
Metoprolol Tartrate and Hydrochlorothiazide Tablets	VB1b	UV-254, 270	oxyprenolol, sulfanilamide
Metoprolol Tartrate	IA1bii		Poten
Injection	VB1b	UV-254	
Tablets	VB1b	UV-254	
Metronidazole	IA1bii		MaG
Gel	VB1b	UV-254	
Injection	VB1b	UV-320	
Tablets	IA1bii		Poten
Metyrapone	IIIB1	260	
Tablets	IIIA4	450	
Metyrosine	IA1bii		Poten
Capsules	IIIB1	274	
Mexiletine Hydrochloride	VB1b	UV-254	
Capsules	VB1b	UV-254	
Mezlocillin Sodium	VB1b	UV-210	
for Injection	VB1b	UV-210	
Mibolerone	VB1b	UV-254	
Oral Solution	VA1	FID-I	
Miconazole	IA1bii		Nb
Injection	VB1b	UV-230	
Miconazole Nitrate	IA1bii		Poten
Cream	VA1	FID-I	cholestane
Topical Powder	VA1	FID-I	cholestane
Vaginal Suppositories	VA1	FID-I	cholestane
Minerals Capsules	VIN1		
Tablets	VIL		
Minocycline Hydrochloride	VB1b	UV-280	
Capsules	VB1b	UV-280	
for Injection	VB1b	UV-280	
Oral Suspension	VB1b	UV-280	
Tablets	VB1b	UV-280	
Minoxidil	VB1b	UV-254	medroxyprogesterone
Tablets	VB1b	UV-254	medroxyprogesterone
Topical Solution	VB1b	UV-254	medroxyprogesterone
Mitomycin	VB1b	UV-365	
for Injection	VB1b	UV-365	
Mitotane	IIIB1	268	
Tablets	IIIB1	268	
Mitoxantrone Hydrochloride	VB1b	UV-254	
Injection	VB1b	UV-254	
Molindone Hydrochloride	VB1b	UV-254	butylparaben
Tablets	VB1b	UV-254	butylparaben
Mometasone Furoate	VB1b	UV-254	beclomethasone diproprionate
Cream	VB1b	UV-254	beclomethasone diproprionate
Ointment	VB1b	UV-254	beclomethasone diproprionate
Topical Solution	VB1b	UV-254	beclomethasone diproprionate

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Monensin	VB2b	520	
Granulated	VB2b	520	
Premix	VB2b	520	
Sodium	VB2b	520	
Mono- and Di-Glycerides	VA1	FID-I	hexadecyl hexadecanoate
Monoethanolamine	IA1b		BcG, MeR
Monosodium Glutamate	IA1bii		Poten
Monothioglycerol	IC1k		ST
Moricizine Hydrochloride	VB1b	UV-254	butamben
Tablets	VB1b	UV-254	butamben
Morphine Sulfate	VB1b	UV-284	
Injection	VB1b	UV-284	
Morrhuate Sodium Injection	IA2a		MeO
Mupirocin	VB1b	UV-229	
Ointment	VB1b	UV-229	
Nadolol	IA1bii		CrV
Tablets	VB1b	UV-220	
and Bendroflumethiazide Tablets	VB1b	UV-270	
Nafcillin Sodium	VB1b	UV-254	
Capsules	VIN1		
for Injection	VB1b	UV-254	
Injection	VB1b	UV-254	
for Oral Solution	VIN1		
Tablets	VIN1		
Naftifine Hydrochloride	VB1b	UV-270	
Cream	VB1b	UV-270	
Gel	VA1	FID	n-propyl alcohol
Nalidixic Acid	IA1aiii		TP
Oral Suspension	VB1b	UV-254	
Tablets	VB1b	UV-254	
Nalorphine Hydrochloride	IIIB1	285	
Injection	IIIB1	285	
Naloxone Hydrochloride	IA1biii		MV
Injection	VB1b	UV-229	
Naltrexone Hydrochloride	VB1b	UV-280	
Tablets	VB1b	UV-280	
Nandrolone Decanoate	VB1a	UV-238	dimethyl phthalate
Injection	IIIB2	380	
Nandrolone Phenpropionate	IIIA1		
Injection	IIIA4		
Naphazoline Hydrochloride	IA1biii		CrV
Nasal Solution	VB1b	UV-280	
Ophthalmic Solution	VB1b	UV-285	
Naproxen	IA1a		Phth
Oral Suspension	VB1b	UV-254	ethylparaben
Tablets	VB1b	UV-254	butyrophenone
Naproxen Sodium	IA1bii		Nb
Tablets	VB1b	UV-254	butyrophenone
Narasin Granular	VB2b	520	
Premix	VB2b	520	
Natamycin	VIN1		
Ophthalmic Suspension	VIN1		
Neomycin Sulfate	VIN1		
Boluses	VIN		
Cream	VIN1		
Ointment	VIN1		
Ophthalmic Ointment	VIN1		
Oral Solution	VIN1		
for Injection	VIN1		
Tablets	VIN1		
and Bacitracin Ointment	VIN1		
and Bacitracin Zinc Ointment	VIN1		
and Dexamethasone Sodium Phosphate Cream	VIN1, IIIA1	525	
and Dexamethasone Sodium Phosphate Ophthalmic Ointment	VIN1, IIIA1	525	
and Dexamethasone Sodium Phosphate Ophthalmic Solution	VIN1, VB1b	525, UV-254	
and Fluocinolone Acetonide Cream	VIN1, VB1b	UV-238	
and Fluorometholone Ointment	VIN1, VB1b	UV-254	fluoxymesterone
and Flurandrenolide Cream	VIN1, VB1b	UV-240	
and Flurandrenolide Ointment	VIN1, VB1b	UV-240	
and Flurandrenolide Lotion	VIN1, VB1b	UV-240	
and Gramicidin Ointment	VIN1		
and Hydrocortisone Cream	VIN1, VB1b	UV-254	
and Hydrocortisone Ointment	VIN1, VB1b	UV-254	
and Hydrocortisone Acetate Cream	VIN1, VB1b	UV-254	fluoxymesterone
and Hydrocortisone Acetate Ointment	VIN1, VB1b	UV-254	fluoxymesterone
and Hydrocortisone Acetate Lotion	VIN1, VB1b	UV-254	fluoxymesterone
and Hydrocortisone Acetate Ophthalmic Ointment	VIN1, VB1b	UV-254	fluoxymesterone
and Hydrocortisone Acetate Ophthalmic Suspension	VIN1, VB1b	UV-254	fluoxymesterone
and Methylprednisolone Acetate Cream	VIN1, IIIA1	525	
Neomycin and Polymyxin B Sulfates	VIN1		
Solution for Irrigation			
Cream	VIN1		
Ophthalmic Ointment	VIN1		
Ophthalmic Solution	VIN1		
and Bacitracin Ointment	VIN1		
and Bacitracin Ophthalmic Ointment	VIN1		
Bacitracin and Hydrocortisone Acetate Ointment	VIN1, VB1b	UV-254	fluoxymesterone

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Bacitracin and Hydrocortisone Acetate Ophthalmic Ointment	VIN1, VB1b	UV-254	fluoxymesterone
and Bacitracin Zinc Ointment	VIN1		
and Bacitracin Zinc Ophthalmic Ointment	VIN1		
Bacitracin Zinc and Hydrocortisone Ointment	VIN1, VB1b	UV-254	
Bacitracin Zinc and Hydrocortisone Ophthalmic Ointment	VIN1, VB1b	UV-254	
Bacitracin Zinc and Hydrocortisone Acetate Ophthalmic Ointment	VIN1, VB1b	UV-254	
Bacitracin Zinc and Hydrocortisone Ophthalmic Suspension	VIN1, VB1b	UV-254	
Bacitracin Zinc and Lidocaine Ointment	VIO		
Bacitracin Zinc and Lidocaine Cream	VIO		
and Dexamethasone Ophthalmic Ointment	VIN1, VB1b	UV-254	
and Dexamethasone Ophthalmic Suspension	VIN1, VB1b	UV-254	
and Flurandrenolide Lotion	VIN1, VB1b	UV-240	testosterone
and Gramicidin Cream	VIN1		
and Gramicidin Ophthalmic Solution	VIN1		
and Gramicidin and Hydrocortisone Acetate Cream	VIN1, VB1b	UV-254	fluoxymesterone
and Hydrocortisone Acetate Cream	VIN1, VB1b	UV-254	fluoxymesterone
and Hydrocortisone Ophthalmic Suspension	VIN1, VB1b	UV-254	
and Hydrocortisone Acetate Ophthalmic Suspension	VIN1, VB1b	UV-254	
and Lidocaine Cream	VIO		
and Prednisolone Acetate Ophthalmic Suspension	VIO		
and Hydrocortisone Otic Solution	VIN1, VB1b	UV-254	
and Hydrocortisone Otic Suspension	VIN1, VB1b	UV-254	
Bacitracin and Lidocaine Ointment	VIN1, VB1b	UV-230	
Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension	VIN1, VB1b	UV-254	betamethasone
Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment	VIN1, IIIA1	525	
Neomycin Sulfate, Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment	VIN1, IC1j, IIIA1	525	
Neomycin Sulfate and Triamcinolone Acetonide Cream	VIN1, VB1b	UV-254	fluoxymesterone
Ointment	VIN1, VB1b	UV-254	fluoxymesterone
Neostigmine Bromide	IA1bii		CV
Tablets	IIIA4		
Neostigmine Methylsulfate	IA1c		MP
Injection	IIIA4		
Netilmicin Sulfate	VIN1		
Injection	VIN1		
Niacin	IIIB1	262	
Injection	IIIA4	450	
Tablets	VB1b	UV-262	
Niacinamide	VB1b	UV-254	
Injection	IIIA4	450	
Tablets	IIIA4	450	
Nicotine	IA1bii		Poten
Transdermal System	VB1b	UV-260	
Nicotine Polacrilex	VB1b	UV-254	
Gum	VB1b	UV-254	
Nifedipine	VB1b	UV-235	
Capsules	VB1b	UV-235	
Nitric Acid	IA1a		MeR
Nitrofurantoin	VB1b	UV-254	theophylline
Capsules	VB1b	UV-254	theophylline
Oral Suspension	VB1b	UV-254	theophylline
Tablets	VB1b	UV-254	theophylline
Nitrofurazone	IIIB1	375	
Ointment	VB1b	UV-365	
Topical Solution	VB1b	UV-365	
Nitrogen	VA1	TC-I	
Nitrogen 97 Percent	VA1	TC-I	
Nitroglycerin Tablets	IIIA4	410, 600	
Diluted tetranitrate	VB1b	UV-220	pentaerythritol
Injection tetranitrate	VB1b	UV-220	pentaerythritol
Ointment tetranitrate	VB1b	UV-220	pentaerythritol
Nitromersol	IB1biii		FAS
Topical Solution	IB1biii		FAS
Nitrous Oxide	VA1	TC-I	
Nizatidine	VB1b	UV-254	
Capsules	VB1b	UV-230	phenol
Nonoxynol 9	VB1b	UV-280	
Norepinephrine Bitartrate	IA1biii		CrV
Injection	VB1b	UV-280	
Norethindrone	IIIB1	240	
Tablets	IIIB2	380	
and Ethinyl Estradiol Tablets	IIIB2, IIIE2	375, 556	
and Mestranol Tablets	VB1b	UV-200	
Norethindrone Acetate	IIIB1	240	
Tablets	IIIB1	240	
Norethindrone Acetate and Ethinyl Estradiol Tablets	VB1b	UV-220	valerophenone
Norethynodrel	IIIB1	240	
Norfloxacin	IA1bii		Poten
Ophthalmic Solution	VB1b	UV-278	
Tablets	VB1b	UV-275	
Norgestrel	IIIB1	241	
Tablets	IIIB2	380	
and Ethinyl Estradiol Tablets	IIIB1, IIIA4	241, 536	
Nortriptyline Hydrochloride	IA1biii		Poten
Capsules	VB1b	UV-239	
Oral Solution	IIIB1	239	
Noscapine	IA1bii		CrV

Appendix B. Assay Index of Official USP-NF Drugs

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Novobiocin Cream	VIN1		
Novobiocin Sodium	VIN1		
Intramammary Infusion	VIN1		
Nystatin	VIN1		
Cream	VIN1		
Lotion	VIN1		
Lozenges	VIN		
Ointment	VIN1		
Topical Powder	VIN1		
Oral Suspension	VIN1		
for Oral Suspension	VIN1		
Tablets	VIN1		
Vaginal Suppositories	VIN1		
Vaginal Tablets	VIN1		
and Neomycin Sulfate, Gramicidin, and Triamcinoline Acetonide Cream	VIO		
and Neomycin Sulfate, Gramicidin, and Triamcinoline Acetonide Ointment	VIO		
and Neomycin Sulfate, Thiostrepton, and Triamcinoline Acetonide Cream	VIO		
and Neomycin Sulfate, Thiostrepton, and Triamcinoline Acetonide Ointment	VIO		
and Triamcinolone Acetonide Cream	VIN1, VB1b	UV-254	fluoxymesterone
Ointment	VIN1, VB1b	UV-254	fluoxymesterone
Octocrylene	VA1	FID-P	
Octyldodecanol	VA1	FID-I	
Octyl Methoxycinnamate	VA1	FID-P	
Octyl Salicylalate	VA1	FID-P	
Ofloxacin	VA1bii		Poten
Ophthalmic Solution	VB1b	UV-294	
Oleovitamin A and D	VIL		
Capsules	VIL		
Omeprazole	VB1b	UV-280	
Ondansetron Hydrochloride	VB1b	UV-216	
Injection	VB1b	UV-216	
Opium	IIIB1	285	
Powdered	IIIB1	285	
Tincture	IIIB1	285	
Bland Lubricating Ophthalmic Ointment	None		
Orphenadrine Citrate	IA1bii		CrV
Injection	IIIA4	410	
Oxacillin Sodium	VB1b	UV-225	
Capsules	VB1b	UV-225	
for Injection	VB1b	UV-225	
Injection	VB1b	UV-225	
for Oral Solution	VB1b	UV-225	
Oxandrolone	IA2bi		Phth
Tablets	VA1	FID-I	*n*-octacosane
Oxazepam	IA1aiii		Poten
Capsules	IIIB1	229	
Tablets	IIIB1	229	
Oxfendazole	IA1bii		
Oral Suspension	VB1b	UV-254	
Oxprenol Hydrochloride	IA1bii		Poten
Extended-release Tablets	IIIB1	274, 300	
Tablets	IIIB1	274, 300	
Oxtriphylline	IB1e		MeB
Extended-release Tablets	VB1b	UV-275	
Oral Solution	VB1b	UV-275	
Tablets, Delayed Release	VB1b	UV-275	
Tablets	VB1b	UV-275	
Oxybenzone	IIIB1	285	
Oxybutynin Chloride	IAbii		CrV
Syrup	IIIA2	415	
Tablets	VB1b	UV-203	
Oxycodone and Acetaminophen Capsules	VB1b	UV-214	
Tablets	VB1b	UV-280	
Oxycodone Hydrochloride	VB1b	UV-206	
Oral Solution	VB1b	UV-280	
Tablets	IIIB1	281	
and Aspirin Tablets	VB1b	UV-300, 280	
Oxycodone Terephthlate	VB1b	UV-280	ethylparaben
Oxygen	VIA		
93 Percent	VIA		
Oxymetazoline Hydrochloride	VB1b	UV-280	
Nasal Solution	VB1b	UV-280	
Ophthalmic Solution	VB1b	UV-280	
Oxymetholone	IIIB1	315	
Tablets	IIIB1	315	
Oxymorphone Hydrochloride	IA1biii		MV
Injection	IIIB1	282	
Suppositories	VB1b	UV-254	procaine hydrochloride
Oxyquinoline Sulfate	IC2f		ST
Oxytetracycline	VB1b	UV-254	
Injection	VB1b	UV-254	
for Injection	VB1b	UV-254	
Tablets	VB1b	UV-254	
and Nystatin Capsules	VIN1		
and Nystatin for Oral Suspension	VIN1		
Oxytetracycline Calcium	VIN1		
Oral Suspension	VIN1		
Oxytetracycline Hydrochloride	VIN1		
Capsules	VIN1		

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
for Injection	VIN1		
Soluble Powder	VIN1		
and Hydrocortisone Ointment	VIN1, VB1b	UV-254	
and Hydrocortisone Acetate Ophthalmic Suspension	VIN1, VB1b	UV-254	
and Polymyxin B Sulfate Ointment	VIN1		
and Polymyxin B Sulfate Ophthalmic Ointment	VIN1		
and Polymyxin B Topical Powder	VIN1		
and Polymyxin B Vaginal Tablets	VIN1		
Oxytocin	VB1b	UV-220	
Injection	VB1b	UV-220	
Nasal Solution	VB1b	UV-220	
Oxytriphylline Tablets	VB1b	UV-275	
Padimate O	IA1bii		Poten
Lotion	VB1b	UV-308	
Pamabrom	VB1B, IA1b	UV-280	caffeine, MeO
Pancreatin	VIF		
Tablets	VIF		
Pancrelipase	VIF		
Capsules	VIF		
Delayed-release Capsules	VIF		
Tablets	VIF		
Panthenol	IA2aiv		CrV
Papain	VIF		
Tablets for Topical Solution	VIF		
Papaverine Hydrochloride	IA1biii		CrV
Injection	IIIB1	251	
Tablets	IIIB1	251	
Parachlorophenol	IC2c		ST
Camphorated	IIB, IIB		
Paramethasone Acetate	IIIB1	242	
Tablets	IIIC1	6.04	
Paregoric	IIIB1	285	
Paromomycin Sulfate	VIN1		
Capsules	VIN1		
Syrup	VIN1		
Pectin	IA2b, IA1a		Phth
Penbutolol Sulfate	VB1b	UV-271	3,4-dimethyl-benzophenone
Tablets	VB1b	UV-270	
Penicillamine	VB1b	UV-210	
Capsules	VB1b	UV-210	
Tablets	VB1b	UV-210	
Penicillin G, Neomycin, Polymyxin B Sulfates, Hydrocortisone Acetate, and Hydrocortoisone Sodium Succinnate Topical Suspension	VIO		
Penicillin G Benzathine	VIN2		SPI
Oral Suspension	VIN2		SPI
Injectable Suspension	VIN2		SPI
Tablets	VIN2		SPI
and Penicillin G Procaine Suspension	VIN2		SPI
Penicillin G Potassium	VB1b	UV-220	
for Oral Solution	VIN2		SPI
Injection	VB1b	UV-225	
for Injection	VB1b	UV-220	
Tablets	VIN2		SPI
Penicillin G Procaine	VIN2		SPI
Intramammary Infusion	VIN1		
Injectable Suspension	VN2, VN1		
for Injectable Suspension	VIN2		SPI
and Dihydrostreptomycin Sulfate Intramammary Infusion	VIN1, VIN2		
and Dihydrostreptomycin Sulfate Injectable Suspension	VIN1, VIN2		
Dihydrostreptomycin Sulfate, Chlorpheniramine Maleate and Dexametasone Injectable Suspension	VIN2, VIN1, VA1, VB1b		brompheniramine, beclomethasone
Dihydrostreptomycin Sulfate and Prednisolone Injectable Suspension	VIN2, VIN1, VC1a		
and Prednisolone Suspension with Aluminum Stearate Suspension	VN2, VN1, IIIA2 V1N2		525 SPI
Neomycin, Polymyxin B Sulfates and Hydrocortisone Acetate Topical Suspension	VIN1, VB1b	UV-254	fluoxymesterone
Novobiocin Sodium Intramammary Infusion	VIN1, VIN2		
Penicillin G Sodium	VB1b	UV-220	
for Injection	VB1b	UV-220	
Penicillin V	VIN2		SPI
for Oral Suspension	VIN2		SPI
Tablets	VIN2		SPI
Penicillin V Benzathine	VIN2		SPI
Oral Suspension	VIN2		SPI
Penicillin V Potassium	VIN2		SPI
for Oral Solution	VIN2		SPI
Tablets	VIN2		SPI
Pentazocine	IA1bii		CrV
Pentazocine Hydrochloride	IA1biii		CrV
and Aspirin Tablets	IIIB1	278, 296	
and Naloxone Tablets	VB1b	UV-229	
Pentazocine Lactate Injection	IIIB1	278	
Pentetic Acid	IC1		
Pentobarbital	IA1aiii		Poten
Elixir	VA1	FID-I	*n*-tricosane
Pentobarbital Sodium	IIIB1	240	
Capsules	VA1	FID-I	*n*-tricosane
Injection	IIA		
Peppermint Oil	IA2bi		Phth
Spirit	VIB		
Perflubron	VA1bii	FID	
Perphenazine	IA1bii		CrV
Injection	IIIA4	480	
Oral Solution	VB1b	UV-254	
Syrup	IIIA4	480	
Tablets	IIIA4	480	
and Amitriptyline Hydrochloride Tablets	VB1b	UV-254	

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Phenazopyridine Hydrochloride	IIIA3	390	
Tablets	VB1b	UV-220	
Phendimetrazine Tartrate	IA1bii		CrV
Capsules	VB1b	UV-256	salicylamide
Tablets	VB1b	UV-256	salicylamide
Phenelzine Sulfate	IC2f		ST
Tablets	VB2b	UV-254	
Pheniramine Maleate	IA1bii		CrV
Phenmetrazine Hydrochloride	IIIB1	256	
Tablets	IIIB1	256	
Phenobarbital	VB1b	UV-254	caffeine
Elixir	VB1b	UV-254	caffeine
Tablets	VB1b	UV-254	caffeine
Phenobarbital Sodium	VB1b	UV-254	caffeine
Injection	VB1b	UV-254	caffeine
for Injection	IIIB1	240	
Phenol	IC2c		ST
Liquefied	IC2c		ST
Phenoxybenzamine Hydrochloride	IA1aiii		Poten
Capsules	IIIB1	275	
Phensuximide	IIIB1	258	
Capsules	VB1b	UV-254	
Phentermine Hydrochloride	IA1biii		Poten
Capsules	VB1b	UV-254	
Tablets	VB1b	UV-254	
Phentolamine Mesylate	IA1aiii		Poten
for Injection	IIIA4	410	
Phenylalanine	IA1bii		Poten
Phenylbenzimidazole Sulfonic Acid	IA1bi		phth
Phenylbutazone	VB1b	UV-254	desoxycorticosterone
Boluses	VB1b	UV-254	desoxycorticosterone
Injection	VB1b	UV-254	desoxycorticosterone
Tablets	VB1b	UV-254	desoxycorticosterone
Phenylephrine Hydrochloride	IC2c		ST
Injection	VB1b	UV-280	
Nasal Jelly	VB1b	UV-280	
Nasal Solution	VB1b	UV-280	
Ophthalmic Solution	VB1b	UV-280	
Phenylmercuric Acetate	IB1b		FAS
Phenylmercuric Nitrate	IB1b		FAS
Phenylpropanolamine Bitartrate	IA1bii		CrV
Phenylpropanolamine Hydrochloride	IA1biii		CrV
Capsules	VB1b	UV-254	theophylline
Capsules, Extended-Release	VB1b	UV-254	theophylline
Extended-release Tablets	VB1b	UV-254	
Oral Solution	VB1b	UV-254	theophylline
Tablets	VB1b	UV-254	theophylline
Phenytoin	IA1aiii		AV
Oral Suspension	VB1b	UV-229	
Tablets	VB1b	UV-254	
Phenytoin Sodium	VB1b	UV-220	
Extended Capsules	VB1b	UV-254	
Injection	VB1b	UV-254	
Prompt Capsules	VB1b	UV-254	
Chromic Phosphate P32 Suspension	VIE		
Sodium Phosphate P32 Solution	VIE		
Phosphoric Acid	IA1a		TP
Diluted	IA1a		TP
Physostigmine	IA1bii		Poten
Physostigmine Salicylate	IA1bii		Poten
Injection	VB1b	UV-254	
Ophthalmic Solution	VB1b	UV-254	
Physostigmine Sulfate	IA1bii		Poten
Ophthalmic Ointment	VB1b	UV-254	
Phytonadione	VB1a	UV-254	cholesteryl benzoate
Injection	VB1b	UV-254	
Tablets	VB1b	UV-254	
Pilocarpine	VB1b	UV-215	
Ocular System	VB1b	UV-215	
Pilocarpine Hydrochloride	VB1b	UV-220	
Ophthalmic Solution	VB1b	UV-220	
Pilocarpine Nitrate	VB1b	UV-220	
Ophthalmic Solution	VB1b	UV-220	
Pimozide	IA1bii		Poten
Tablets	VB1b	UV-280	3,4-dimethyl-benzophenone
Pindolol	VB1b	UV-219	
Tablets	VB1b	UV-254	nortriptyline
Piperacillin	VB1b	UV-220	
Piperacillin Sodium	VB1b	UV-220	
for Injection	VB1b	UV-220	
Piperazine	IA1bii		Poten
Piperazine Citrate	IA1bii		CrV
Syrup	IIB		
Tablets	IIB		
Piroxicam	VB1b	UV-254	
Capsules	VB1b	UV-254	
Plague Vaccine	None		
Plantago Seed	None		
Plasma Protein Fraction	None		
Platelet Concentrate	None		
Plicamycin	VB1b	UV-278	
for Injection	VB1b	UV-278	
Podophyllum	VIG		
Polacrilin Potassium	IIID	766	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Poloxalene	IIIA2	630	
PEG 3350 and Electrolytes for Oral Solution	VB1b	RI	
Polymyxin B Sulfate	VIN1		
for Injection	VIN1		
and Bacitracin Zinc Topical Aerosol	VIN1		
and Bacitracin Zinc Topical Powder	VIN1		
and Hydrocortisone Otic Solution	VIN1, VB1b	UV-254	
Polyvinyl Acetate Phthalate	IIIB1		
Sulfurated Potash		IIB	
Potassium Acetate	IA1bii		CrV
Injection	IIIF1	766.5	
Potassium Benzoate	IA1bii		CrV
Potassium Bicarbonate	IA1b		MeR
Effervescent Tablets for Oral Solution	IIIF1	766.5	
and Potassium Chloride for Effervescent Oral Solution	IB2aii, IIIF1	766.5	FAS
and Potassium Chloride Effervescent Tablets for Oral Solution	IB2aii, IIIF1	766.5	FAS
Sodium Bicarbonate and Citric Acid Effervescent Tablets for Oral Solution	IIID, IA1a		Ph
Potassium Bitartrate	IA1a		Phth
Potassium Carbonate	IA1b		MeO
Potassium Chloride	IB1a		EY
Extended Release Capsules	IIIF1	766.5	
Extended Release Tablets	IIIF1	766.5	
for Injection Concentrate	IIIF1	766.5	
Oral Solution	IIIF1	766.5	
for Oral Solution	IIIF1	766.5	
in Dextrose Injection	VIC1, IB1a		DCF
in Dextrose and Sodium Chloride Injection	IIIF1, IB1a		DCF
in Lactated Ringer's and Dextrose Injection	IC1a, IIID, IB1a		
in Sodium Chloride Injection	IIIF1		lithiumnitrate
Potassium Bicarbonate and Potassium Citrate Effervescent Tablets for Oral Solution	VIO		
Potassium Citrate	IA1bii		CrV
and Citric Acid Oral Solution	IIID, IA1a	766	Poten, Phth
Extended-release Tablets	IIIA4	425	
Potassium Gluconate	IIIF1	766.5	
Elixir	IIIF1	766.5	
Tablets	IIIF1	766.5	
and Potassium Citrate Oral Solution	IIIF1		
and Ammonium Chloride Oral Solution	IIIF1, IVB1		
and Potassium Chloride Oral Solution	IIIF1, IVB1		
and Potassium Chloride for Oral Solution	IIIF1, IVB1		
Potassium Guaiacolsulfonate	IIIB1	279	
Potassium Hydroxide	IA1b		Phth, MeO
Potassium Iodide	IB1a		Poten
Delayed-release Tablets	IB1a		Poten
Oral Solution	IB1a		Poten
Tablets	IB1a		Poten
Potassium Metabisulfite	IC2a		ST
Potassium Metaphosphate	IA2b		Phth
Potassium Nitrate	IA1a		Phth
Solution	IA1a		Phth
Potassium Permanganate	IC2e		
Monobasic Potassium Phosphate	IA1a		Poten
Dibasic Potassium Phosphate	IA2a		Poten
Potassium Phosphates Injection	IA1a, b		Poten
Potassium Sodium Tartrate	IA2aii		MeB
Potassium Sorbate	IA1bii		CrV
Povidone-Iodine	IC11		ST
Ointment	IC11		Poten
Topical Aerosol Solution	IC11		Poten
Topical Cleansing Solution	IC11		Poten
Topical Solution	IC11		Poten
Pralidoxime Chloride	IIIB1	336	
for Injection	IIIB1	336	
Pramoxine Hydrochloride	IA1biii		CrV
Cream	VB1b	UV-224	dibutyl phthlate
Jelly	IIIB1	286	
Praziquantel	VB1b	UV-210	
Tablets	VB1b	UV-210	
Prazosin Hydrochloride	VB1b	UV-254	
Capsules	VB1b	UV-254	
Prednisolone	VB1b	UV-254	betamethasone
Cream	IIIA4	410	
Tablets	VB1b	UV-254	betamethasone
Syrup	VB1b	UV-254	betamethasone
Prednisolone Acetate	VB1b	UV-254	betamethasone
Ophthalmic Suspension	VB1b	UV-254	
Injectable Suspension	VB1b	UV-254	
Prednisolone Hemisuccinate	IIIB1	243	
Prednisolone Sodium Phosphate	IIIB1	241	
Injection	IIIB1	241	
Ophthalmic Solution	IIIB1	241	
Prednisolone Sodium Succinate for Injection	IIIA1	525	
Prednisolone Tebutate	VB1a	UV-254	
Injectable Suspension	IIIB1	254	
Prednisone	VB1a	UV-254	acetanilide
Oral Solution	VB1b	UV-254	
Injectable Suspension	VB1b	UV-254	
Syrup	VB1b	UV-254	
Tablets	VB1a	UV-254	acetanilide
Prilocaine Hydrochloride	IA1biii		CrV
Injection	VB1b	UV-254	
and Epinephrine Injection	VB1b	UV-254, EC	
Primaquate Phosphate	IC1j		Poten
Tablets	IC1j		Poten

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Primidone	IIIB1	257	
Oral Suspension	VA1	FID-I	androsterone
Tablets	IIIB1	257	
Probenecid	VB1b	UV-254	
Tablets	IIIB1	257	
and Colchicine Tablets	IIIB1	244, 350	
Probucol	VB1b	UV-242	
Tablets	VB1b	UV-242	
Procainamide Hydrochloride	VB1b	UV-254	procaine hydrochloride
Capsules	VB1b	UV-254	procaine hydrochloride
Injection	VB1b	UV-254	procaine hydrochloride
Tablets	VB1b	UV-280	
Tablets, Extended-Release	VB1b	UV-280	
Procaine Hydrochloride	IC1j		Poten
Injection	IIIB1	280	
and Epinephrine Injection	IIIB1	280	
Tetracaine Hydrochloride and Levonordefrin Injection	IC1j, IIIA4	530	SPI
Procarbazine Hydrochloride	IA1a		Poten
Capsules	IVA1		
Prochlorperazine	IA1bii		CrV
Oral Solution	VB1b	UV-254	
Suppositories	IIIB1	254, 278	
Prochlorperazine Edisylate	IA1bii	CrV	
Injection	VB1b	UV-254	
Prochlorperazine Maleate	IA1bii		Poten
Tablets	VB1b	UV-254	trifluoperazine
Procyclidine Hydrochloride	IA1biii		Poten
Tablets	IIIA2	405	
Progesterone	VB1b	UV-254	methyltestosterone
Injection	VB1b	UV-254	methyltestosterone
Intrauterine Contraceptive System	IIIB1	241	
Injectable Suspension	VB1b	UV-254	methyltestosterone
Proline	IA1bii		CrV
Promazine Hydrochloride	IIIB1	301	
Injection	IIIB1	301	
Oral Solution	IIIB1	301	
Syrup	IIIB1	301	
Tablets	IIIB1	301	
Promethazine Hydrochloride	IA1biii		CrV
Injection	IIIA4	470	
Suppositories	IIIA4	470	
Syrup	IIIB1	298	
Tablets	IIIA4	470	
Propafenone Hydrochloride	IA1b		Poten
Propane	VA1	TC-I	
Propantheline Bromide	IA1biii		Poten
Tablets	VB1b	UV-254	
Proparacaine Hydrochloride	IA1biii		CrV
Ophthalmic Solution	VB1b	UV-270	
Propionic Acid	IA1a		Phth
Propoxycaine Hydrochloride	IC1j		SPI
Procaine Hydrochloride and Levonordefrin Injection	IIIB1, IIIA4	272, 296, 530	
Procaine Hydrochloride and Norepinephrine Bitartrate Injection	IIIB1, IIIA4	272, 296, 530	
Propoxyphene Hydrochloride	IA1biii		CrV
Capsules	VB1b	UV-220	
and Acetaminophen Tablets	IIIB1, VA1	249, FID-I	*n*-tricosane
Aspirin and Caffeine Capsules	IIIA4, VA1	530, FID-I	*n*-tricosane
Propoxyphene Napsylate	IA1bii		CrV
Oral Suspension	VA1	FID-I	*n*-tricosane
Tablets	VA1	FID-I	*n*-tricosane
and Acetaminophen Tablets	VB1b	UV-210, 245	
and Aspirin Tablets	VA1, IIIA4	FID-I, 530	*n*-tricosane
Propranol Hydrochloride	VB1b	UV-290	
Propranolol Hydrochloride	VB1b	UV-220	
Extended-release Capsules	VB1b	UV-220	
Injection	VB1b	UV-290	
Tablets	VB1b	UV-290	
and Hydrochlorothiazide Extended-release capsules	VB1b	UV-220	
and Hydrochlorothiazide Tablets	VB1b	UV-270	
Propyl Gallate	IIIB1	273	
Propylene Carbonate	IA1b		Phth
Propylene Glycol	VA1	TC-P	
Alginate	IA2bi		Phth
Monostearate	IA2b		Phth
Propylhexedrine	IA1b		MeR
Inhalant	IA2a		MeR
Propylparaben	IA2b		BtB
Propylparaben Sodium	IC2f		ST
Propylidone	IC1lii		ST
Injectable Oil Suspension	IC1lii		ST
Propylthiouracil	IA1ai		BtB
Tablets	VB1b	UV-272	
Protamine Sulfate	VIF		
Injection	VIF		
for Injection	VIF		
Protriptyline Hydrochloride	IA1biii		CrV
Tablets	IIIB1	292	
Pseudoephedrine Hydrochloride	IA1biii		CrV
Syrup	VB1b	UV-254	
Tablets	VB1b	UV-214	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Pseudoephedrine Sulfate	IA1bii		Poten
Pyrantel Pamoate	VB1b	UV-288	
Oral Suspension	VB1b	UV-288	
Pyrazinamide	IA1c		MeR
Tablets	VB1b	UV-270	
Pyridostigmine Bromide	IA1biii		QR
Injection	IIIB1	269	
Syrup	IIIA2	415	
Tablets	VB1b	UV-270	
Pyridoxine Hydrochloride	VB1b	UV-280	*p*-hydroxybenzoic acid
Injection	IIIA4		
Tablets	IIIA4		
Pyrilamine Maleate	IA1bii		CrV
Tablets	IIIB1	312	
Pyrimethamine	IA1bii		QR
Tablets	IIIB1	273	
Pyrvinium Pamoate	IIIA3	505	
Oral Suspension	IIIA3	505	
Tablets	IIIA3	505	
Quazepam	IA1B		Poten
Tablets	VB1b	UV-254	ethylparaben
Quinidine Gluconate	IA1bii		Nb
Extended-release Tablets	VB1b	UV-235	
Injection	VB2b	UV-235	
Quinidine Sulfate	IA1bii		Nb
Capsules	VB2b	UV-235	
Tablets	VB2b	UV-235	
Tablets, Extended-Release	VB2b	UV-232	
Quinine Sulfate	IA1bii		Nb
Capsules	VB2b	UV-235	
Tablets	VB2b	UV-235	
Rabies Immune Globulin	None		
Vaccine	None		
Racepinephrine	IIIA4	530	
Inhalation Solution	VB1b	UV-280	
Hydrochloride	VB1b	UV-278	
Raclopride C 11 Injection	VIE		
Ranitidine Hydrochloride	VB1b	UV-230	
Injection	VB1b	UV-322	
Tablets	VB1b	UV-322	
Oral Solution	VB1b	UV-322	
in Sodium Chloride Injection	VB1b, IB1a	UV-322	Poten
Rauwolfia Serpentia	IIIA4	390	
Powdered	IIIA4	390	
Tablets	IIIA4	390	
Rehydration Salts, Oral	VIC1, IIIF1, 121a		
Reserpine	VB1b	UV-268	
Elixir	IIIA4	390	
Injection	IIIA4	390	
Tablets	VB1b	UV-268	
and Chlorothiazide Tablets	IIIE2, IIIB1	292	
Hydralazine Hydrochloride and Hydrochlorothiazide Tablets	IIIA4, IIIB1, IIIA4	390, 271, 510	
and Hydrochlorothiazide Tablets	IIIA4, IIIB1	500, 274	
Resorcinol	IC2c		ST
and Sulfur Lotion	IC1k, VB1b	UV-280	ST, caffeine
Ribavirin	VB1b	UV-207	
for Inhalation Solution	VB1b	UV-207	
Riboflavin	IIIE1	530	
Injection	IIIE1	530	
Tablets	IIIE1	530	
5′-Phosphate Sodium	IIIE1	530	
Rifabutin	VB1b	UV-254	
Capsules	VB1b	UV-254	
Rifampin	VB1b	UV-254	
Capsules	VB1b	UV-254	
for Injection	VB1b	UV-207	
Oral Suspension		None	
and Isoniazid Capsules	VIN1, IC1h		Poten
Rimexolone	VB1b	UV-242	
Ophthalmic Suspension	VB1b	UV-242	
Ringer's Injection	IIID, IB1a	766	DCF
Irrigation	IIID, IB1a	766	DCF
and Dextrose Injection	IIID, IB1a, VIC1	766	DCF
Lactated, Injection	IC1a, IIID, IB1a, VB1b	766, UV-210	HNB, DCF
Lactated and Dextrose Injection	IC1a, IIID, IB1a, VIC1	766	HNB, DCF
Half-strength Lactated and Dextrose Injection	IC1a, IIID, IB1a, VIC1	766	HNB, DCF
Modified Lactated and Dextrose Injection	IC1a, IIID, IB1a, VIC1	766	HNB, DCF
Ritodrine Hydrochloride	VB1b	UV-254	
Injection	VB1b	UV-275	
Tablets	VB1b	UV-275	
Roxarsone	VB1b	UV-280	
Rubidium Chloride Rb 82 Injection	VIE		
Saccharin	IA1a		Phth
Saccharin Calcium	IA1ai		Phth
Saccharin Sodium	IA1ai		Phth
Oral Solution	VB1b	UV-257	
Tablets	IIIB1	269	
Salicylamide	IA1aiii		TB
Salicylic Acid	IA1a		Phth
Collodion	IA1a		BtB
Gel	IA1a		Phth
Plaster	IC2c		ST
Topical Foam	VB1b	UV-280	benzoic acid
Salsalate	VB1b	UV-263	
Capsules	VB1b	UV-263	
Tablets	VB1b	UV-263	

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Sargramostim	VIE		
for Injection	VIE		
Scopolamine Hydrobromide	IA1biii		CrV
Injection	VA1	TC-I	homatropine hydrobromide
Ophthalmic Ointment	VA1	TC-I	homatropine hydrobromide
Ophthalmic Solution	VA1	TC-I	homatropine hydrobromide
Tablets	VA1	TC-I	homatropine hydrobromide
Secobarbital	IA1aiii		TB
Elixir	VA1	FID-I	butabarbital
Secobarbital Sodium	IIB		
Capsules	VA1	FID-I	butabarbital
Injection	IIIB1	260	
for Injection	IIB		
and Amobarbital Sodium Capsules	VA1	FID-I	aprobarbital
Selegiline Hydrochloride	VB1b	UV-205	
Tablets	VB1b	UV-205	
Selenious Acid	IC2c		ST
Injection	IIIF1		
Selenium Sulfide	IC1lii		ST
Lotion	IC1lii		ST
Selenomethionine	IA1bii		CrV
Sennosides A and B	IIIE2	505	
Tablets	IIIE2	505	
Serine	IA1bii		Poten
Silicon Dioxide	IIC		
Colloidal Silicon Dioxide	IIC		
Silver Nitrate	IB1b		FAS
Ophthalmic Solution	IB1b		FAS
Toughened	IB1b		FAS
Silver Sulfadiazine	VB1b	UV-254	
Cream	VB1b	UV-254	sulfamerazine
Simethicone	IIIC1	7.9	
Capsules	IIIC1	7.9	
Emulsion	IIIC1	7.9	
Oral Suspension	IIIC1	7.9	
Tablets	IIIC1	7.9	
Simvastatin	VB1b	UV-238	
Tablets	VB1b	UV-238	
Sincalide for Injection	VIH		
Sisomicin Sulfate	VIN1		
Injection	VIN1		
Soda Lime	VIK		
Sodium Acetate	IA1bii		Nb
C 11 Injection	VB1b, VIE	UV-210	
Injection	IIID	589	
Solution	IA1bii		Nb
Sodium Alginate	IA2b		Phth
Sodium Ascorbate	IC1k		ST
Sodium Benzoate	IA1bii		CrV
Sodium Bicarbonate	IA1b		MeR
Injection	IA1b		MeR
Oral Powder	IA1b		MeO
Tablets	IA1b		MeR
Sodium Borate	IA1b		MeR
Sodium Carbonate	IA1b		MeR
Sodium Chloride	IB1a		DCF
Inhalation Solution	IB1a		DCF
Injection	IB1a		DCF
Bacteriostatic Injection	IB1a		DCF
Irrigation	IB1a		DCF
Ophthalmic Ointment	IB1a		DCF
Ophthalmic Solution	IB2aii		FAS
Tablets	IB2aii		FAS
Tablets for Solution	IB2aii		FAS
and Dextrose Tablets	IB2aii, VIC1		FAS
Sodium Citrate	IA1bii		Poten
and Citric Acid Oral Solution	IIID, IA1a		Phth
Sodium Dehydroacetate	IA1bii		Nb
Sodium Fluoride	IVB1		
Oral Solution	IVB1		
Tablets	IVB1		
and Acidulated Phosphate Topical Solution	IVB1		
and Phosphoric Acid Gel	IVB1		
and Phosphoric Acid Topical Solution	IVB1		
Sodium Formaldehyde Sulfoxylate	IC1k		ST
Sodium Gluconate	IA1bii		QR
Sodium Hydroxide	IA1b		Phth
Sodium Hypochlorite Solution	IC1lii		ST
Sodium Iodide	IC1n		
Sodium Lactate Injection	IA1bii		Poten
Solution	IA1bii		Poten
Sodium Lauryl Sulfate	None		
Sodium Metabisulfite	IC2a		ST
Sodium Monofluorophosphate	IB1d		SAS
Sodium Nitrite	IC2e		
Injection	IC2e		
Sodium Nitroprusside	IB1a		Poten
for Injection	VB1b	UV-210	
Monobasic Sodium Phosphate	IA1b		Phth
Dibasic Sodium Phosphate	IA2a		Poten
Sodium Phosphates Enema	IA1a		Poten
Injection	IA1a, b		Poten
Oral Solution	IA1a		Poten
Sodium Polystyrene Sulfonate	VB1b	RI	
Suspension			

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Sodium Propionate	IA1bii		CrV
Sodium Salicylate	IA1bii		CrV
Tablets	IA1b		BpB
Sodium Starch Glycolate	IA1bii		Poten
Sodium Stearate	VA2	FID-I	
Sodium Stearyl Fumarate	IA1a		QR
Sodium Sulfate	IIB		
Injection	IIB		
Sodium Thiosulfate	IC1k		ST
Injection	IC1k		ST
Sorbic Acid	IA1a		Phth
Sorbitan Monolaurate	IIA, IIA		
Sorbitan Monooleate	IIA, IIA		
Sorbitan Monopalmitate	IIA, IIA		
Sorbitan Monostearate	IIA, IIA		
Sorbitol	VB1b	RI	
Noncrystallizing Solution	VB1b	RI	
Solution	VB1b	RI	
Spectinomycin Hydrochloride	VA2	FID-I	triphenylantimony
for Injectable Suspension	VA2	FID-I	triphenylantimony
Spironolactone	VB1b	UV-254	
Tablets	VB1b	UV-254	
and Hydrochlorothiazide Tablets	VB1b	UV-254	
Stannous Fluoride	IC1n, IVB1	590	
Gel	IVB1		
Stanozolol	IA1bii		CrV
Tablets	IIIB1	235	
Stearic Acid	VA2	FID-I	
Purified	VA2	FID-I	
Stearyl Alcohol	VA1	FID-I	
Streptomycin Sulfate	VIN1		
Injection	VIN1		
for Injection	VIN1		
Strontium Chloride Sr 89 Injection	IIIF1		
Succinylcholine Chloride	VB1b	UV-214	
Injection	VB1b	UV-214	
for Injection	VB1b	UV-214	
Sucralfate	VB1b	RI	
Tablets	VB1b	RI	
Sucrose Octaacetate	IA2b		Phth
Sufentanil Citrate	IAbii		NPB
Injection	VB1b	UV-240	
Compressible Sugar	VIC1		
Sugar, Inverted, Injection	IIB		
Sulbactam Sodium	VB1b	UV-230	
Sulconazole Nitrate	VB1b	UV-230	
Sulfabenzamide	IA1aiii		TB
Sulfacetamide	IC1j		Poten
Sulfacetamide Sodium	IC1j		Poten
Ophthalmic Ointment	VB1b	UV-254	
Ophthalmic Solution	VB1b	UV-254	
and Prednisolone Acetate Ophthalmic Ointment	VB1b	UV-254	norethindrone
and Prednisolone Acetate Ophthalmic Suspension	VB1b	UV-254	
Sulfachlorpyridazine	VB1b	UV-265	
Sulfadiazine	VB1b	UV-254	
Tablets	VB1b	UV-254	
Silver Sulfadiazine	VB1b	UV-214	sulfamerazine
Cream	VB1b	UV-214	sulfamerazine
Sulfadiazine Sodium	IC1j		Poten
Injection	IC1j		Poten
Sulfadoxine	IC1j		Poten
and Pyrimethamine Tablets	VB1b	UV-254	phenacetin
Sulfamethazine	IC1j		Poten
Granulated	VB2b	450	
Sulfamethizole	IC1j		Poten
Oral Suspension	IC1j		Poten
Tablets	IC1j		Poten
Sulfamethoxazole	IC1j		Poten
Oral Suspension	IC1j		Poten
Tablets	IC1j		Poten
and Trimetoprin for Injection	VB1b	UV-254	
and Trimethoprim Oral Suspension	VB1b	UV-254	
and Trimethoprim Tablets	VB1b	UV-254	
Sulfapyridine	IC1j		Poten
Tablets	IC1j		Poten
Sulfaquinoxaline	VB1b	UV-254	
Oral Solution	VB1b	UV-254	
Sulfasalazine	IIIB1	359	
Delayed-release Tablets	IIIB1	359	
Tablets	IIIB1	359	
Sulfathiazole	IC1j		Poten
Sulfinpyrazone	IA1a		Phth
Capsules	VB1b	UV-235	benzoic acid
Tablets	VB1b	UV-235	benzoic acid
Sulfisoxazole	IA1aiii		TB
Tablets	IA1aiii		TB
Sulfisoxazole Acetyl	IC1j		Poten
Oral Suspension	IC1j		Poten
Sulfur, Precipitated	IA1a		Phth
Ointment	IIB		
Sublimed	IA1a		Phth
Sulfur Dioxide	IC1k		ST
Sulfuric Acid	IA1a		MeO
Sulindac	IA1a		Poten
Tablets	VB1a	UV-332	
Sulisobenzone	IA1a		Poten
Suprofen	VB1b	UV-254	
Ophthalmic Solution	VB1b	UV-254	
Tamoxifen Citrate	IA1bii		Poten
Tablets	VB1b	UV-254	
Technetium Tc 99m (All)	VIE		
Temazepam	VB1b	UV-220	
Capsules	VB1b	UV-254	benzophenone

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Terbutaline Sulfate	VB1b	UV-280	
Injection	VB1b	UV-280	
Inhalation Aerosol	VB1b	UV-280	
Tablets	VB1b	UV-280	
Terpin Hydrate	VA1	FID-I	biphenyl
Elixir	VA1	FID-I	biphenyl
and Codeine Elixir	VA1	FID-I	biphenyl, *N*-phenylcarbazole
Testolactone	IIIA4	415	
Tablets	IIIA4	415	
Testosterone	IIIB1	241	
Injectable Suspension	IIIB1	241	
Testosterone Cypionate	VA1	FID-I	cholesteryl caprylate
Injection	VA1	FID-I	cholesteryl caprylate
Testosterone Enanthate	IIIA4	380	
Injection	IIIA4	380	
Testosterone Propionate	IIIA4	380	
Injection	IIIA4	380	
Tetracaine	IC1j		SPI
Ointment	IIIB1	310	
Ophthalmic Ointment	IIIB1	310	
and Menthol Ointment	VA1, IIIB1	FID-I, 310	1-decanol
Tetracaine Hydrochloride	IC1j		Poten
Cream	IIIB1	310	
Injection	VB1b	UV-305	
Ophthalmic Solution	IIIB1	310	
Topical Solution	IIIB1	310	
for Injection	IIIB1	310	
in Dextrose Injection	VIC1		
Tetracycline	VB1b	UV-280	
Boluses	VIN1		
Oral Suspension	VB1b	UV-280	
Tetracycline Hydrochloride	VB1b	UV-280	
Capsules	VB1b	UV-280	
for Injection	VB1b	UV-280	
Ointment	VB1b	UV-280	
Ophthalmic Ointment	VIN1		
for Topical Solution	IIIB1	366	
Soluble Powder	VIN1		
Ophthalmic Suspension	VB1b	UV-280	
Tablets	VB1b	UV-280	
and Novobiocin Sodium Tablets	VIN1		
Novobiocin Sodium and Prednisol one Tablets	VIN1, VB1b	UV-254	betamethasone
and Nystatin Capsules	VIN1		
Tetrahydrozoline Hydrochloride	IA1biii		QR
Nasal Solution	IIIA4	570	
Ophthalmic Solution	VB1b	UV-280	
Thallous Chloride Tl 201 Injection	VIE		
Theophylline	VB1b	UV-280	theobromine
Capsules	VB1b	UV-280	theobromine
Capsules, Extended Release	VB1b	UV-280	theobromine
in Dextrose Injection	VB1b, VIC1	UV-280	theobromine
Tablets	VB1b	UV-280	theobromine
Ephedrine Hydrochloride and Phenobarbital Tablets	VB1b	UV-241	butabarbital sodium
and Guaifenesin Capsules	VB1b	UV-280	caffeine
and Guaifenesin Oral Solution	VB1b	UV-280	
Theophylline Sodium Glycinate	VB1b	UV-280	theobromine
Elixir	VB1b	UV-280	theobromine
Tablets	IB2ai		FAS
Thiabendazole	IA1biii		CrV
Oral Suspension	VB1b	UV-254	
Tablets	VB1b	UV-254	
Thiacetarsamide	VB1b	UV-232	
Sodium Injection	VB1b	UV-232	
Thiamine Hydrochloride	VB1b	UV-254	methylbenzoate
Elixir	VB1b	UV-254	methylparaben
Injection	VB1b	UV-254	methylparaben
Tablets	IIIE2	365	
Thiamine Mononitrate	VB1b	UV-254	methylbenzoate
Elixir	VB1b	UV-254	methylparaben
Thiethylperazine Maleate	IA1bii		Poten
Suppositories	VB1b	UV-265	
Tablets	VB1b	UV-265	
Thimerosal	IIIF1	254	
Topical Aerosol	IIIF1	254	
Topical Solution	IIIF1	254	
Tincture	IIIF1	254	
Thioguanine	IIIB1	348	
Tablets	IIIB1	348	
Thiopental Sodium	IIIB1	304	
for Injection	IIIB1	304	
Thioridazine	IA1bii		Poten
Oral Suspension	IIIB1	265	
Thioridazine Hydrochloride	IA1bii		Poten
Oral Solution	IIIB1	265	
Tablets	VB1b	UV-265	
Thiostrepton	VB1b	UV-254	benzophenone
Thiotepa	VB1b	UV-215	
for Injection	IIIC1	10.75	
Thiothixene	VB1b	UV-254	
Capsules	VB1b	UV-254	
Thiothixene Hydrochloride	VB1b	UV-254	
Injection	VB1b	UV-254	
for Injection	VB1b	UV-254	
Oral Solution	VB1b	UV-254	
Threonine	IA1bii		Poten

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Thymol	IC1h		MeO
Thyroid	VB1b	UV-230	
Tablets	VB1b	UV-230	
Ticarcillin Disodium	VB1b	UV-220	
for Injection	VB1b	UV-220	
and Clavulanic Acid Injection	VB1b	UV-220	
and Clavulanic Acid for Injection	VB1b	UV-220	
Ticarcillin Monosodium	VB1b	UV-220	
Tiletamine Hydrochloride	IA1bii		CrV
Tiletamine and Zolazepam for Injection	VA1	FID	tetraphenylethylene
Tilmicosin	VB1b	UV-280	
Injection	VB1b	UV-280	
Timolol Maleate	IA1bii		Poten
Ophthalmic Solution	VB1b	UV-295	
Tablets	VB1b	UV-295	
and Hydrocholorothiazide Tablets	VB1b	UV-295	
Tioconazole	VB1b	UV-219	
Titanium Dioxide	IC1bi		
Tobramycin	VB2b	UV-365	
Injection	VIN1		
for Injection	VIN1		
Ophthalmic Ointment	VB2b	UV-365	
Ophthalmic Solution	VB2b	UV-365	
and Dexamethasone Ophthalmic Ointment	VB2b, VB1b	UV-365, 206	
and Dexamethasone Ophthalmic Suspension	VIN1, VB1b	UV-254	
and Fluorometholone Acetate Ophthalmic Suspension	VB2b	UV-365	
Tocainide Hydrochloride	IA1bii		Poten
Tablets	VB1b	UV-254	
Tocopherols Excipient	VA1	FID-I	hexadecyl hexadecanoate
Tolazamide	VB1a	UV-254	tolbutamide
Tablets	VB1a	UV-254	tolbutamide
Tolazoline Hydrochloride	IA1biii		Poten
Injection	IIIA4	568	
Tolbutamide	VB1a	UV-254	tolazamide
Tablets	VB1a	UV-254	tolazamide
for Injection	VB1a	UV-254	tolazamide
Tolmetin Sodium	IA1bii		Poten
Capsules	VB1b	UV-254	
Tablets	VB1b	UV-254	
Tolnaftate	IIIB1	258	
Topical Aerosol Powder	VB1b	UV-254	progesterone
Cream	IIIB1	258	
Gel	IIIB1	258	
Topical Powder	VB1b	UV-254	progesterone
Topical Solution	IIIB1	258	
Trazodone Hydrochloride	VB1b	UV-254	butylparaben
Tablets	VB1b	UV-254	
Trenbolone Acetate	VB1b	UV-344	

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Tretinoin	IA1aiii		TB
Cream	VB1b	UV-365	
Gel	IIIB1	365	
Topical Solution	IIIB1	352	
Triacetin	IA2bi		Phth
Triamcinolone	VB1b	UV-254	hydrocortisone
Tablets	VB1b	UV-254	hydrocortisone
Triamcinolone Acetonide	VB1b	UV-254	fluoxymesterone
Topical Aerosol	VB1b	UV-254	fluoxymesterone
Cream	VB1b	UV-254	fluoxymesterone
Lotion	VB1b	UV-254	fluoxymesterone
Ointment	VB1b	UV-254	fluoxymesterone
Dental Paste	VB1b	UV-254	fluoxymesterone
Injectable Suspension	VB1b	UV-254	fluoxymesterone
Triamcinolone Diacetate	VB1b	UV-254	
Injectable Suspension	VB1b	UV-254	
Syrup	VB1b	UV-254	
Triamcinolone Hexacetonide	VB1b	UV-254	
Injectable Suspension	VB1b	UV-254	fluoxymesterone
Triamterene	IA1bii		Poten
Capsules	VB1b	UV-280	
and Hydrochlorothiazide Capsules	VB1b	UV-280	
and Hydrochlorothiazide Tablets	VB1b	UV-280	
Triazolam	VB1b	UV-254	alprazolam
Tablets	VB1b	UV-254	alprazolam
Trichlorfon	IB1a		Poten
Trichlormethiazide	VB1b	UV-254	
Tablets	VB1b	UV-254	methylparaben
Trichloromonofluorometane	VA1	FID	
Tricitrates Oral Solution	IA1a, b, IIID	766	Phth
Triclosan	VA1	FID	
Trientine Hydrochloride	IAb		
Capsules	IIIA4	580	
Triethyl Citrate	IB2b		Phth
Trifluoperazine Hydrochloride	IA1biii		CrV
Injection	IIIB1	255	
Syrup	IIIB1	255	
Tablets	VB1b	UV-262	
Triflupromazine	IA1bii		CrV
Oral Suspension	IIIB1	255	
Triflupromazine Hydrochloride	IA1biii		CrV
Injection	IIIB1	255	
Tablets	IIIB1	255	
Trifluridine	VB1b	UV-254	
Trihexyphenidyl Hydrochloride	VB1b	UV-210	
Capsules, Extended-Release	VB1b	UV-210	
Elixir	VB1b	UV-210	
Tablets	VB1b	UV-210	
Trikates Oral Solution	IIIF1	766.5	
Trimeprazine Tartrate	VB1b	UV-254	
Syrup	VB1b	UV-254	
Tablets	VB1b	UV-254	

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DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Trimethobenzamide Hydrochloride	IA1biii		Poten
Capsules	IIIB1	258	
Injection	IIIB1	258	
Trimethoprim	IA1bii		Poten
Tablets	VB1b	UV-254	
Trimethoprim Sulfate	IA1bii		Poten
Trioxsalen	VB1b	UV-254	
Tablets	IIIB1	252	
Tripelenamine Hydrochloride	IA1biii		CrV
Tablets	IIIB1	313	
Triprolidine Hydrochloride	IA1biii		Poten
Syrup	VB1b	UV-254	
Tablets	VB1b	UV-254	
and Pseudoephedrine Hydrochloride Syrup	VB1b	UV-254	
and Pseudoephedrine Hydrochloride Tablets	VB1b	UV-254	
Trisulfapyrimidines Oral Suspension	VB1b	UV-254	
Tablets	VB1b	UV-254	
Trolamine Salicylate	IA1b		MeR
Troleandomycin	VIN1		
Capsules	VIN1		
Tromethamine	IA1b		BcP
for Injection	IA1b		BcP
Tropicamide	IA1bii		CrV
Ophthalmic Solution	IIIB1	253	
Crystallized Trypsin	VIF		
for Inhalation Aerosol	VIF		
Tryptophan	IA1bii		Poten
Tubocurarine Chloride	VB1b	UV-220	
Injection	VB1b	UV-220	
Tylosin	VIN		
Granulated	VIN		
Tyrosine	IA1bii		Poten
Tyrothricin	VIN1		
Undecylenic Acid	IA1a		Phth
Compound Ointment	IIIF1, VA2	214, FID-I	tridecanoic acid
Urea	IA1c		MRB
Urea for Injection	IA1c		MRB
Ursodiol	VB1b	RI	epiandrosterone
Capsules	VB1b	RI	epiandrosterone
Valine	IA1bii		Poten
Valproic Acid	VA1	FID	nonanoic acid
Capsules	VA1	FID-I	biphenyl
Syrup	VA1	FID-I	biphenyl
Vancomycin	VIN1		
Injection	VIN1		
Vancomycin Hydrochloride	VIN1		
Capsules	VIN1		
for Injection	VIN1		
for Oral Solution	VIN1		
Sterile	VIN1		
Vanillin	IIIB1	308	
Varicella-Zoster Immune Globulin	None		
Vasopressin	VB1b	UV-220	
Injection	VB1b	UV-220	
Verapamil Hydrochloride	IA1biii		Poten
Extended-release Tablets	VB1b	UV-278	
Injection	VB1b	UV-278	
Tablets	VB1b	UV-278	
Vidarabine	VB1b	UV-262	
Ophthalmic Ointment	VB1b	UV-254	
Vinblastine Sulfate	VB1b	UV-262	
for Injection	VB1b	UV-262	
Vincristine Sulfate	VB1b	UV-297	
Injection	VB1b	UV-297	
for Injection	VB1b	UV-297	
Vitamin A	VIL		
Capsules	VIL		
Vitamin E	VA1	FID-I	hexadecyl hexadecanoate
Preparation	VA1	FID-I	hexadecyl hexadecanoate
Capsules	VA1	FID-I	hexadecyl hexadecanoate
Water-soluble Vitamins Capsules	VIL		
Water-soluble Vitamins Tablets	VIL		
Water-soluble Vitamins with Mineral Capsules	VIL		
Water-soluble Vitamins with Mineral Tablets	VIL		
Oil- and Water-soluble Vitamins Capsules	VIL		
Tablets	VIL		
with Mineral Capsules	VIL		
with Mineral Tablets	VIL		
Oil-soluble Vitamins Capsules	VIL		
Oil-soluble Vitamins Tablets	VIL		
Warfarin Sodium	VB1b	UV-280	propylparaben
for Injection	VB1b	UV-280	propylparaben
Tablets	VB1b	UV-280	propylparaben
Xanthan Gum	IA2b		Phth
Xenon Xe 127	VIE		
Xenon Xe 133	VIE		
Injection	VIE		

DRUG	ASSAY CATEGORY	ANALYTICAL WAVELENGTH AND/OR DETECTOR	INDICATOR OR INTERNAL STANDARD
Xylazine	VB1b	UV-226	
Injection	VB1b	UV-254	
Xylazine Hydrochloride	VB1b	UV-254	
Xylitol	VA1		erithritol
Xylometazoline Hydrochloride	IA1biii		Poten
Nasal Solution	IIIA4	565	
Xylose	IIIA4	520	
Zalcitabine	VB1b	UV-270	
Tablets	VB1b	UV-280	
Zidovudine	VB1b	UV-265	
Capsules	VB1b	UV-265	
Injection	VB1b	UV-265	
Oral Solution	VB1b	UV-265	
Zinc Acetate	ID1a		EBT
Zinc Carbonate	IA2a		MeO
Zinc Chloride	ID1a		EBT
Injection	IIIF1	213.8	
Zinc Gluconate	ID1a		EBT
Zinc Oxide	IA2a		MeO
Ointment	ID1a		EBT
Paste	IIC		
and Salicylic Acid Paste	IA1aiii		TB, PR
Zinc Stearate	ID1a		EBT
Zinc Sulfate	ID1a		EBT
Injection	IIIF1	213.8	
Ophthalmic Solution	ID1a		PAN
Zinc Undecylenate	IA2a		MeO
Zolazepam Hydrochloride	IA1bii		Poten