SOLID DOSAGE FORMS AND SOLID MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

6 Powders and Granules

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate a powder from a granule
2. Explain how a drug's powder particle size influences the pharmaceutical dosage forms that will be used to administer it
3. Define micromeritics, the angle of repose, levigation, spatulation, and trituration
4. Compare and contrast the various types of medicated powders, for example, bulk, divided
5. Provide examples of medicated powders used in prescription and nonprescription products
6. Differentiate between the fusion method and wet method for the preparation of effervescent granulated salts

Most active and inactive pharmaceutical ingredients occur in the solid state as amorphous powders or as crystals of various morphologic structures. The term "powder" has more than one connotation in pharmacy. It may be used to describe the physical form of a material, that is, a dry substance composed of finely divided particles. Or, it may be used to describe a type of pharmaceutical preparation, that is, a medicated powder intended for internal (i.e., oral powder) or external (i.e., topical powder) use. A powder is defined as a dosage form composed of a solid or mixture of solids reduced to a finely divided state and intended for internal or external use.

HISTORICAL USE

Originally, powders were found to be a convenient mode of administering drugs derived from hard vegetables such as roots (e.g., rhubarb), barks (e.g., cinchona), and woods (e.g., charcoal). As synthetic drugs were introduced, powders were used to administer insoluble drugs such as calomel, bismuth salts, mercury, and chalk.

Powders as a solid dosage form have been used historically as internal and external medications. For internal use, they can be taken orally, administered through the nose as snuffs, or blown into a body cavity as an insufflation. For external use, solid powders can be applied to compromised areas of the body. Powders have also been used to make solutions for topical and oral use and for use as douches. Such traditional applications and modes of administration of the dosage form continue today. Additional applications have also been developed; for example, powders containing a bioadhesive material can be applied to a specific body area such that the medication will adhere for a prolonged drug effect.

APPLICATIONS

Powders have qualities that make them an attractive dosage form for certain situations. Unlike a standardized capsule or tablet,

powders enable a primary care provider to easily alter the quantity of medication for each dose. Powders can also aid in clinical studies of drug preparations because the dose can be so readily adjusted. Doses can be individually weighed and placed in powder papers, envelopes, or small vials/bottles ("Powder in a bottle" research studies are an example). In another example, infants and young children who cannot swallow tablets or capsules will accept powders that can be mixed with a formula or sprinkled in applesauce or some other appropriate food. Also, if a drug is too bulky to be prepared as a capsule or tablet, it may be suitable for a powder dosage form. Powders provide a rapid onset of action because they are readily dispersed, have a large surface area, and usually require only dissolution, not disintegration, before absorption.

Although the use of *medicated powders* per se in therapeutics is limited, the use of powdered substances in the preparation of other dosage forms is extensive. For example, powdered drugs may be blended with powdered fillers and other pharmaceutical ingredients to fabricate solid dosage forms as tablets and capsules; they may be dissolved or suspended in solvents or liquid vehicles to make various liquid dosage forms; or they may be incorporated into semisolid bases in the preparation of medicated ointments and creams.

Granules, which are prepared agglomerates of powdered materials, may be used per se for the medicinal value of their content, or they may be used for pharmaceutical purposes, as in making tablets, as described later in this and Chapters 7 and 8.

POWDERS

Composition

Properly prepared, powders have a uniform, small particle size that has an elegant appearance. In general, powders are more stable than are liquid dosage forms and are rapidly soluble, enabling the drug to be absorbed quickly.

The properties of powders are related to the size and surface area of the particles. For example, large particles that are more dense tend to settle more rapidly than do small particles; particles that are more bulky will settle more slowly. This characteristic must be considered in mixing or storing and shipping, when powders of different particle size may become segregated. Another concern stems from the fact that powder dosage forms have a large surface area that is exposed to atmospheric conditions. Thus, powders should be dispensed in tight containers. Further, because powders of small particle size present a greater surface area to the atmosphere, they are more reactive in nature and can adsorb larger quantities of gases, such as carbon dioxide. However, if the powder has a smaller particle size, it can dissolve at a more rapid rate, unless adsorbed gases prevent the water from surrounding the individual particles and wetting them, thereby decreasing their wetting properties. An increase in surface free energy can increase the absolute solubility of the drug and have a positive effect on its bioequivalence.

Topical Powders

Topical powders should have a uniform, small particle size that will not irritate the skin when applied. They should be impalpable and free flowing, should easily adhere to the skin, and should be passed through at least a No. 100-mesh sieve to minimize skin irritation. The powder should be prepared so that it adheres to the skin.

Highly sorptive powders should not be used for topical powders that are to be applied to oozing wounds, as a hard crust may form. A more hydrophobic, water-repellent powder will prevent loss of water from the skin and will not cake on the oozing surfaces. Talc, or any other naturally derived product that is to be used on open wounds, should first be sterilized to avoid an infection in the area.

Topical powders usually consist of a base or vehicle, such as cornstarch or talc; an adherent, such as magnesium stearate, calcium stearate, or zinc stearate; and possibly an active ingredient, along with an aromatic material. The powder should provide

a large surface area, flow easily, and spread uniformly. The large surface area will aid in absorbing perspiration and give a cooling sensation to the skin.

Insufflated Powders

Insufflated powders are finely divided powders that are intended to be applied in a body cavity, such as the ears, nose, vagina, tooth socket, or throat. When using an insufflator, or "puffer," the patient simply "puffs" the desired quantity of powder onto the affected area or into the cavity. This device is particularly appropriate for anti-infectives. Also, a moisture-activated adherent, such as Polyox, can be incorporated into the powder. Polyox is an ethylene oxide polymer with a high molecular weight that forms a viscous, mucoadhesive gel when in contact with moisture. The gel serves to provide a depot for long-term drug delivery spanning several hours.

Physicochemical Considerations

Before their use in the preparation of pharmaceutical products, solid materials first are characterized to determine their chemical and physical features, including morphology, purity, solubility, flowability, stability, particle size, uniformity, and compatibility with any other formulation components (1). Drug and other materials commonly require chemical or pharmaceutical processing to imbue the features desired to enable both the efficient production of a finished dosage form and the optimum therapeutic efficacy. This usually includes the adjustment and control of a powder's particle size.

Particle Size and Analysis

The particles of pharmaceutical powders and granules may range from being extremely coarse, about 10 mm (1 cm) in diameter, to extremely fine, approaching colloidal dimensions of 1 μm or less. In order to characterize the particle size of a given powder, the *United States Pharmacopeia* (USP) uses these descriptive terms: very coarse, coarse, moderately coarse, fine, and very fine, which are related to the proportion of powder that is capable

of passing through the openings of standard sieves of varying fineness in a specified period while being shaken, generally in a mechanical sieve shaker (2). Table 6.1 presents the standard sieve numbers and the openings in each, expressed in millimeters and in microns. Sieves for such pharmaceutical testing and measurement are generally made of wire cloth woven from brass, bronze, or other suitable wire. They are not coated or plated.

Powders of vegetable and animal origin drugs are officially defined as follows (2):

- Very coarse (No. 8): All particles pass through a No. 8 sieve, and not more than 20% pass through a No. 60 sieve.
- Coarse (No. 20): All particles pass through a No. 20 sieve, and not more than 40% pass through a No. 60 sieve.
- Moderately coarse (No. 40): All particles pass through a No. 40 sieve, and not more than 40% pass through a No. 80 sieve.

Table 6.1	OPENING OF STANDARD SIEVES
SIEVE NUMBER	**SIEVE OPENING**
2.0	9.50 mm
3.5	5.60 mm
4.0	4.75 mm
8.0	2.36 mm
10.0	2.00 mm
20.0	850.00 μm
30.0	600.00 μm
40.0	425.00 μm
50.0	300.00 μm
60.0	250.00 μm
70.0	212.00 μm
80.0	180.00 μm
100.0	150.00 μm
120.0	125.00 μm
200.0	75.00 μm
230.0	63.00 μm
270.0	53.00 μm
325.0	45.00 μm
400.0	38.00 μm

Source: USP 31–NF 26.

- Fine (No. 60): All particles pass through a No. 60 sieve, and not more than 40% pass through a No. 100 sieve.
- Very fine (No. 80): All particles pass through a No. 80 sieve. There is no limit to greater fineness.

Granules typically fall within the range of 4- to 12-sieve size, although granulations of powders prepared in the 12- to 20-sieve range are sometimes used in tablet making.

- Dissolution rate of particles intended to dissolve; drug micronization can increase the rate of drug dissolution and its bioavailability.
- Suspendability of particles intended to remain undissolved but uniformly dispersed in a liquid vehicle (e.g., fine dispersions have particles ~0.5 to 10 μm)
- Uniform distribution of a drug substance in a powder mixture or solid dosage form to ensure dose-to-dose content uniformity (3)
- Penetrability of particles intended to be inhaled for deposition deep in the respiratory tract (e.g., 1 to 5 μm) (4)
- Lack of grittiness of solid particles in dermal ointments, creams, and ophthalmic preparations (e.g., fine powders may be 50 to 100 μm in size)

A number of methods exist for the determination of particle size, including the following (Physical Pharmacy Capsule 6.1):

PHYSICAL PHARMACY CAPSULE **6.1**

Micromeritics

Micromeritics is the science of small particles; a particle is any unit of matter having defined physical dimensions. It is important to study particles because most drug dosage forms are solids, solids are not static systems, the physical state of particles can be altered by physical manipulation, and particle characteristics can alter therapeutic effectiveness.

Micromeritics is the study of a number of characteristics, including particle size and size distribution, shape, angle of repose, porosity, true volume, bulk volume, apparent density, and bulkiness.

PARTICLE SIZE

A number of techniques can be used to determine particle size and size distributions. Particle size determinations are complicated by the fact that particles are not uniform in shape. Only two relatively simple examples are provided for a detailed calculation of the average particle size of a powder mixture. Other methods are generally discussed. The techniques used include the microscopic method and the sieving method.

The microscopic method can include not fewer than 200 particles in a single plane using a calibrated ocular on a microscope. Given the following data, what is the average diameter of the particles?

SIZE OF COUNTED PARTICLES (μM)	MIDDLE VALUE μM "D"	NO. OF PARTICLES PER GROUP "N"	"ND"
40–60	50	15	750
60–80	70	25	1,750
80–100	90	95	8,550
100–120	110	140	15,400
120–140	130	80	10,400
		$\Sigma n = 355$	$\Sigma nd = 36,850$

PHYSICAL PHARMACY CAPSULE 6.1 CONT.

$$d_{av} = \frac{\Sigma nd}{\Sigma n} = \frac{36,850}{355} = 103.8\,\mu m$$

The sieving method entails using a set of US standard sieves in the desired size range. A stack of sieves is arranged in order, the powder placed in the top sieve, the stack shaken, the quantity of the powder resting on each sieve weighed, and this calculation performed:

SIEVE	ARITHMETIC MEAN OPENING (MM)	WEIGHT RETAINED (G)	% RETAINED	% RETAINED × MEAN OPENING (MM)
20/40	0.630	15.5	14.3	9.009
40/60	0.335	25.8	23.7	7.939
60/80	0.214	48.3	44.4	9.502
80/100	0.163	15.6	14.3	2.330
100/120	0.137	3.5	3.3	0.452
		108.7	100.0	29.232

$$d_{av} = \frac{\sum(\%\,retained) \times (average\ size)}{100} = \frac{29,232}{100} = 0.2923\,mm$$

Another method of particle size determination entails sedimentation using the Andreasen pipette, a special cylindrical container from which a sample can be removed from the lower portion at selected intervals. The powder is dispersed in a nonsolvent in the pipette and agitated, and 20-mL samples are removed over time. Each 20-mL sample is dried and weighed. The particle diameters can be calculated from this equation:

$$d = \frac{18h\eta}{(\rho_i - \rho_e)gt}$$

where

    d is the diameter of the particles,
    h is the height of the liquid above the sampling tube orifice,
    h is the viscosity of the suspending liquid,
    $\rho_i - \rho_e$ is the density difference between the suspending liquid and the particles,
    g is the gravitational constant, and
    t is the time in seconds.

Other methods of particle size determinations include elutriation, centrifugation, permeation, adsorption, electronic sensing zone (the Coulter counter), and light obstruction. The last includes both standard light and laser methods. In general, the resulting average particle sizes by these techniques can provide the average particle size by weight (sieve method, light scattering, sedimentation method) and the average particle size by volume (light scattering, electronic sensing zone, light obstruction, air permeation, and even the optical microscope).

ANGLE OF REPOSE

The angle of repose is a relatively simple technique for estimating the flow properties of a powder. It can easily be determined by allowing a powder to flow through a funnel and fall freely

PHYSICAL PHARMACY CAPSULE 6.1 CONT.

onto a surface. The height and diameter of the resulting cone are measured, and the angle of repose is calculated from this equation:

$$\tan \theta = h/r$$

where

h is the height of the powder cone and
r is the radius of the powder cone.

EXAMPLE 1

A powder was poured through the funnel and formed a cone 3.3 cm high and 9 cm in diameter. What is the angle of repose?

$$\tan \theta = h/r = 3.3/4.5 = 0.73$$

$$\text{arc } \tan 0.73 = 36.25°$$

Powders with a low angle of repose flow freely, and powders with a high angle of repose flow poorly. A number of factors, including shape and size, determine the flow properties of powders. Spherical particles flow better than needles. Very fine particles do not flow as freely as large particles. In general, particles in the size range of 250 to 2,000 mm flow freely if the shape is amenable. Particles in the size range of 75 to 250 mm may flow freely or cause problems, depending on shape and other factors. With most particles smaller than 100 mm, flow is a problem.

POROSITY, VOID, AND BULK VOLUME

If spheres and the different ways they pack together are used as an example, two possibilities arise. The closest packing may be rhombus–triangle, in which angles of 60 and 120 degrees are common. The space between the particles, the void, is about 0.26, resulting in porosity, as described later, of about 26%. Another packing, cubical, with the cubes packed at 90-degree angles to each other, may be considered. This results in a void of about 0.47 or a porosity of about 47%. This is the most open type of packing. If particles are not uniform, the smaller particles will slip into the void spaces between the larger particles and decrease the void areas.

Packing and flow are important, as they affect the size of the container required for packaging, the flow of granulations, the efficiency of the filling apparatus for making tablets and capsules, and the ease of working with the powders.

The characteristics used to describe powders include porosity, true volume, bulk volume, apparent density, true density, and bulkiness. The photo is a tapped density tester.

Tapped density tester (Courtesy of Varian Inc.)

PHYSICAL PHARMACY CAPSULE 6.1 CONT.

Porosity is

$$\text{Void} \times 100$$

This value should be determined experimentally by measuring the volume occupied by a selected weight of a powder, V_{bulk}. The true volume, V, of a powder is the space occupied by the powder exclusive of spaces greater than the intramolecular space.

Void can be defined as

$$\frac{V_{bulk} - V}{V_{bulk}}$$

therefore, porosity is

$$\frac{V_{bulk} - V}{V_{bulk}} \times 100$$

and the bulk volume is

$$\text{true volume} + \text{porosity.}$$

APPARENT DENSITY, TRUE DENSITY, AND BULKINESS

The apparent density, ρ_a, is

$$\frac{\text{weight of the sample}}{V_{bulk}}$$

The true density, ρ, is

$$\frac{\text{weight of the sample}}{V}$$

The bulkiness, B, is the reciprocal of the apparent density,

$$B = 1/\rho_a$$

EXAMPLE 2

A selected powder has a true density (ρ) of 3.5 g/cc. Experimentally, 2.5 g of the powder measures 40 mL in a cylindrical graduate. Calculate the true volume, void, porosity, apparent density, and bulkiness.

True volume:

$$\text{Density} = \text{mass(weight)/volume}$$
$$\text{Volume} = \text{mass(weight)/density}$$
$$2.5\,\text{g}/(3.5\,\text{g/cc})0.715\,\text{cc}$$

Void:

$$\frac{V_{bulk} - V}{V_{bulk}} = \frac{40\,\text{mL} - 0.715\,\text{mL}}{40\,\text{mL}} = 0.982$$

PHYSICAL PHARMACY CAPSULE 6.1 CONT.

Porosity:

$$\text{Void} \times 100 = 0.982 \times 100 = 98.2\%$$

Apparent density:

$$(\text{Pa}) = \frac{2.5\ \text{g}}{40\ \text{mL}} = 0.0625\ \text{g/mL}$$

Bulkiness:

$$1/\text{Pa} = \frac{1}{0.06265(\text{g/mL})} = 16\ \text{mL/g}$$

Powders with a low apparent density and a large bulk volume are considered light, and those with a high apparent density and a small bulk volume are considered heavy.

- Sieving, in which particles are passed by mechanical shaking through a series of sieves of known and successively smaller size and the proportion of powder passing through or being withheld on each sieve is determined (range about 40 to 9,500 μm, depending upon sieve sizes) (2).
- Microscopy, in which sample particles are sized through the use of a calibrated grid background or other measuring device (range 0.2 to 100 μm)
- Sedimentation rate, in which particle size is determined by measuring the terminal settling velocity of particles through a liquid medium in a gravitational or centrifugal environment (range 0.8 to 300 μm). Sedimentation rate may be calculated from Stokes law.
- Light energy diffraction or light scattering, in which particle size is determined by the reduction in light reaching the sensor as the particle, dispersed in a liquid or gas, passes through the sensing zone (range 0.2 to 500 μm) (4). Laser scattering utilizes a He–Ne laser, silicon photo diode detectors, and an ultrasonic probe for particle dispersion (range 0.02 to 2,000 μm) (5).
- Laser holography, in which a pulsed laser is fired through an aerosolized particle spray and is photographed in three dimensions with a holographic camera, allowing the particles to be individually imaged and sized (range 1.4 to 100 μm) (6).
- Cascade impaction, which is based on the principle that a particle driven by an airstream will hit a surface in its path, provided its inertia is sufficient to overcome the drag force that tends to keep it in the airstream (7). Particles are separated into various size ranges by successively increasing the velocity of the airstream in which they are carried.
- Online methods for determining particle sizes during production are available (8).

These methods and others may be used for the analysis of particle size and shape. For some materials, a single method may be sufficient; however, a combination of methods is frequently preferred to provide greater certainty of size and shape parameters. Most commercial particle size analyzers are automated and linked with computers for data processing, distribution analysis, and printout.

The science of small particles is discussed further in Physical Pharmacy Capsule 6.1, Micromeritics. Physical Pharmacy Capsule 6.2, Particle Size Reduction, points out that a reduction in particle size increases the number of particles and the total surface area.

PHYSICAL PHARMACY CAPSULE **6.2**

Particle Size Reduction

Comminution, reduction of the particle size of a solid substance to a finer state, is used to facilitate crude drug extraction, increase the dissolution rates of a drug, aid in the formulation of pharmaceutically acceptable dosage forms, and enhance the absorption of drugs. The reduction in the particle size of a solid is accompanied by a great increase in the specific surface area of that substance. An example of the increase in the number of particles formed and the resulting surface area is as follows:

EXAMPLE

INCREASE IN NUMBER OF PARTICLES

If a powder consists of cubes 1 mm on edge and it is reduced to particles 10 mm on edge, what is the number of particles produced?

1. 1 mm equals 1,000 mm.
2. 1,000/10 mm = 100 pieces produced on each edge; that is, if the cube is sliced into 100 pieces on the x-axis, each 10 mm long, 100 pieces result.
3. If this is repeated on the y- and z-axes, the result is $100 \times 100 \times 100 = 1$ million particles produced, each 10 mm on edge, for each original particle 1 mm on edge. This can also be written as $(10^2)^3 = 10^6$.

INCREASE IN SURFACE AREA

What increase in the surface area of the powder is produced by decreasing the particle size from 1 to 10 mm?

1. The 1-mm cube has six surfaces, each 1 mm on edge. Each face has a surface area of 1 mm^2. Because there are six faces, this is 6-mm^2 surface area per particle.
2. Each 10-mm cube has six surfaces, each 10 mm on edge. Each face has a surface area of $10 \times 10 = 100$ mm^2. Because there are six faces, this is 6×100 mm^2, or 600 mm^2 surface area per particle. Since 10^6 particles resulted from comminuting the 1-mm cube, each 10 mm on edge, the surface area now is 600 $mm^2 \times 10^6$, or 6×10^8 mm^2.
3. To get everything in the same units for ease of comparison, convert the 6×10^8 mm^2 into square millimeters as follows.
4. Since there are 1,000 mm/mm, there must be $1,000^2$, or 1 million mm^2/mm^2. This is more appropriately expressed as 10^6 mm^2/mm^2,

$$\frac{6 \times 10^8 \, \mu m^2}{10^6 \, \mu m^2/mm^2} = 6 \times 10^2 \, mm^2$$

The surface areas have been increased from 6 to 600 mm^2 by the reduction in particle size of cubes 1 mm on edge to cubes 10 mm on edge, a 100-fold increase in surface area. This can have a significant increase in the rate of dissolution of a drug product.

Comminution of Drugs

On a small scale, the pharmacist reduces the size of chemical substances by grinding with a mortar and pestle. A finer grinding action is accomplished by using a mortar with a rough surface (as a porcelain mortar) than one with a smooth surface (as a glass mortar). Grinding a drug in a mortar to reduce its particle size is termed *trituration or comminution*. On a large scale, various types of mills and pulverizers may be used to reduce particle size. Figure 6.1 shows one such piece of

FIGURE 6.1 A FitzMill comminutor, model VFS-D6A-PCS, used for particle reduction, with attached containment system for protection of environment and prevention of product contamination. (Courtesy of the Fitzpatrick Company.)

equipment, a FitzMill comminuting machine with a product containment system. Through the grinding action of rapidly moving blades in the comminuting chamber, particles are reduced in size and passed through a screen of desired dimension to the collection container. The collection and containment system protects the environment from chemical dust, reduces product loss, and prevents product contamination.

Levigation is commonly used in small-scale preparation of ointments and suspensions to reduce the particle size and grittiness of the added powders. A mortar and pestle or an ointment tile may be used. A paste is formed by combining the powder and a small amount of liquid (the *levigating agent*) in which the powder is insoluble. The paste is then triturated, reducing the particle size. The levigated paste may then be added to the ointment base and the mixture made uniform and smooth by rubbing them together with a spatula on the ointment tile. A figure

8 track is commonly used to incorporate the materials. Mineral oil and glycerin are commonly used levigating agents.

Blending Powders

When two or more powdered substances are to be combined to form a uniform mixture, it is best to reduce the particle size of each powder individually before weighing and blending. Depending on the nature of the ingredients, the amount of powder, and the equipment, powders may be blended by spatulation, trituration, sifting, and tumbling.

Spatulation is blending small amounts of powders by movement of a spatula through them on a sheet of paper or an ointment tile. It is not suitable for large quantities of powders or for powders containing potent substances, because homogeneous blending is not as certain as other methods. Very little compression or compacting of the powder results from spatulation, which is especially suited to mixing solid substances that form *eutectic mixtures* (or liquefy) when in close and prolonged contact with one another (Table 6.2). To diminish contact, a powder prepared from such substances is commonly mixed in the presence of an inert diluent, such as light magnesium oxide or magnesium carbonate, to separate the troublesome agents physically.

Trituration may be employed both to comminute and to mix powders. If simple admixture is desired without the special need for comminution, the glass mortar is usually preferred. When a small amount of a potent substance is to be mixed with a large amount of diluent, the *geometric dilution* method is used to ensure the uniform distribution of the potent drug. This method is especially indicated when the potent substance and other ingredients are the same color and a visible sign of mixing is lacking. By this method, the potent drug is placed with an approximately equal volume of the diluent in a mortar and is mixed thoroughly by trituration. Then, a second portion of diluent equal in volume to the mixture is added and the trituration repeated. This process is continued by adding an equal volume of diluent to the powder

Table 6.2	SUBSTANCES THAT SOFTEN OR LIQUIFY WHEN MIXED

Acetanilide

Acetophenetidin

Aminopyrine

Antipyrine

Aspirin

Benzocaine

Beta-naphthol

Camphor

Chloral hydrate

Lidocaine

Menthol

Phenacetin

Phenol

Phenyl salicylate

Prilocaine

Resorcinol

Salicylic acid

Thymol

FIGURE 6.2 Industrial-size solid-state processor or twin shell blender used to mix solid particles. (Courtesy of Abbott Laboratories.)

sift or percolate through coarse particles and end up at the bottom of the container and actually "lift" the larger particles to the surface. Fine, aerated powders with differences in particle size or density may result in a striation pattern and may occur during powder transfer. Dusting occurs when the finer, lighter

mixture and repeating this until all of the diluent is incorporated. Some pharmacists add an inert colored powder to the diluent before mixing to permit visual inspection of the mixing process.

Powders may also be mixed by passing them through sifters like those used in the kitchen to sift flour. Sifting results in a light, fluffy product. This process is not acceptable for the incorporation of potent drugs into a diluent powder.

Another method of mixing powders is tumbling the powder in a rotating chamber. Special small-scale and large-scale motorized powder blenders mix powders by tumbling them (Figs. 6.2 to 6.5). Mixing by this process is thorough but time consuming. Such blenders are widely employed in industry, as are mixers that use motorized blades to blend powders in a large vessel.

Segregation is an undesirable separation of the different components of the blend. Segregation may occur by sifting or percolation, air entrapment (fluidization), and particle entrapment (dusting). Fine particles tend to

FIGURE 6.3 Ribbon blender used for mixing powders and preparing granulations. (Courtesy of Littleford Day.)

FIGURE 6.4 Laboratory-scale V-blender. (Courtesy of GlobePharma.)

particles remain suspended in air longer and do not settle as quickly as the larger or denser particles. General guidelines to minimize or prevent segregation include (*a*) minimum number of transfer steps and drop heights; (*b*) control of dust generation; (*c*) control of fluidization of the powder; (*d*) slow fill/transfer rate; (*e*) appropriate venting; (*f*) use of a deflector, vane, or distributor; and (*g*) proper hopper design and operating valves (if present).

Eutectics

Some powders may become sticky or pasty, or they may liquefy when mixed together, such as those listed in Table 6.2. To keep the

FIGURE 6.5 Laboratory-scale Triple V-type blender. (Courtesy of GlobePharma.)

powders dry, one can mix them with a bulky powder adsorbent such as light magnesium oxide or magnesium carbonate. Also, these powders should be triturated very lightly on a pill tile by using a spatula for mixing rather than a mortar and pestle. The latter will cause compression and make the problem worse. It may also be advisable to double wrap the papers. Mixing these powders with the bulky powders first and then performing a light blending can minimize the problem. Another approach is to first make the eutectic and then adsorb the paste or liquid that results onto a bulky powder. One also has the option of dispensing the ingredients separately. After preparation, the charts can be dispensed in a plastic bag.

Hygroscopic and Deliquescent Powders

Hygroscopic powders will absorb moisture from the air. Deliquescent powders will absorb moisture from the air to the extent that they will partially or wholly liquefy. These problems must be overcome for the powder to be acceptable to the patient and usable. The best approach is to dispense the ingredients in tight containers and incorporate a desiccant packet or capsule when necessary. The patient should be instructed to store the powder in a dry place in a tightly closed container. To lessen the extent of the problem, the compounding pharmacist can in some situations dilute the powder with an inert drying powder to reduce the amount of surface area exposed to the moisture. Common hygroscopic and deliquescent powders are listed in Table 6.3.

Efflorescent Powders

An *efflorescent powder* (Table 6.4) is a crystalline powder that contains water of hydration or crystallization. This water can be liberated either during manipulations or on exposure to a low-humidity environment. If this occurs, the powder will become sticky and pasty, or it may even liquefy. One approach is to use an anhydrous salt form of the drug, keeping in mind the potency differential between its anhydrous form and its hydrated

Table 6.3	COMMON HYGROSCOPIC AND DELIQUESCENT POWDERS

Ammonium bromide

Ammonium chloride

Ammonium iodide

Calcium bromide

Calcium chloride

Ephedrine sulfate

Hydrastin hydrochloride

Hydrastine sulfate

Hyoscyamine hydrobromide

Hyoscyamine sulfate

Iron and ammonium citrate

Lithium bromide

Pepsin

Phenobarbital sodium

Physostigmine hydrobromide

Physostigmine hydrochloride

Physostigmine sulfate

Pilocarpine alkaloid

Potassium acetate

Potassium citrate

Sodium bromide

Sodium iodide

Sodium nitrate

Zinc chloride

Table 6.4	COMMON EFFLORESCENT POWDERS

Alums

Atropine sulfate

Caffeine

Calcium lactate

Citric acid

Cocaine

Codeine

Codeine phosphate

Codeine sulfate

Ferrous sulfate

Morphine acetate

Quinine bisulfate

Quinine hydrobromide

Quinine hydrochloride

Scopolamine hydrobromide

Sodium acetate

Sodium carbonate (decahydrate)

Sodium phosphate

Strychnine sulfate

Terpin hydrate

form. Another method is to include a drying bulky powder and to use a light, noncompacting method of mixing the powders.

Explosive Mixtures

Some combinations of powders (Table 6.5) may react violently when mixed together. Special precautions must be taken if it is necessary to prepare a formulation containing these mixtures.

Incorporation of Liquids

A liquid that is to be incorporated into a dry powder can be adsorbed onto an inert material (carrier) such as lactose or starch and then geometrically introduced into the bulk of the powder. Pasty material can be added to dry powder by mixing it with increasing quantities of the powder, which will dry out the paste. It is best to add some materials by preparing an alcoholic solution and spraying it evenly on the powder, which has been spread out on a pill tile. The alcohol, or another suitable solvent, should then be allowed to evaporate, leaving the ingredient uniformly dispersed. This method may be especially suitable for high-potency drugs or flavoring agents because it minimizes the possibility that clumps of active drug will develop in the powder blend.

MEDICATED POWDERS

Some medicated powders are intended to be used internally and others, externally. Most powders for internal use are taken orally after mixing with water or in the case of infants in their infant formulas. Some

Table 6.5	COMMON OXIDIZING AND REDUCING AGENTS THAT MAY REACT VIOLENTLY WHEN MIXED

OXIDIZING AGENTS	REDUCING AGENTS
Bromine	Alcohol
Chlorates	Bisulfites
Chloric acid	Bromides
Chlorine	Charcoal
Chromates	Glycerin
Dichromates	Hydriodic acid
Ethyl nitrite spirit	Hypophosphites
Hydrogen peroxide	Hypophosphorous acid
Hypochlorites	Iodides
Hypochlorous acid	Lactose
Iodine	Nitrites (in some situations)
Nitrates	Organic substances (in general)
Nitric acid	Phosphorus
Nitrites	Sugar
Nitrohydrochloric acid	Sulfides
Nitrous acid	Sulfites
Perborates	Sulfur
Permanganates	Sulfurous acid
Permanganic acid	Tannic acid
Peroxides	Tannins
Potassium chlorate	Thiosulfates
Potassium dichromate	Volatile oils
Potassium nitrate	
Potassium permanganate	
Sodium peroxide	
Silver nitrate	
Silver oxide	
Silver salts	
Trinitrophenol	

powders are intended to be inhaled for local and systemic effects. Other dry powders are commercially packaged for constitution with a liquid solvent or vehicle, some for administration orally, others for use as an injection, and still others for use as a vaginal douche. Medicated powders for external use are dusted on the affected area from a sifter-type container or applied from a powder aerosol. Powders intended for external use should bear a label marked EXTERNAL USE ONLY or a similar label.

Medicated powders for oral use may be intended for local effects (e.g., laxatives) or systemic effects (e.g., analgesics) and may be preferred to counterpart tablets and capsules by patients who have difficulty swallowing solid dosage forms. The doses of some drugs are too bulky to be formed into tablets or capsules of convenient size, so they may be administered as powders. For administration, they can be mixed with a liquid or soft food. Powders taken orally for systemic use may be expected to result in faster rates of dissolution and absorption than solid dosage forms, because there is immediate contact with the gastric fluids; however, the actual advantage in terms of therapeutic response may be negligible or only minimal, depending on the drug release characteristics of the counterpart products. A primary disadvantage of the use of oral powders is the undesirable taste of the drug.

Some medications, notably antibiotics for children, are intended for oral administration as liquids but are relatively unstable in liquid form. They are provided to the pharmacist by the manufacturer as a dry powder or granule for constitution with a specified quantity of purified water at the time of dispensing. Under labeled conditions of storage, the resultant product remains stable for the prescribed period of use, generally up to 2 weeks. Sterile dry powders intended to be constituted with water or another suitable solvent prior to administration by injection are discussed in Chapter 15.

Aerosol Powders

Some medicated powders are administered by inhalation with the aid of dry powder inhalers (DPIs), which deliver micronized particles of medication in metered quantities (Fig. 6.6). A DPI is a device used to administer an inhalation powder in a finely divided state

FIGURE 6.6 Metered inhalation aerosol containing a micronized medicated powder and inert propellants. Each dose is delivered through the mouthpiece upon activation of the aerosol unit's valve.

suitable for oral inhalation by the patient. An inhalation powder is one used with a device that aerosolizes and delivers an accurately metered amount.

Most of these products are used in the treatment of asthma and other bronchial disorders that require distribution of medication deep in the lungs (Fig. 6.7). To accomplish this, the particle size of the micronized medication is prepared in the range of 1 to 6 μm in diameter. In addition to the therapeutic
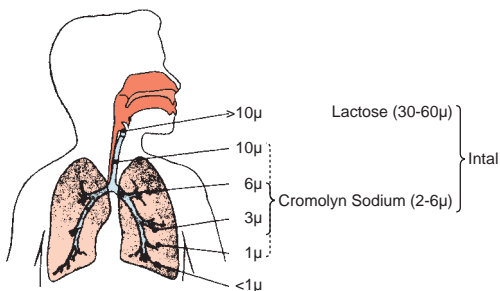
agent, these products contain inert propellants and pharmaceutical diluents, such as crystalline alpha-lactose monohydrate, to aid the formulation's flow properties and metering uniformity and to protect the powder from humidity (9). Powder blowers or insufflators (Fig. 6.8) may be used to deliver dry powders to various parts of the body, for example, the nose, throat, lung, and vagina. Depression of the device's rubber bulb causes turbulence of the powder in the vessel, forcing it out through the orifice in the tip.

Inhalation powders, commonly known as dry DPIs, consist of a mixture of active pharmaceutical ingredients (APIs) and typically the carrier; and all formulation components exist in a finely divided solid state packaged in a suitable container closure system. The dose is released from the packaging by a mechanism and is mobilized into a fine dispersion upon oral inhalation by the patient. The formulation may be packaged in premetered or device-metered units. Premetered DPIs contain a previously measured amount of formulation in individual units (e.g., capsules, blisters) that are inserted into the device before use. Premetered DPIs may also contain premetered dose units as ordered multidose assemblies in the delivery system. Premetered DPIs include a mechanism designed to pierce the capsule or open the unit-dose container and allow mobilization and aerosolization of the powder

FIGURE 6.7 Relation of particle size to airway penetration. (Courtesy of Fisons Corporation.)

FIGURE 6.8 A general-purpose powder blower or insufflator. The powder is placed in the vessel. When the rubber bulb is depressed, internal turbulence disperses the powder and forces it from the orifice. Powders may be delivered to various body locations such as the nose, throat, tooth sockets, or skin. (Courtesy of DeVilbiss Company.)

by the patient inhaling through the integral mouthpiece. Device-metered DPIs have an internal reservoir that contains a sufficient quantity of formulation for multiple doses that are metered by the device during actuation by the patient. To facilitate dosing compliance, device-metered DPIs incorporate a dosing administration information mechanism, such as a dose counter or a dose indicator system.

Example Oral Inhalation Powders

Advair Diskus 100/50, 250/50, and 500/50 contains fluticasone propionate 100, 250, and 500 mg, respectively, along with salmeterol 50 mg in a powder for inhalation. Fluticasone propionate is a corticosteroid, and salmeterol xinafoate is a highly selective β_2-adrenergic bronchodilator. The Advair Diskus is a specially designed plastic device containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister in the device contains 100, 250, or 500 mg of microfine fluticasone propionate and 72.5 mg of microfine salmeterol xinafoate salt, the equivalent of 50 mg of salmeterol base, in 12.5 mg of formulation also containing lactose. Each blister contains one complete dose of medication. The blister is opened by activating the device, and the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece (10).

Fluticasone propionate inhalation powder is available alone as Flovent Rotadisk 50, 100, and 250 mg marketed to be used with the Diskhaler inhalation device. Each double-foil Rotadisk contains four blisters; each blister contains 50, 100, or 250 mg of fluticasone propionate blended with lactose to a total weight of 25 mg per blister. When the Rotadisk is placed in the Diskhaler, a blister containing the medication is pierced, and the fluticasone propionate is dispersed into the airstream as with the Advair Diskus unit (11).

The Foradil Aerolizer is a capsule dosage form for oral inhalation only in the Aerolizer inhaler. The capsule contains a dry powder formulation of 12 mg of formoterol fumarate and 25 mg of lactose as a carrier. Formoterol fumarate is a long-acting selective β_2-adrenergic receptor agonist acting locally in the lung as a bronchodilator. To use this delivery system, the capsule is placed inside the well of the Aerolizer inhaler, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The patient inhales rapidly and deeply through the mouthpiece, dispersing the formoterol fumarate formulation into the air for inhalation (12).

Zanamivir for inhalation (Relenza) is used to treat influenza. It is a neuraminidase inhibitor. Relenza is packaged in Rotadisks and is administered using a Diskhaler, as previously described. For Relenza, the usual dose is two inhalations (one blister per inhalation) twice daily for 5 days; therefore, four blisters will be used each day. Relenza should be stored at room temperature; it is not a childproof container (13).

Bulk and Divided Powders

Medicated powders may be provided to the patient in bulk or may be divided into unit-of-use packages. Some powders are packaged by manufacturers, whereas others are prepared and packaged by the pharmacist.

Bulk Powders

Among the bulk powders available in prepackaged amounts are (*a*) antacids (e.g., sodium bicarbonate) and laxatives (e.g., psyllium [Metamucil]), which the patient takes by mixing with water or another beverages before swallowing; (*b*) douche powders (e.g., Massengill powder), dissolved in warm water by the patient for vaginal use; (*c*) medicated powders for external application to the skin, usually topical anti-infectives (e.g., bacitracin zinc and polymyxin B sulfate) or antifungals (e.g., tolnaftate); and (*d*) brewer's yeast powder containing B-complex vitamins and other nutritional supplements. In some cases, a small measuring scoop, spoon, or other device is dispensed with the powder for measuring the dose of the drug.

Dispensing powder medication in bulk quantities is limited to nonpotent substances. Powders containing substances that should

be administered in controlled dosage are supplied to the patient in divided amounts in folded papers or packets. Patients should be educated about appropriate handling, storage, measurement, and preparation of bulk powder prescription and nonprescription products in addition to the customary counseling at the time of dispensing or purchase. Generally, these products are stored at room temperature in a clean, dry place. These products should be kept out of the reach of children and animals. Patients should be instructed how to measure the appropriate amount of the powder and be told the type of liquid or vehicle to use to deliver the medication consistent with package and/or physician instructions.

Divided Powders

After a powder has been properly blended (using the geometric dilution method for potent substances), it may be divided into individual dosing units based on the amount to be taken or used at a single time. Each divided portion of powder may be placed on a small piece of paper (Latin *chartula*; abbrev. chart.; powder paper) that is folded to enclose the medication. A number of commercially prepared premeasured products are available in folded papers or packets, including headache powders (e.g., BC powders), powdered laxatives (e.g., psyllium mucilloid, cholestyramine resin), and douche powders (e.g., Massengill powder packets).

Divided powders may be prepared by the pharmacist as follows. Depending on the potency of the drug substance, the pharmacist decides whether to weigh each portion of powder separately before enfolding in a paper or to approximate each portion by using the block-and-divide method. By the latter method, used only for nonpotent drugs, the pharmacist places the entire amount of the prepared powder on a flat surface such as a porcelain or glass plate, pill tile, or large sheet of paper and, with a large spatula, forms a rectangular or square block of the powder having a uniform depth. Then, using the spatula, the pharmacist cuts into the powder lengthwise and crosswise to delineate the appropriate number of smaller, uniform

blocks, each representing a dose or unit of medication. Each of the smaller blocks is separated from the main block with the spatula, transferred to a powder paper, and wrapped.

The powder papers may be of any size convenient to hold the amount of powder required, but the most popular commercially available sizes are 2.75 × 3.75 inch, 3 × 4.5 inch, 3.75 × 5 inch, and 4.5 × 6 inch. The papers may be (*a*) simple bond paper; (*b*) vegetable parchment, a thin, semiopaque paper with limited moisture resistance; (*c*) glassine, a glazed, transparent paper, also with limited moisture resistance; and (*d*) waxed paper, a transparent waterproof paper. The selection of the type of paper is based primarily on the nature of the powder. If the powder contains hygroscopic or deliquescent materials, waterproof or waxed paper should be used. In practice, such powders are double wrapped in waxed paper, and then for esthetic appeal, they are wrapped in bond paper. Glassine and vegetable parchment papers may be used when only a limited barrier against moisture is necessary. Powders containing volatile components should be wrapped in waxed or glassine papers. Powders containing neither volatile components nor ingredients adversely affected by air or moisture are usually wrapped in a white bond paper.

A certain degree of expertise is required in the folding of a powder paper, and practice is required for proficiency. For the technique and details of folding powder papers, see the ninth edition of this text.

Today, compounded powder papers are rarely used on an out-patient, community practice basis. Their use is usually limited to institutional and research practice. Commercial drug products that are provided in this drug delivery form include polyethylene glycol 3350 (i.e., MiraLAX), cholestyramine resin, pectin, L-glutamine, sodium phenylbutyrate, and wheat dextrin (i.e., Benefiber).

GRANULES

Granules are defined as a dosage form composed of dry aggregates of powder particles that may contain one or more APIs, with

or without other ingredients. They may be swallowed as such, dispersed in food, or dissolved in water. Granules are frequently compacted into tablets or filled into capsules, with or without additional ingredients.

As indicated previously, *granules* are prepared agglomerates of smaller particles of powder. They are irregularly shaped but may be prepared to be spherical. They are usually in the 4- to 12-mesh sieve size range, although granules of various mesh sizes may be prepared depending upon their application.

Granules are prepared by wet methods and dry methods. One basic wet method is to moisten the powder or powder mixture and then pass the resulting paste through a screen of the mesh size to produce the desired size of granules. The granules are placed on drying trays and are dried by air or under heat. The granules are periodically moved about on the drying trays to prevent adhesion into a large mass. Another type of wet method is fluid bed processing, in which particles are placed in a conical piece of equipment and are vigorously dispersed and suspended while a liquid excipient is sprayed on the particles and the product dried, forming granules or pellets of defined particle size (Figs. 6.9 and 6.10).

The dry granulation method may be performed in a couple of ways. By one method, the dry powder is passed through a roll compactor and then through a granulating machine (Fig. 6.11). A roll compactor, also
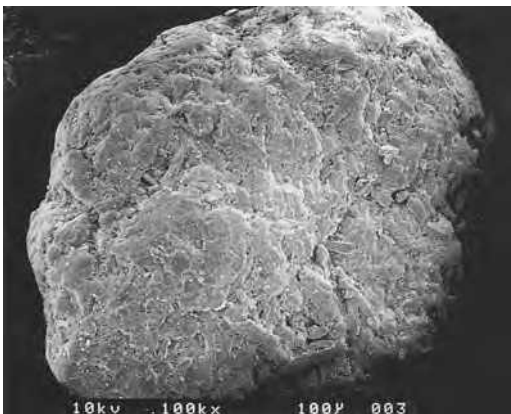

FIGURE 6.10 Large oven for drying granulations. (Courtesy of O'Hara Technologies.)

called a roll press or roller compactor, processes a fine powder into dense sheets or forms by forcing it through two mechanically rotating metal rolls running counter to each other (10). The surface of the compacting rolls may be smooth or may have pocket

FIGURE 6.9 Granule prepared with fluid bed technology. (Courtesy of Glatt Air Techniques.)

FIGURE 6.11 High-speed granulator–mixer. (Courtesy of Paddock Laboratories.)

indentations or corrugations that allow compaction of different forms and textures. The compacted powder is granulated to uniform particle size in a mechanical granulator. Powder compactors are generally combined in sequence in integrated compactor–granulation systems.

An alternative dry method, termed slugging, is the compression of a powder or powder mixture into large tablets or slugs on a compressing machine under 8,000 to 12,000 lb of pressure, depending on the physical characteristics of the powder. The slugs are generally flat-faced and are about 2.5 cm (1 inch) in diameter (14). The slugs are granulated into the desired particle size, generally for use in the production of tablets. The dry process often results in the production of fines, that is, powder that has not agglomerated into granules. These fines are separated, collected, and reprocessed. The wet and dry granulation methods as they pertain to tablet making are discussed in greater detail in Chapter 7.

Granules flow well compared to powders. For comparison, consider the pouring and flowing characteristics of granulated sugar and powdered sugar. Because of their flow properties, granulations are commonly used in tablet making to facilitate the free flow of material from the feeding container (or hopper) into the tablet presses.

Granules have other important characteristics. Because their surface area is less than that of a comparable volume of powder, granules are usually more stable to the effects of atmospheric humidity and are less likely to cake or harden upon standing. Granules also are more easily wetted by liquids than are certain light and fluffy powders (which tend to float on the surface) and are often preferred for dry products intended to be constituted into solutions or suspensions.

A number of commercial products containing antibiotic drugs that are unstable in aqueous solution are prepared as small granules for constitution by the pharmacist with purified water just prior to dispensing. The granules are prepared to contain not only the medicinal agent but also colorants, flavorants, and other pharmaceutical ingredients. Upon constitution, the resultant liquid has all of the desired medicinal and pharmaceutical features of a liquid pharmaceutical. Examples include Biaxin granules for oral suspension (clarithromycin, Abbott), Omnicef for oral suspension (cefdinir, Abbott), Augmentin ES-600 (amoxicillin/clavulanate potassium, GlaxoSmithKline), and Ceftin for oral suspension (cefuroxime axetil, GlaxoSmithKline).

Other types of granulated commercial products include Lactinex granules, a mixed culture of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* in 1-g packets used in the treatment of uncomplicated diarrhea and diarrhea due to antibiotic therapy. The granules are measured and mixed with water or another beverages, sprinkled on food, or eaten plain. Granulations of effervescent products may be compressed into tablet form, as Zantac EFFERdose tablets (GlaxoSmithKline). Effervescent granules and tablets are dissolved in water before use. The preparation of effervescent granulated salts is as follows.

Granular dosage forms are also used in veterinary medicine where they may be placed on top of or mixed with an animal's food. They are frequently provided with a measuring device to allow addition to feeds. The resultant mix facilitates dosing.
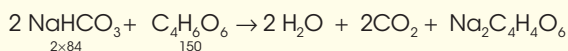
Effervescent Granulated Salts

An effervescent dosage form, frequently tablets or granules, contains ingredients that, when in contact with water, rapidly release carbon dioxide. The dosage form is dissolved or dispersed in water to initiate the effervescence prior to ingestion.

Effervescent salts are granules or coarse to very coarse powders containing a medicinal agent in a dry mixture usually composed of sodium bicarbonate, citric acid, and tartaric acid. When added to water, the acids and the base react to liberate carbon dioxide, resulting in effervescence. The resulting carbonated solution masks undesirable taste of any medicinal agent. Using granules or coarse particles of the mixed powders rather than small powder particles decreases the

rate of solution and prevents violent and uncontrollable effervescence. Sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution.

Using a combination of citric and tartaric acids rather than either acid alone avoids certain difficulties. When tartaric acid is used as the sole acid, the resulting granules readily lose their firmness and crumble. Citric acid alone results in a sticky mixture difficult to granulate.

A summary of the chemistry of effervescent granules may be found in Physical Pharmacy Capsule 6.3, Effervescent Granules.

Effervescent granules are prepared by two general methods: (*a*) the dry or fusion method and (*b*) the wet method.

PHYSICAL PHARMACY CAPSULE **6.3**

Effervescent Granules

Granules are dosage forms that consist of particles ranging from about 4 to 10 mesh in size (4.76 to 2.00 mm), formed by moistening blended powders and passing through a screen or a special granulator. These moist granules are either air- or oven-dried. A special form of granules can be used to provide a pleasant vehicle for selected drug products, especially those with a bitter or salty taste. This special formulation, an effervescent granule, may consist of mixtures of citric acid and/or tartaric acid and/or sodium biphosphate combined with sodium bicarbonate.

EXAMPLE

R_x

Active drug	500 mg/5 g tsp
in effervescent granule qs	120 g

Sig: Dissolve 1 teaspoonful in one-half glass of cool water, and drink. Repeat this every 8 hours.

It is desired to dispense this as a granule, so that the patient will measure out a teaspoonful (5 g) dose, mix, and administer. Since each dose weighs 5 g and the prescription consists of 120 g, there are 24 doses. Each dose contains 0.5 g of the active drug, which comes to 12 g of the active drug for the entire prescription. This requires 120 g – 12 g = 108 g of effervescent vehicle. A good effervescent blend consists of both citric acid and tartaric acid (1:2 ratio), since the former is rather sticky and the latter produces a chalky, friable granule. It is necessary to calculate the amount of each ingredient required to prepare 108 g of the granulation.

CITRIC ACID

$$\underset{3\times84}{3NaHCO_3} + \underset{210}{C_6H_8O_7 \cdot H_2O} \rightarrow 4H_2O + 3CO_2 + Na_3C_6H_5O_7$$

Citric acid 1 g (MW = 210) of citric acid reacts with 1.2 g (MW = 84) of sodium bicarbonate as obtained from the following:

$$\frac{1}{210} = \frac{x}{3 \times 84}$$

$$x = 1.2 \text{ g}$$

PHYSICAL PHARMACY CAPSULE 6.3 CONT.

TARTARIC ACID

$$2\ NaHCO_3 + \ C_4H_6O_6 \rightarrow 2\ H_2O\ +\ 2CO_2 +\ Na_2C_4H_4O_6$$
$$\quad\ \ 2\times84 \qquad\quad 150$$

Since it is desired to use a 1:2 ratio of citric acid to tartaric acid, 2 g (MW = 150) of tartaric acid reacts with sodium 2.24 g of bicarbonate according to the following calculation:

$$\frac{2}{150} = \frac{x}{2} \times 84$$

$$x = 2.24\ g$$

Therefore, 1.2 g and 2.24 g of sodium bicarbonate is required to react with 1 + 2 g of the combination of citric acid and tartaric acid. Since it is desired to leave a small amount of the acids unreacted to enhance palatability and taste, of the required 3.44 g (2.24 g + 1.2 g), only 3.4 g of sodium bicarbonate will be used.

Therefore, the ratio of the effervescent ingredients is 1:2:3.4 for the citric acid/tartaric acid/sodium bicarbonate. Since the prescription requires 108 g of the effervescent mix, the quantity of each ingredient can be calculated as follows:

1 + 2 + 3.4 = 6.4
1/6.4 × 108 g = 16.875 g of citric acid
2/6.4 × 108 g = 33.750 g of tartaric acid
3.4/6.4 × 108 g = 57.375 g of sodium bicarbonate
Total = 108 g
The prescription will require 12 g of the active drug and 108 g of this effervescent vehicle.

$$d_{av} = \frac{\Sigma nd}{\Sigma n} = \frac{36,850}{355} = 103.8\,\mu m$$

Dry or Fusion Method

In the fusion method, the one molecule of water present in each molecule of citric acid acts as the binding agent for the powder mixture. Before mixing the powders, the citric acid crystals are powdered and then mixed with the other powders of the same sieve size to ensure uniformity of the mixture. The sieves and the mixing equipment should be made of stainless steel or other material resistant to the effect of the acids. The mixing of the powders is performed as rapidly as is practical, preferably in an environment of low humidity to avoid absorption of moisture and a premature chemical reaction. After mixing, the powder is placed on a suitable dish in an oven at 34°C to 40°C. During the heating process, an acid-resistant spatula is used to turn the powder. The heat releases the water of crystallization from the citric acid, which, in turn, dissolves a portion of the powder mixture, setting the chemical reaction and consequently releasing some carbon dioxide. This causes the softened mass of powder to become somewhat spongy, and when it has reached the proper consistency (as bread dough), it is removed from the oven and rubbed through a sieve to produce granules of the desired size. A No. 4 sieve produces large granules, a No. 8 sieve prepares medium size granules, and a No. 10 sieve prepares small granules. The granules are dried at a temperature not exceeding 54°C and are immediately placed in containers and tightly sealed.

Wet Method

The wet method differs from the fusion method in that the source of binding agent is not the water of crystallization from the citric acid but the water added to alcohol as

the moistening agent, forming the pliable mass for granulation. In this method, all of the powders may be anhydrous as long as water is added to the moistening liquid. Just enough liquid is added (in portions) to prepare a mass of proper consistency; then the granules are prepared and dried in the same manner as previously described.

QUALITY CONTROL

Bulk Powders

The pharmacist should compare the final weight of the preparation with the theoretical weight. The powder should be examined for uniformity of color, particle size, flowability, and freedom from caking.

Divided Powders

For divided powders, the pharmacist should individually weigh the divided papers and then compare that weight with the theoretical weight. The packets should be checked to confirm uniformity.

PACKAGING/DISPENSING

The powder mixture is packaged according to its use. Bulk oral powders can be packaged in glass, plastic, metal, or other containers that have a wide mouth to allow use of the powder measure. Divided powders, or powder papers, must be individually folded. Topical powders can be poured into sifter-top containers or powder shakers, and insufflations can be filled into plastic puffer units.

Granules for reconstitution may be packaged in unit-of-use containers or in containers with sufficient quantities to accommodate a typical course of therapy (frequently 10 days to 2 weeks with antibiotic products). Packaging should provide suitable protection from moisture; this is particularly true for effervescent granules. Granules may be stored under controlled room temperature conditions unless other conditions are specifically noted. Many granule products specify refrigerated storage following reconstitution and direct the patient to discard unused contents after a specified date that is based on the stability of the API in the reconstituted preparation.

Effervescent granules (and tablets) are to be labeled to indicate they are not be swallowed directly. Reconstitution of granules must ensure complete wetting of all ingredients and sufficient time and agitation to allow the soluble components to dissolve. Specific instructions for reconstitution provided by the manufacturer should be carefully followed.

PATIENT COUNSELING

Reconstituted suspensions should be thoroughly mixed or shaken before use to resuspend the dispersed particulates. This is especially true of suspension preparations dosed from multiple-dose containers. For particularly viscous suspensions prone to air entrapment, instructions may advise the user how to shake the preparation to resuspend settled particles while minimizing air entrapment.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

A pharmaceutical manufacturer is planning to market a topical powder consisting of an antifungal agent in an inert powder vehicle. However, in the pilot plant scale-up, assay of the containers revealed that they did not have a uniform potency of the antifungal active ingredient. The USP 36–NF 31 monograph for a typical antifungal topical powder states that it is to contain not less than 90.0% and not more than 110.0% of the labeled amount of the active drug. This problem must be corrected before the product can proceed to full-scale manufacturing.

PHARMACEUTICS CASE STUDY CONT.

OBJECTIVE INFORMATION

The antifungal occurs as a white or nearly white crystalline powder with not more than a slight odor. It is only very slightly soluble in water and in ether and slightly soluble in alcohol. It has a true density in the range of 4.5 to 5.0 g/mL and an apparent density of 0.12 g/mL. It was sifted through a 40-mesh screen prior to blending.

The inert vehicle is talc that occurs as a very fine white or grayish-white crystalline powder. It is unctuous, adheres readily to the skin, and is free of grittiness. It is practically insoluble in dilute acids and alkalis, organic solvents, and water. It has a true density in the range of 2.7 to 2.8 and an apparent density of 0.05 g/mL. It has a specific surface area of 2.41 to 2.42 m²/g.

The powders are weighed and blended in a large V-blender. The powder is then moved to the hopper of a large packaging device. The machine vibrates significantly during packaging.

ASSESSMENT

It appears that the difference in the size and density of the two ingredients is sufficient to suggest a separation in the hopper of the packaging machine. The density of the antifungal is greater than that of the vehicle, and the particle size of the antifungal (40 mesh) is larger than that of the talc (very fine, ~ an 80-mesh powder). One would normally expect the finer powder to settle to the bottom, but since there is a difference in the density of these two powders, the antifungal appears to be settling. This would result in containers that would have varying amounts of the active drug.

PLAN

One approach to solving this problem is to reduce the particle size of the antifungal agent to be closer to that of the talc so their apparent densities are closer. Another possibility is to use a different packaging device with minimal vibration. Can you think of other reasonable approaches to solving this problem?

CLINICAL CASE STUDY

SUBJECTIVE INFORMATION

CC: E.M. is an 86-year-old adult ambulatory male (AAM) who resides in a nursing home with complaints of pain in his right heel.

PMH: HTN

Hyperlipidemia

Type II diabetes

Meds: Hydrochlorothiazide 50 mg po q am

Enalapril 5 mg po bid

Atorvastatin 10 mg po qhs

Metformin 1,000 mg po bid

Glyburide 5 mg po qd

ASA 81 mg po qd

Centrum 1 tablet po qd

PSH: Tonsillectomy at age 10

FH: Mother HTN, breast cancer, metastatic bone cancer

Father hyperlipidemia, type II diabetes

CLINICAL CASE STUDY CONT.

SH: (per KF)

(–) Tobacco

(–) EtOH

(–) Illicit drugs

(–) Caffeine

ALL: NKDA

OBJECTIVE INFORMATION

BP: 125/78
HR: 72
Ht: 5′7″
Wt: 230 lb
Wound with a high volume of yellow slough and exudate on right heel area

ASSESSMENT

Decubitus ulcer

PLAN

Recommend Debrisan (dextranomer) beads twice a day. Sprinkle the beads onto the ulcer to 3-mm (~0.1-inch) thickness. To prevent maceration, apply a nonocclusive dressing, and seal on all four sides. Remove the beads before they become fully saturated by irrigating the wound with sterile water or normal saline using a syringe. Apply a new layer of beads while the area is still moist to prevent pain. Change the dressing before the beads become fully saturated. The number of changes per day will depend on the amount of exudate produced and will vary from one to three times a day. Also, it is suggested that for easier removal, the dressing be changed before it is completely dry. Avoid contact with the eyes. Contact the physician if the condition worsens or persists beyond 14 to 21 days. The patient's position should be frequently changed to prevent continuous pressure on any single part of the body. Avoid positioning the patient on the right heel.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Create a listing of oral prescription antibiotic products, including concentration of active ingredient(s), prepared as small powders for reconstitution.
2. Create a listing of oral nonprescription products, including concentration of active ingredient(s), prepared as small granules or powders for reconstitution by the consumer.
3. Locate a compounding formulation for a powder dosage form, and, using appropriate pharmaceutics terms (i.e., comminute, levigate, spatulate, powder, particle size), describe the steps in its preparation.
4. Create a listing of 10 prescription drug products, including concentration of active ingredient(s) and suggested dosage regimen, which are available as encapsulated granules that when opened can be added to food or drink prior to administration. List three counseling points the pharmacist should provide the patient (or caregiver) when using these products.
5. Make a listing of conceivable ways a consumer/patient may misuse a medicated powder.

Individual Activities

1. In layman's terms, explain the proper administration of a metered inhalation aerosol containing a micronized medicated powder with inert ingredients.
2. Give examples of situations where pharmacists will use spatulation, trituration,

APPLYING THE PRINCIPLES AND CONCEPTS Cont.

and levigation techniques in the practice of pharmacy.

3. List counseling points to discuss with a patient who has trouble swallowing and is picking up a prescription for Celebrex. Discuss the potential application of the Pill Glide for the patient.

4. Create a listing of 10 prescription medications, including concentration of active ingredient(s) and suggested dosage regimen, prepared as small granules for reconstitution, and discuss the demographics of patients most likely to utilize this dosage form.

5. Describe drawbacks associated with the use of topical powder dosage forms, and provide examples of other dosage forms that would overcome these drawbacks.

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7 Capsules

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between hard gelatin and soft gelatin capsules
2. Compare and contrast advantages and disadvantages of hard gelatin and soft gelatin capsules
3. List categories of inert ingredients, with examples, which are employed in the compounding or manufacture of capsules
4. State USP compendial requirements for capsules
5. Define and differentiate weight variation from content uniformity
6. Describe appropriate techniques for compounding, inspecting, packaging, and storing capsules

When medications are to be administered orally to adults, capsules and tablets usually are preferred because they are conveniently carried, readily identified, and easily taken.

Consider the convenience of a patient carrying a day's, a week's, or a month's supply of capsules or tablets compared with equivalent doses of a liquid medication. With capsules and tablets, there is no need for spoons or other measuring devices, which may be inconvenient and may result in less than accurate dosing. Also, most capsules and tablets are tasteless when swallowed, which is not the case with oral liquid medication.

Numerous characteristics help to identify capsules and tablets, including the shapes and colors of capsules and tablets and the manufacturer's name and product code number commonly embossed or imprinted on their surface making them readily identifiable. This enhances communication between the patient and health care providers, assists patient compliance, and fosters safe and effective medication use.

Capsules and tablets are available for many medications in a variety of dosage strengths, providing flexibility to the prescriber and accurate individualized dosage for the patient.

From a pharmaceutical standpoint, solid dosage forms are efficiently and productively manufactured; they are packaged and shipped by manufacturers at lower cost and with less breakage than comparable liquid forms. They are also more stable and have a longer shelf life than do their liquid counterparts.

As discussed later in this chapter, the pharmacist often uses empty hard gelatin capsules for extemporaneous compounding of prescriptions. On occasion, a pharmacist may use commercially available capsules and tablets as the *source* of a medicinal agent when it is not otherwise available. In these instances, the pharmacist must consider any excipients in the commercial product to ensure compatibility with the other ingredients in the compounded prescription. Capsules and tablets designed to provide modified drug release are discussed in Chapter 9.

Dosage forms that must be left intact include enteric-coated tablets, designed to pass

through the stomach for drug release and absorption in the intestine; extended-release dosage forms, designed to provide prolonged release of the medication; and sublingual or buccal tablets, formulated to dissolve under the tongue or in the mouth (1). If the patient cannot swallow an intact solid dosage form, an alternative product, such as a chewable tablet, instant dissolving tablet, oral liquid, oral or nasal inhalation solution, suppository, or injection, may be employed.

OVERVIEW OF CAPSULES

Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin. Gelatin capsule shells may be *hard* or *soft*, depending on their composition. The shells may be composed of two pieces, a body and a cap, or they may be composed of a single piece. Two-piece capsules are commonly referred to as hard-shell capsules, and one-piece capsules are often referred to as soft-shell capsules.

Most filled capsules are intended to be swallowed whole. However, it is fairly common in hospitals and extended care facilities for a caregiver to open capsules or crush tablets to mix with food or drink, especially for children or other patients unable to swallow solid dosage forms. This should be done only with the concurrence of the pharmacist, since the drug-release characteristics of certain dosage forms can be altered and can adversely affect the patient's welfare.

HARD GELATIN CAPSULES

Hard gelatin capsule shells are used in most commercial medicated capsules. They are also commonly employed in clinical drug trials to compare the effects of an investigational drug with those of another drug product or placebo. The community pharmacist also uses hard gelatin capsules in the extemporaneous compounding of prescriptions. The empty capsule shells are made of gelatin, sugar, and water (Fig. 7.1). As such, they can be clear, colorless, and essentially tasteless. They may be colored with various FD&C and D&C dyes and made opaque

FIGURE 7.1 Preparation of a gelatin mixture for making empty capsules. (Courtesy of Shionogi Qualicaps.)

by adding agents such as titanium dioxide. Most commercially available medicated capsules contain combinations of colorants and opaquants to make them distinctive, many with caps and bodies of different colors.

Gelatin is obtained by the partial hydrolysis of collagen obtained from the skin, white connective tissue, and bones of animals. In commerce, it is available in the form of a fine powder, a coarse powder, shreds, flakes, or sheets.

Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist. Normally, hard gelatin capsules contain 13% to 16% of moisture (2). However, if stored in an environment of high humidity, additional moisture is absorbed by the capsules, and they may become distorted and lose their rigid shape. In an environment of extreme dryness, some of the moisture normally present in the gelatin capsules is lost, and the capsules may become brittle and crumble when handled. Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness.

Because moisture may be absorbed by gelatin capsules and may affect hygroscopic agents within, many capsules are packaged along with a small packet or cylinder of a desiccant material to protect against the absorption of atmospheric moisture. The desiccant

materials most often used are dried silica gel, clay, and activated charcoal.

Prolonged exposure to high humidity can affect in vitro capsule dissolution. Such changes have been observed in capsules containing tetracycline, chloramphenicol, and nitrofurantoin (3). Because such changes could forewarn of possible changes in bioavailability, capsules subjected to such stress conditions must be evaluated case by case (3).

Capsule shells are usually made from gelatin; however, they may also be made from cellulose polymers or other suitable material. Most capsules are designed for oral administration. When no deliberate effort has been made to modify the API release rate, they are referred to as immediate release.

Although gelatin is insoluble, it does soften in cold water through the absorption of water up to 10 times its weight of water. Some patients prefer to swallow a capsule wetted with water or saliva because a wetted capsule slides down the throat more readily than a dry capsule. Gelatin is soluble in hot water and in warm gastric fluid; a gelatin capsule rapidly dissolves and exposes its contents. Gelatin, being a protein, is digested by proteolytic enzymes and absorbed.

A number of methods have been developed to track the passage of capsules and tablets through the gastrointestinal tract to map their transit time and drug-release patterns. Among these is gamma *scintigraphy*, a noninvasive procedure that entails the use of a gamma ray–emitting radiotracer incorporated into the formulation with a gamma camera coupled to a data recording system (4,5). The quantity of material added to allow gamma scintigraphy is small and does not compromise the usual in vivo characteristics of the dosage form being studied. When scintigraphy is combined with pharmacokinetic studies, the resultant *pharmacoscintographic* evaluation provides information about the transit and drug-release patterns of the dosage form as well as the rate of drug absorption from the various regions of the gastrointestinal tract (4). This method is particularly useful in (*a*) determining whether a correlation exists between in vitro and in vivo bioavailability for immediate-release products, (*b*) assessing the integrity and transit time of enteric-coated tablets through the stomach en route to the intestines, and (*c*) drug and dosage form evaluation in new product development (4,5). A separate technique using a pH-sensitive nondigestible radiotelemetric device termed the Heidelberg capsule, the approximate size of a No. 0 gelatin capsule, has been used as a *non*radioactive means to measure gastric pH, gastric residence time, and gastric emptying time of solid dosage forms in fasting and nonfasting human subjects (6).

As discussed in Chapter 5, drug absorption from the gastrointestinal tract depends on a number of factors, including the solubility of the drug substance, the type of product formulation (i.e., immediate release, modified release, or enteric coated), the gastrointestinal contents, and intersubject differences in physiologic character and response.

The Manufacture of Hard Gelatin Capsule Shells

Hard gelatin capsule shells are manufactured in two sections, the capsule body and a shorter cap. The two parts overlap when joined, with the cap fitting snugly over the open end of the capsule body. Some capsule shells are designed to lock in place when closed. The shells are produced industrially by the mechanical dipping of pins or pegs of the desired shape and diameter into a temperature-controlled reservoir of melted gelatin mixture (Figs. 7.2 and 7.3). The pegs, made of manganese bronze, are affixed to plates, each capable of holding up to about 500 pegs. Each plate is mechanically lowered to the gelatin bath and the pegs submerged to the desired depth and maintained for the desired period to achieve the proper length and thickness of coating. Then the plate and the pegs are slowly lifted from the bath, and the gelatin is dried by a gentle flow of temperature- and humidity-controlled air. When dried, each capsule part is trimmed mechanically to the proper length and removed from the pegs, and the capsule bodies and caps are joined together. It is important that the thickness of the gelatin walls be strictly controlled so that the capsule's body and cap fit snugly

FIGURE 7.2 Body of capsules and their caps are shown as they move through an automated capsule-making machine. Each machine is capable of producing 30,000 capsules per hour. It takes a 40-minute cycle to produce a capsule. (Courtesy of SmithKline Beecham.)

to prevent disengagement. The pegs on which the caps are formed are slightly larger in diameter than the pegs on which the bodies are formed, allowing the telescoping of the caps over the bodies. In capsule shell production, there is a continuous dipping, drying, removing, and joining of capsules as the peg-containing plates rotate in and out of the gelatin bath. As noted earlier, capsule shells
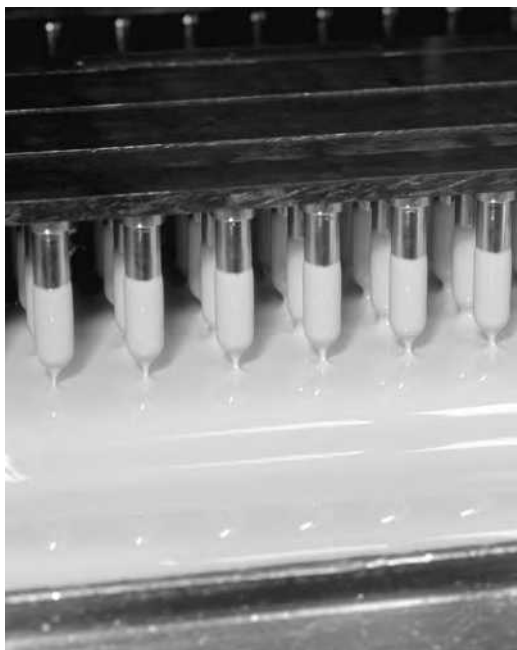
FIGURE 7.3 Capsules being dipped for coloring on automated capsule-making equipment. (Courtesy of Shionogi Qualicaps.)

may be made distinctive by adding colorants and/or opaquants to the gelatin bath.

A manufacturer also may prepare distinctive-looking capsules by altering the usual rounded shape of the capsule-making pegs. By tapering the end of the body-producing peg while leaving the cap-making peg rounded, one manufacturer prepares capsules differentiated from those of other manufacturers (Pulvules, Eli Lilly). Another manufacturer uses capsules with the ends of both the bodies and caps highly tapered (Spansule Capsules, SmithKline Beecham). Yet another innovation in capsule shell design is the Snap-fit, Coni-snap, and Coni-snap Supro hard gelatin capsules depicted in Figures 7.4 and 7.5. The original Snap-fit construction enables the two halves of the capsule shells to be positively joined through locking grooves in the shell walls. The two grooves fit into each other and thus ensure reliable closing of the filled capsule. During the closing process, the capsule body is inserted into the cap. With the high-capacity filling rates of the modern capsule-filling machines (more than 180,000 capsules per hour), splitting (telescoping) and denting of the capsule shell occur with the slightest contact between the two rims when they are joined. This problem, which exists primarily with straight-walled capsule shells, led to the development of the Coni-snap capsule, in which the rim of the capsule body is not straight but tapered slightly (Fig. 7.5). This reduces the risk of the capsule rims touching on joining and essentially eliminates the problem of splitting during large-scale filling operations. In the Coni-snap Supro capsules, the upper capsule part extends so far over the lower part that only the rounded edge of the latter is visible (Fig. 7.5). Opening of such a filled capsule is difficult because the lower surface offers less gripping surface to pull the two halves apart. This increases the security of the contents and the integrity of the capsule.

After filling, some manufacturers render their capsules tamper evident through various sealing techniques. These methods are discussed later in this section. Capsules and tablets also may be imprinted with the names or monograms of the manufacturer,
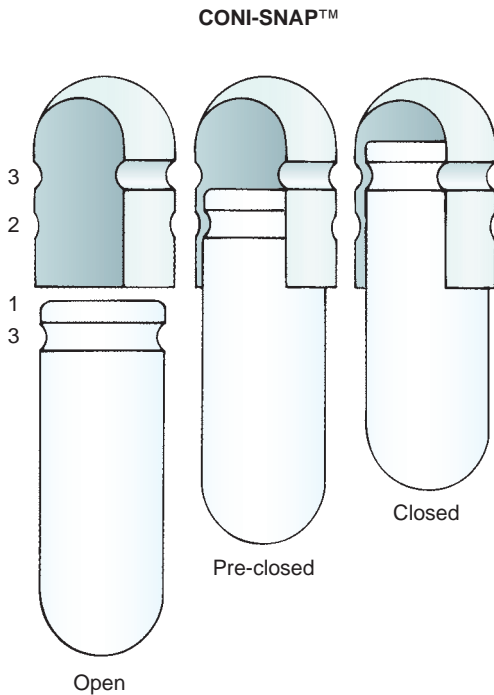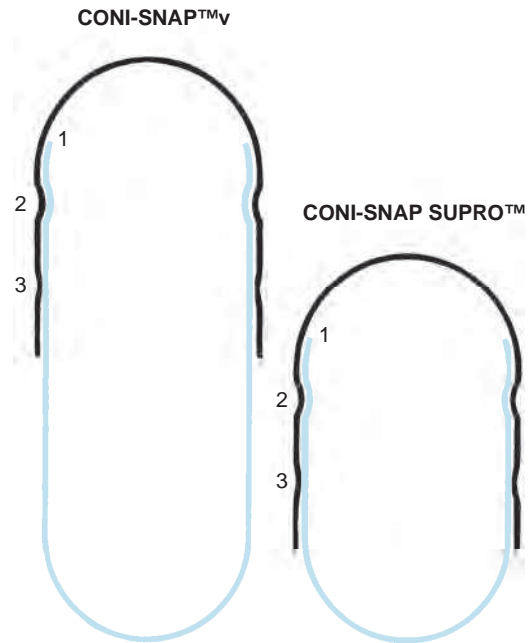
CONI-SNAP™

FIGURE 7.4 Line drawings of the CONI-SNAP capsule in open, preclosed, and closed positions. The tapered rims (*1*) avoid telescoping; the indentations (*2*) prevent premature opening; and the grooves (*3*) lock the two capsule parts together after the capsule is filled. (Courtesy of Capsugel Division, Warner–Lambert.)

the assigned national drug code number, and other markings making the product identifiable and distinguishable from other products.

Capsule Sizes

Empty gelatin capsules are manufactured in various lengths, diameters, and capacities. The size selected for use is determined by the amount of fill material to be encapsulated. The density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell (7) (Fig. 7.6). For estimation, a comparison may be made with powders of well-known features (Table 7.1) and an initial judgment made as to the approximate capsule size needed to hold a specific amount of material. However, the final determination may be largely the result of trial and error. For human use, empty capsules ranging in size from 000 (the largest) to 5 (the smallest) are commercially available (Fig. 7.7). Larger capsules are available for veterinary use.

CONI-SNAP™v

CONI-SNAP SUPRO™

1. Tapered rim to avoid telescoping (CONI-SNAP™)

2. Grooves which lock the two halves together once the capsule has been filled (SNAP-FIT™ principle)

3. Indentations to prevent premature opening

FIGURE 7.5 Line drawings of the CONI-SNAP and CONI-SNAP SUPRO (*right*) capsules. The latter is designed to be smaller and to have the lower portion of the capsule shell concealed except for the rounded end. This makes separation of the two parts more difficult and contributes to capsule integrity. (Courtesy of Capsugel Division, Warner-Lambert.)

For prescriptions requiring extemporaneous compounding, hard gelatin capsules permit a wide number of options for the physician. The pharmacist may compound capsules of a single medicinal agent or combination of agents at the precise dosage prescribed for the individual patient.

Preparation of Filled Hard Gelatin Capsules

The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps:

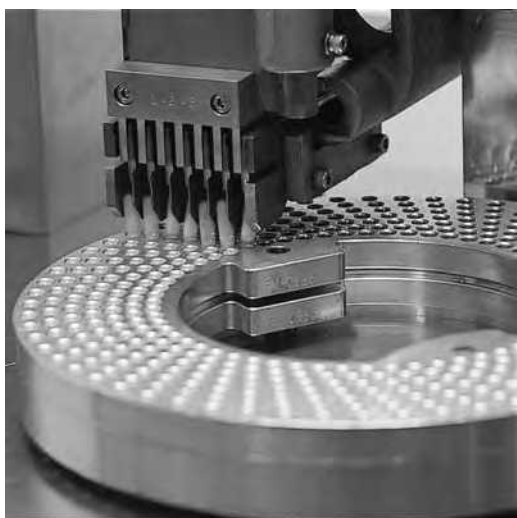1. Developing and preparing the formulation and selecting the capsule size

FIGURE 7.6 Capsule ring containing capsule halves being filled with powder. (Courtesy of Shionogi Qualicaps.)

2. Filling the capsule shells
3. Capsule sealing (optional)
4. Cleaning and polishing the filled capsules

Developing the Formulation and Selecting the Capsule Size

In developing a capsule formulation, the goal is to prepare a capsule with accurate dosage, good bioavailability, ease of filling and production, stability, and elegance.

In dry formulations, the active and inactive components must be blended thoroughly to ensure a uniform powder mix for the fill. Care in blending is especially important for low-dose drugs, since lack of homogeneity in blending may result in significant therapeutic consequences. Preformulation studies are performed to determine whether all of the formulation's bulk powders may be effectively blended together as such or require reduction of particle size or any other processing to achieve homogeneity.

A diluent or filler may be added to the formulation to produce the proper capsule fill volume. Lactose, microcrystalline cellulose, and starch are commonly used for this purpose. In addition to providing bulk, these materials often provide cohesion to the powders, which is beneficial in the transfer of the powder blend into capsule shells (2). Disintegrants are frequently included in a capsule formulation to assist the breakup and distribution of the capsule's contents in the stomach. Among the disintegrants used are pregelatinized starch, croscarmellose, and sodium starch glycolate.

To achieve uniform drug distribution, it is advantageous if the density and particle size of the drug and nondrug components are similar. This is particularly important when a drug of low dosage is blended with other drugs or nondrug fill (8). When necessary, particle size may be reduced by *milling* to produce particles ranging from about 50 to 1,000 mm. Milled powders may be blended effectively for uniform distribution throughout a powder mix when the drug's dosage is 10 mg or greater (8). For drugs of lower dose or when smaller particles are required, *micronization* is employed. Depending on the materials and equipment used, micronization produces particles ranging from about 1 to 20 mm.

In preparing capsules on an industrial scale using high-speed automated equipment, the powder mix or granules must be

Table 7.1	APPROXIMATE CAPACITY OF EMPTY GELATIN CAPSULES							
	CAPSULE SIZE							
	000	**00**	**0**	**1**	**2**	**3**	**4**	**5**
VOLUME (ML)	**1.40**	**0.95**	**0.68**	**0.50**	**0.37**	**0.30**	**0.21**	**0.13**
DRUG SUBSTANCE (mg)[a]								
Quinine sulfate	650	390	325	227	195	130	97	65
Sodium bicarbonate	1,430	975	715	510	390	325	260	130
Aspirin	1,040	650	520	325	260	195	162	97

[a]Amount may vary with the degree of pressure used in filling the capsules.

FIGURE 7.7 Actual sizes of hard gelatin capsules. From left to right, sizes 000, 00, 0, 1, 2, 3, 4, and 5.

free-flowing to allow steady passage of the capsule fill from the hopper through the encapsulating equipment and into the capsule shells. The addition of a *lubricant* or *glidant* such as fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, or talc (about 0.25% to 1%) to the powder mix enhances flow properties (2).

When magnesium stearate is used as the lubricant, the waterproofing characteristics of this water-insoluble material can retard penetration by the gastrointestinal fluids and delay drug dissolution and absorption. A surface-active agent, such as sodium lauryl sulfate, is used to facilitate wetting by the gastrointestinal fluids to overcome the problem (9). Even if a water-insoluble lubricant is used, after the gelatin capsule shell dissolves, gastrointestinal fluids must displace the air that surrounds the dry powder and penetrate the drug before it can be dispersed and dissolved. Powders of poorly soluble drugs have a tendency to resist such penetration. Disintegration agents in a capsule

formulation facilitate the breakup and distribution of the capsule's contents.

Be it a lubricant, surfactant, disintegrating agent, or some other pharmaceutical excipient, formulation can influence the bioavailability of a drug substance and can account for differences in drug effects between two capsule products of the same medicinal substance. Pharmacists must be aware of this possibility when product interchange, for example, generic substitution, is considered.

Inserting tablets or small capsules into capsules is sometimes useful in the commercial production of capsules and in a pharmacist's extemporaneous preparation of capsules (Fig. 7.8). This may be done to separate chemically incompatible agents or to add premeasured amounts of potent drug substances. Rather than weighing a potent drug, a pharmacist may choose to insert a prefabricated tablet of the desired strength in each capsule. Other less potent agents and diluents may then be weighed and added. On an industrial scale, coated pellets designed
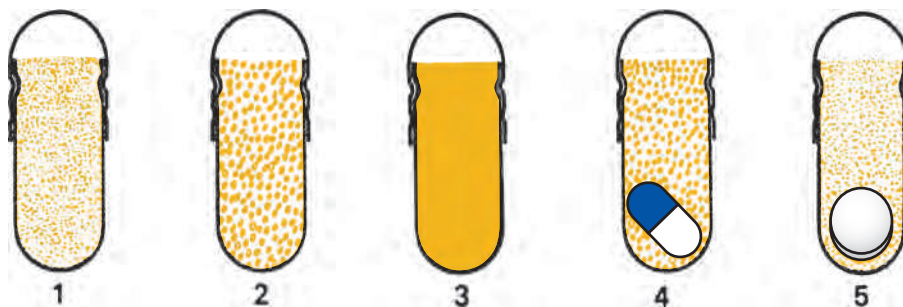

FIGURE 7.8 Examples of fill in hard gelatin capsules. 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet. (Courtesy of Capsugel Division, Warner-Lambert.)

for modified-release drug delivery are also commonly placed in capsule shells.

Gelatin capsules are unsuitable for aqueous liquids because water softens gelatin and distorts the capsules, resulting in leakage of the contents. However, some liquids, such as fixed or volatile oils, that do not interfere with the stability of the gelatin shells may be placed in locking gelatin capsules (or the capsules may be sealed with a solution of gelatin thinly coating the interface of the cap and body) to ensure retention of the liquid. Rather than placing a liquid as such in a capsule, the liquid may be mixed with an inert powder to make a wet mass or paste, which may then be placed in capsules in the usual manner (Fig. 7.8). *Eutectic mixtures* of drugs, or mixtures of agents that have a propensity to liquefy when admixed, may be mixed with a diluent or absorbent such as magnesium carbonate, kaolin, or light magnesium oxide to separate the interacting agents and to absorb any liquefied material that may form.

In large-scale capsule production, liquids are placed in *soft gelatin* capsules that are sealed during filling and manufacturing. Soft capsules are discussed later in this chapter.

In most instances, the amount of drug in a capsule is a single dose. When the usual dose of the drug is too large for a single capsule, two or more capsules may be required. The total amount of formula prepared is the amount necessary to fill the desired number of capsules. On an industrial scale, this means hundreds of thousands of capsules. In community practice, an individual prescription may call for preparation of a few to several hundred capsules. Any slight loss in fill material during preparation and capsule filling will not materially affect an industrial size batch, but in the community pharmacy, a slight loss of powder could result in an inadequate quantity to fill the last capsule. To ensure enough fill in the compounding of small numbers of capsules, the community pharmacist may calculate for the preparation of one or two more capsules than required to fill the prescription. However, this procedure must not be followed for capsules containing a controlled substance, since the amount of drug used and that called for in the prescription must strictly coincide.

The selection of the capsule size for a commercial product is done during product development. The choice is determined by requirements of the formulation, including the dose of the active ingredient and the density and compaction characteristics of the drug and other components. If the dose of the drug is inadequate to fill the volume of the capsule body, a diluent is added. Information on the density and compaction characteristics of a capsule's active and inactive components and comparison to other similar materials and prior experiences can serve as a guide in selecting capsule size (7).

Hard gelatin capsules are used to encapsulate about 65 mg to 1 g of powdered material. As shown in Table 7.1, the smallest capsule (No. 5) may be expected to hold 65 mg of powder or more, depending on the characteristics of the powder. Oftentimes, in the extemporaneous compounding of prescriptions, the best capsule size to use is determined by trial. Use of the smallest size capsule, properly filled, is preferred. A properly filled capsule should have its body filled with the drug mixture, not the cap. The cap is intended to fit snugly over the body to retain the contents.

An easy method to select the proper capsule is to weigh the ingredients for the required number of capsules to be prepared. Place the powders in a graduated cylinder, and obtain the volume occupied by the powders. Divide the volume by the number of capsules to be prepared, and this provides the volume that will be occupied by the powder for each capsule. Compare this volume (in mL) with the appropriate line of Table 7.1, and select the size that will accommodate the powder. If the capsule is too large, simply multiply the capsule size in volume by the number of capsules to be prepared to obtain the final volume of the powder that is required. Then add additional diluent to the graduated cylinder containing the other powders to the mark indicated for the total volume of powder required. For documentation, weigh the total powder blend and subtract the initial quantities that were weighed, and the quantity of additional diluent that was added will be obtained.

The following examples demonstrate the drug and nondrug contents of a few commercially available capsules:

Tetracycline Capsules

Active ingredient:	Tetracycline hydrochloride 250 mg
Filler:	Lactose
Lubricant/glidant:	Magnesium stearate
Capsule colorants:	FD&C Yellow No. 6, D&C Yellow No. 10, D&C Red No. 28, FD&C Blue No. 1
Capsule opaquant:	Titanium dioxide

Acetaminophen with Codeine Capsules

Active ingredients:	Acetaminophen 325 mg Codeine phosphate 30mg
Disintegrant:	Sodium starch glycolate
Lubricant/glidants:	Magnesium stearate, stearic acid
Capsule colorants:	D&C Yellow No. 10, Edible Ink, FD&C Blue No. 1 (FD&C Green No. 3 and FD&C Red No. 40)

Diphenhydramine Hydrochloride Capsules

Active ingredient:	Diphenhydramine HCl 25 mg
Filler:	Confectioner's sugar
Lubricants/glidants:	Talc, colloidal silicon dioxide
Wetting agent:	Sodium lauryl sulfate
Capsule colorants:	FD&C Blue No. 1, FD&C Red No. 3
Capsule opaquant:	Titanium dioxide

Filling Hard Capsule Shells

When filling a small number of capsules in the pharmacy, the pharmacist may use the punch method. The pharmacist takes the precise number of empty capsules to be filled from the stock container. By counting the capsules as the initial step rather than taking a capsule from stock as each one is filled, the pharmacist guards against filling the wrong number of capsules and avoids contaminating the stock container with drug powder. The powder to be encapsulated is placed on a sheet of clean paper or on a glass or porcelain plate. Using the spatula, the powder mix is formed into a cake having a depth of approximately one-fourth to one-third the length of the capsule body. Then an empty capsule body is held between the thumb and forefinger and punched vertically into the powder cake repeatedly until filled. Some pharmacists wear surgical gloves (latex or other material) or finger cots to avoid handling the capsules with bare fingers. Because the amount of powder packed into a capsule depends on the degree of compression, the pharmacist should punch each capsule in the same manner and weigh the product after capping. When nonpotent materials are placed in capsules, the first filled capsule should be weighed (using an empty capsule of the same size on the opposite balance pan to counter the weight of the shell) to determine the capsule size to use and the degree of compaction to be used. After this determination, the other capsules should be prepared and weighed periodically to check the uniformity of the process. When potent drugs are being used, *each capsule* should be weighed after filling to ensure accuracy. Such weighings protect against uneven filling of capsules and premature exhaustion or underuse of the powder. After the body of a capsule has been filled and the cap placed on the body, the body may be squeezed or tapped gently to distribute some powder to the cap end to give the capsule a full appearance.

Granular material that does not lend itself to the punch method of filling capsules may be poured into each capsule from the powder paper on which it is weighed.

Pharmacists who prepare capsules on a regular or extensive basis may use a hand-operated filling machine (Fig. 7.9). The various types of machines have capacities ranging from 24 to 300 capsules and, when efficiently operated, are capable of
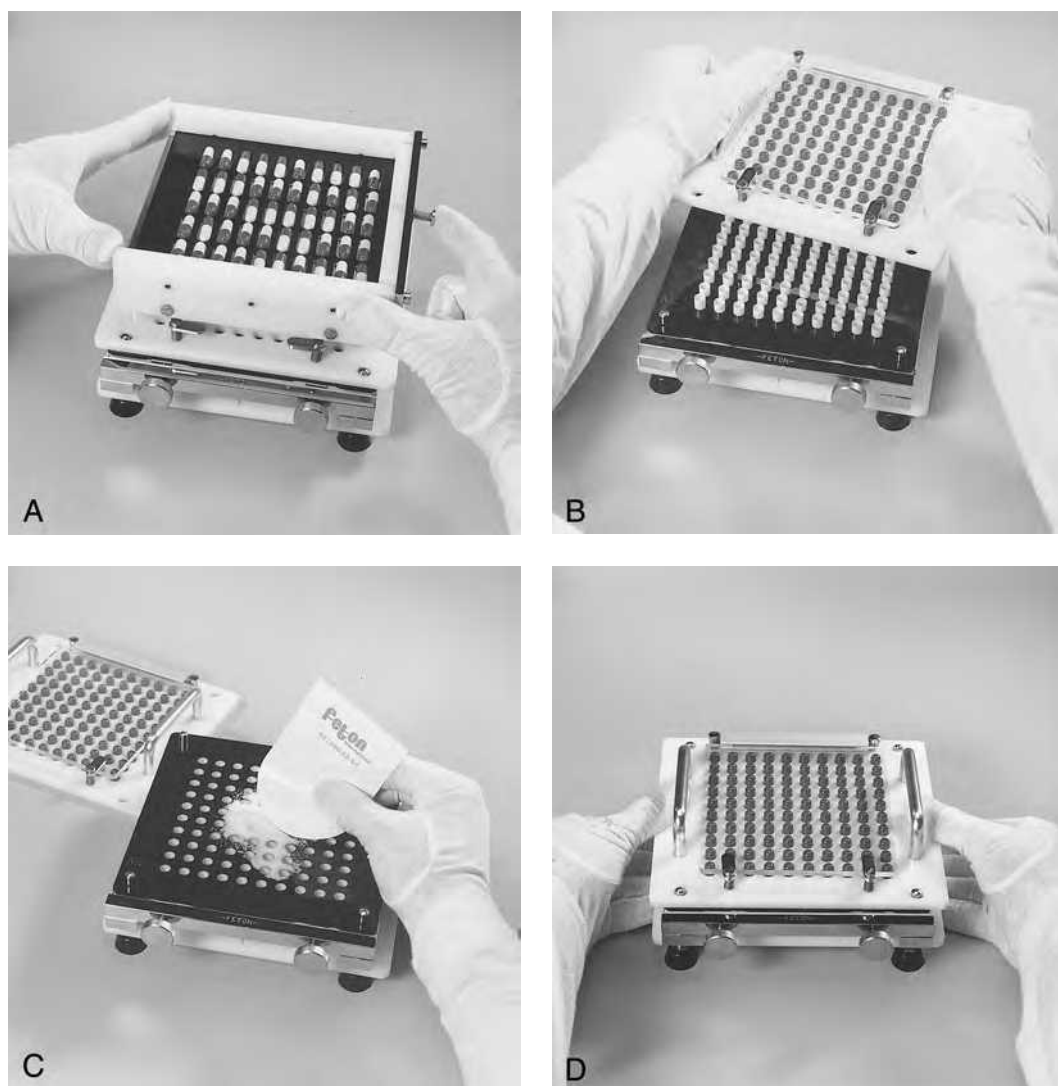
FIGURE 7.9 The Feton capsule-filling machine. **A:** With empty capsules in the loader tray, the tray placed on top of the filler unit. **B:** The loader inserts the capsules into the filling unit and is removed, and the top plate is lifted to separate the caps from the bodies. **C:** The powder is placed on the unit, and the capsule bodies are filled. **D:** The top plate is returned to the unit, and the caps are placed on filled capsule bodies. (Courtesy of Chemical and Pharmaceutical Industry Company.)

producing about 200 to 2,000 capsules per hour. These are operated by weighing and mixing all the ingredients followed by thoroughly mixing. The required number of empty capsules is placed in the lower plate and the upper plate added followed by locking the capsules in the plates. The upper plate is removed separating the caps from the bodies of the capsules. The lower plate is loosened allowing the capsules to fall flush with the plate surface. A border dam is added to retain the powder in the area followed by the powder. The powder is moved around on the plate allowing the capsules to fill. It is generally necessary to use a tamper to aid in packing the powder in the capsules to allow more powder to be accommodated. After all the powder is filled in the capsule bodies, the plate with the capsule caps is then placed on the lower plate and the plates are pressed together. The upper plate is removed and all the capsules checked to

FIGURE 7.10 Osaka Automatic Capsule Filler model R-180, capable of filling up to 165,000 capsules per hour. (Courtesy of Sharples-Stokes Division, Stokes-Merrill, Pennwalt Corporation.)

confirm a good seal is made with all of them. The lower plate is removed and the capsules allowed to fall out of the plate onto a surface for examination.

Machines developed for industrial use automatically separate the caps from empty capsules, fill the bodies, scrape off the excess powder, replace the caps, seal the capsules as desired, and clean the outside of the filled capsules at up to 165,000 capsules per hour (Figs. 7.10 and 7.11). The formulation must be such that the filled body contains the accurate drug dosage. This is verified through the use of automated in-process sampling and analysis (Figs. 7.12 and 7.13).

As described later, the USP requires adherence to standards for *content uniformity* and *weight variation* for capsules to ensure the accuracy of dosage units.

Capsule Sealing

As mentioned previously, some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. One manufacturer makes distinctive-looking capsules by sealing them with a colored band of gelatin (Kapseals, Parke-Davis). If removed, the band cannot be restored without expert resealing with gelatin. Capsules may also be sealed through a heat-welding process that fuses the capsule cap to the body through the double wall thickness at their juncture (10). The process results in a distinctive ring around the capsule where heat welded. Still another process uses a liquid wetting agent that lowers the melting point in the contact areas of the capsule's cap and body and then thermally bonds the two parts using low temperatures (40°C to 45°C) (11). Industrial capsule-sealing machines are capable of producing 60,000 to 150,000 gelatin-banded, heat-welded, or thermally coupled capsules per hour (12). Figure 7.14 depicts a sealed hard gelatin capsule. Although it is difficult and tedious, extemporaneously prepared capsules may be sealed by lightly coating the inner surface of the cap with a warm gelatin solution immediately prior to placement on the filled capsule body.

CLEANING AND POLISHING CAPSULES

Small amounts of powder may adhere to the outside of capsules after filling. The powder may be bitter or otherwise unpalatable and should be removed before packaging or dispensing. On a small scale, capsules may be cleaned individually or in small numbers by rubbing them with a clean gauze or cloth. On a large scale, many capsule-filling machines are affixed with a cleaning vacuum that removes any extraneous material from the capsules as they exit the equipment. Figure 7.15 shows industrial cleaning and polishing of filled hard capsules using the Accela-Cota apparatus.

SOFT GELATIN CAPSULES

Soft gelatin capsules are made of gelatin to which glycerin or a polyhydric alcohol such as sorbitol has been added. Soft gelatin capsules, which contain more moisture than hard capsules, may have a preservative, such

FIGURE 7.11 Automated capsule preparation machine. (Courtesy of Shionogi Qualicaps.)

as methylparaben and/or propylparaben, to retard microbial growth. Soft gelatin capsules may be oblong, oval, or round. They may be single colored or two toned and may be imprinted with identifying markings. As with hard gelatin capsules, they may be prepared with opaquants to reduce transparency and render characteristic features to the capsule shell.

Soft gelatin capsules are used to encapsulate and hermetically seal liquids, suspensions, pasty materials, dry powders, and even preformed tablets. Soft gelatin capsules are pharmaceutically elegant and are easily swallowed.

Preparation of Soft Gelatin Capsules

Soft gelatin capsules may be prepared by the plate process, using a set of molds to form the capsules, or by the more efficient and productive rotary or reciprocating die processes by which are produced, filled, and sealed in a continuous operation (Fig. 7.16) (13).

By the plate process, a warm sheet of plain or colored gelatin is placed on the bottom plate of the mold, and the medication-containing liquid is evenly poured on it. Then a second sheet of gelatin is carefully placed on top of the medication, and the top plate of the mold is put into place. Pressure is then applied to the mold to form, fill, and seal the capsules simultaneously. The capsules are removed and washed with a solvent harmless to the capsules.

Most soft gelatin capsules are prepared by the rotary die process, a method developed in 1933 by Robert P. Scherer. By this method, liquid gelatin flowing from an overhead tank is formed into two continuous ribbons by the rotary die machine and brought together between twin rotating dies (Fig. 7.17). At the same time, metered fill material is injected between the ribbons precisely at the moment that the dies form pockets of the gelatin ribbons. These pockets of fill-containing gelatin are sealed by pressure and heat and then severed from the ribbon. Use of ribbons of two different colors results in bicolored capsules.

The reciprocating die process is similar to the rotary process in that ribbons of gelatin are formed and used to encapsulate the fill, but
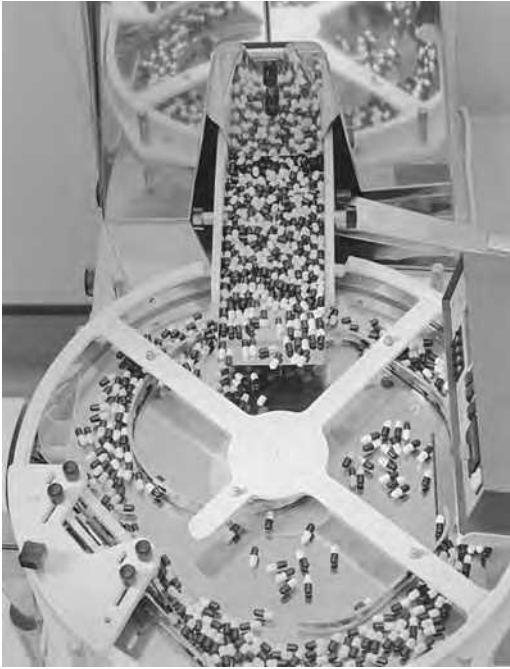
FIGURE 7.12 Automatic capsule weighing apparatus: Vericap 1800A Checkweigher, which rejects capsules not having the precise weight. (Courtesy of Elan Corporation.)

it differs in the actual encapsulating process. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into refrigerated tanks that prevent the capsules from adhering to one another.

Use of Soft Gelatin Capsules

Soft gelatin capsules are prepared to contain a variety of liquid, paste, and dry fills. Liquids that may be encapsulated into soft gelatin capsules include the following (13):

1. Water-immiscible volatile and nonvolatile liquids such as vegetable and aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers, esters, alcohols, and organic acids
2. Water-miscible nonvolatile liquids, such as polyethylene glycols, and nonionic surface-active agents, such as polysorbate 80
3. Water-miscible and relatively nonvolatile compounds such as propylene glycol and isopropyl alcohol, depending on factors such as concentration used and packaging conditions

Liquids that can easily migrate through the capsule shell are not suitable for soft gelatin capsules. These materials include water above 5% and low molecular weight water-soluble and volatile organic compounds such as alcohols, ketones, acids, amines, and esters.

Solids may be encapsulated into soft gelatin capsules as solutions in a suitable liquid solvent, suspensions, dry powders, granules, pellets, or small tablets.

COMPENDIAL REQUIREMENTS FOR CAPSULES

Added Substances

Substances added to official preparations, including capsules, to enhance their stability, usefulness, or elegance or to facilitate their manufacture may be used only if they (14):

1. Are harmless in the quantities used
2. Do not exceed the minimum amounts required to provide their intended effect
3. Do not impair the product's bioavailability, therapeutic efficacy, or safety
4. Do not interfere with requisite compendial assays and tests

Containers for Dispensing Capsules

The USP lists specifications prescribing the type of container suitable for the repackaging or dispensing of each official capsule and tablet. Depending on the item, the container may be required to be *tight*, *well closed*, *light resistant*, and/or a combination of these.

Disintegration Test for Capsules

The disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described in the
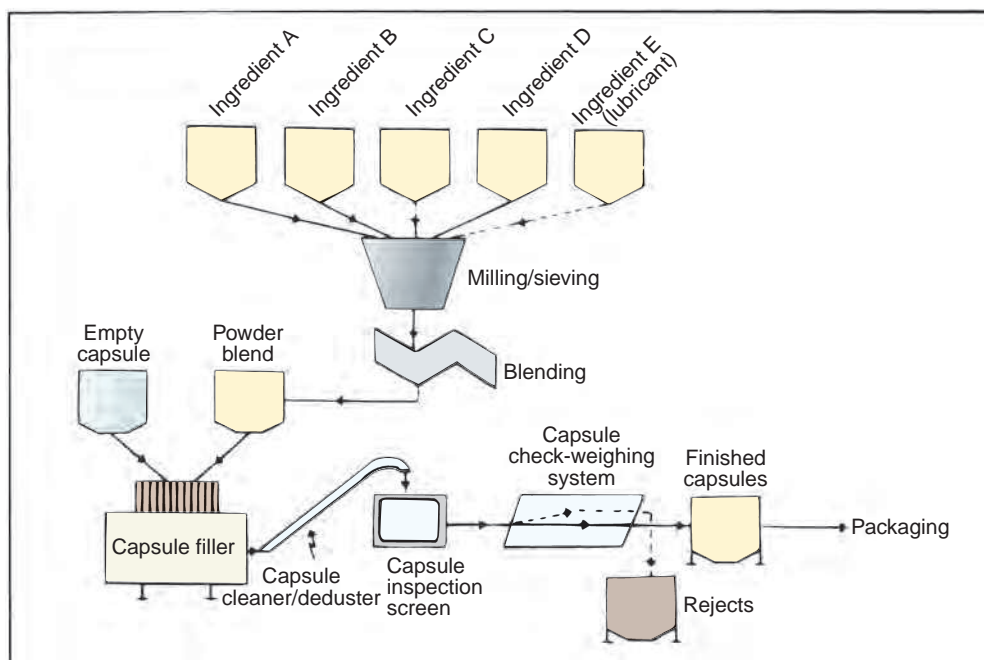
FIGURE 7.13 Process flow diagram for automated capsule filling. (Reprinted with permission from Yelvig M. Principles of process automation for liquid and solid dosage forms. Pharm Technol 1984;8:47.)

next chapter for uncoated tablets. The capsules are placed in the basket rack assembly, which is immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To satisfy the test, the capsules disintegrate completely into a soft mass having no palpably firm core and only some fragments of the gelatin shell.

Dissolution Test for Capsules

The dissolution test for capsules uses the same apparatus, dissolution medium, and test as that for uncoated and plain-coated tablets described in Chapter 8. However, if the capsule shells interfere with the analysis,

FIGURE 7.14 Z-Weld's gelatin seal fuses the two capsule halves to create a one-piece capsule that is tamper evident. (Courtesy of Raymond Automation.)

FIGURE 7.15 Cleaning and polishing hard-filled capsules using the Accela-Cota apparatus. (Courtesy of Eli Lilly and Company.)
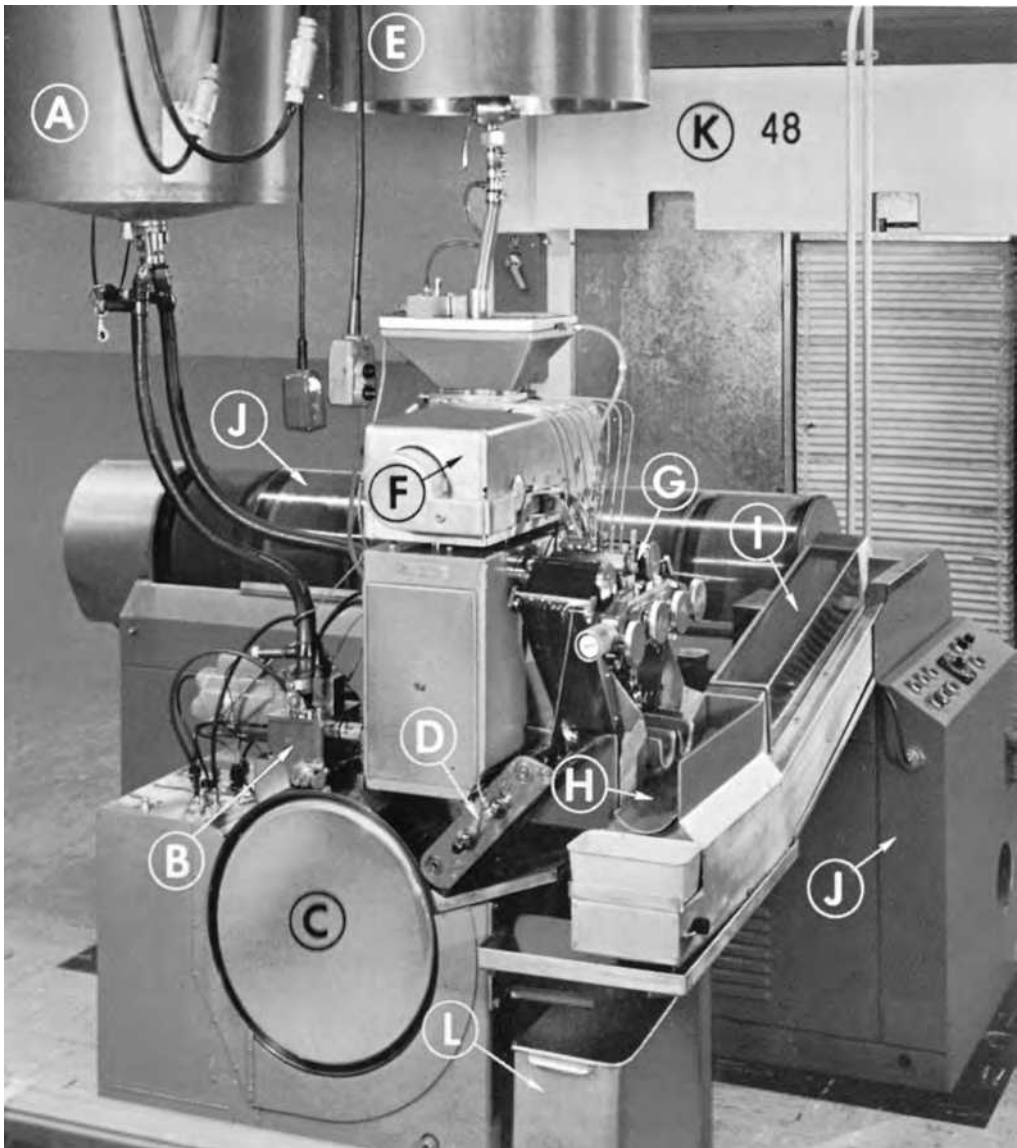
FIGURE 7.16 Rotary die process equipment. *A*, gelatin tank; *B*, spreader box; *C*, gelatin ribbon casting drum; *D*, mineral oil lubricant bath; *E*, medicine tank; *F*, filling pump; *G*, encapsulating mechanism; *H*, capsule conveyor; *I*, capsule washer; *J*, infrared dryer; *K*, capsule drying tunnel; *L*, gelatin net receiver. (Courtesy of R.P. Scherer Corporation.)

the contents of a specified number of capsules can be removed and the empty capsule shells dissolved in the dissolution medium before proceeding with the sampling and chemical analysis. If the capsule floats on the surface of the dissolution fluid, a small, loose piece of nonreactive material, such as a few turns of a wire helix, may be attached to the dosage form to force it to sink to the bottom of the vessel.

Weight Variation

The uniformity of dosage units may be demonstrated by determining *weight variation* and/or *content uniformity*. The weight variation method is as follows.

Hard Capsules

Ten capsules are individually weighed and their contents removed. The emptied shells
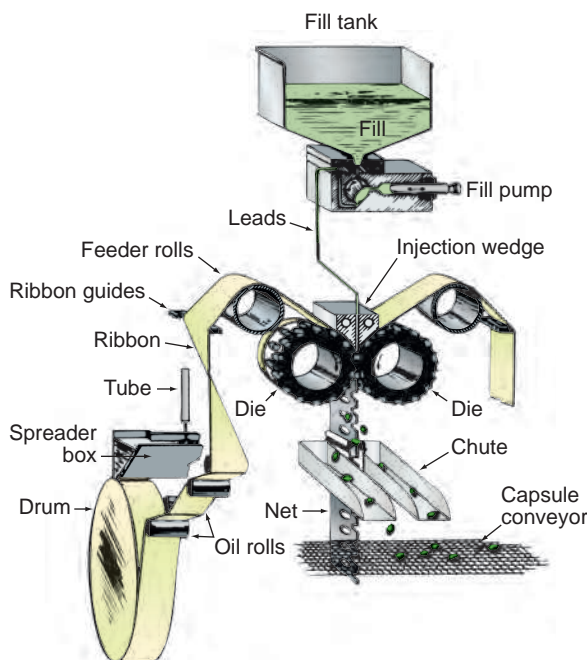
FIGURE 7.17 Rotary die process. (Courtesy of R.P. Scherer Corporation.)

are individually weighed, and the net weight of the contents is calculated by subtraction. From the results of an assay performed as directed in the individual monograph, the content of the active ingredient in each of the capsules is determined.

Soft Capsules

The gross weight of 10 intact capsules is determined individually. Then each capsule is cut open, and the contents are removed by washing with a suitable solvent. The solvent is allowed to evaporate at room temperature over about 30 minutes, with precautions to avoid uptake or loss of moisture. The individual shells are weighed and the net contents calculated. From the results of the assay directed in the individual monograph, the content of the active ingredient in each of the capsules is determined.

Content Uniformity

Unless otherwise stated in the USP monograph for an individual capsule, the amount of active ingredient, determined by assay, is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed, with no unit outside the range of 70% to 125%

of the label claim. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.

Content Labeling Requirement

All official capsules must be labeled to express the quantity of each active ingredient in each dosage unit.

Stability Testing

Stability testing of capsules is performed as described in Chapter 4 to determine the intrinsic stability of the active drug molecule and the influence of environmental factors such as temperature, humidity, light, formulative components, and the container and closure system. The battery of stress testing, long-term stability, and accelerated stability tests help determine the appropriate conditions for storage and the product's anticipated shelf life.

Moisture Permeation Test

The USP requires determination of the moisture permeation characteristics of single-unit and unit-dose containers to ensure their suitability

for packaging capsules. The degree and rate of moisture penetration are determined by packaging the dosage unit together with a color-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating the absorption of moisture), and comparing the pretest and posttest weight of the packaged unit.

OFFICIAL AND COMMERCIALLY AVAILABLE CAPSULES

Approximately 200 officially recognized medications in capsule form are listed in the USP. However, many times, this number of capsule products is available from various manufacturers for various drugs and in various dosage strengths.

Examples of official and commercially available medications in hard and soft gelatin capsules are presented in Tables 7.2 and 7.3.

INSPECTING, COUNTING, PACKAGING, AND STORING CAPSULES

Capsules produced on a small or a large scale should be uniform in appearance. Visual or electronic inspection should be undertaken to detect any flaws in the integrity and appearance of the capsules. Defective capsules should be rejected. In commercial manufacture, Current Good Manufacturing Practice regulations require that if the number of production flaws is excessive, the cause must be investigated and documented and steps undertaken to correct the problem.

In the pharmacy, capsules may be counted manually or by automated equipment. Specially designed trays, such as the type depicted in Figure 7.18, are used for counting small numbers of solid dosage units. In using this tray, the pharmacist pours a supply of capsules or tablets from the bulk source onto

Table 7.2 · EXAMPLES OF SOME OFFICIAL CAPSULES

OFFICIAL CAPSULE	REPRESENTATIVE COMMERCIAL CAPSULES	STRENGTH (MG)	CATEGORY
Acyclovir	Various	200	Antiviral
Amoxicillin	Wymox (Wyeth-Ayerst)	250, 500	Antibacterial
Ampicillin	Omnipen (Wyeth-Ayerst)	250, 500	Antibacterial
Cephalexin	Keflex (Victory)	250, 333, 500, 750	Antibacterial
Diphenhydramine HCl	Benadryl (McNeil)	25	Antihistaminic
Docusate sodium	Various	250	Stool softener
Doxycycline hyclate	Vibramycin (Pfizer)	100	Antibacterial
Erythromycin estolate	Ilosone (Eli Lilly)	250	Antibacterial
Fluoxetine HCl	Various	10, 20, 40	Antidepressant
Flurazepam HCl	Various	15, 30	Hypnotic
Indomethacin	Indocin (Merck)	25, 50	Anti-inflammatory, antipyretic, analgesic
Loperamide HCl	Imodium (Janssen)	2	Antidiarrheal
Minocycline hydrochloride	Various	50, 75, 100	Antibacterial
Oxazepam	Various	10, 15, 30	Antianxiety
Paromomycin	Caraco Pharm Labs	250	Antiamoebic
Tetracycline HCl	Various	250, 500	Antibacterial
Vancomycin HCl	Vancocin (ViroPharma)	125, 250	Antibacterial
Zidovudine	Zidovudine (Aurobindo Pharma)	100	Antiretroviral

Table 7.3   SOME MEDICATIONS COMMERCIALLY PREPARED INTO SOFT GELATIN CAPSULES

DRUG	TRADE NAME (MANUFACTURER)	CONTENTS AND COMMENTS[a]
Acetazolamide	Diamox Sequels (Duramed)	Carbonic anhydrase inhibitor, slightly water-soluble powder. Contains coated pellets of sustained-release drug
Chloral hydrate	Various	Sedative–hypnotic
Cyclosporine	Sandimmune (Novartis)	Immunosuppressive, slightly water-soluble crystalline powder. Contains corn oil, polyoxyethylated glycolyzed glycerides
Cyclosporine	Neoral (Novartis)	Contains dehydrated alcohol; corn oil mono-, di-, and triglycerides; and polyoxyl 40 hydrogenated castor oil; forms microemulsion in contact with aqueous fluids for enhanced bioavailability
Docusate sodium	UDL	Stool softener–laxative
Ethosuximide	Zarontin (Parke–Davis)	Anticonvulsant, water-soluble powder. Contains polyethylene glycol 400
Ranitidine HCl	Zantac GELdose (Glaxo Wellcome)	Histamine H_2 receptor inhibitor, water-soluble granular powder in nonaqueous matrix of synthetic coconut oil, triglycerides

[a]Only a partial listing of the capsule contents is given. The soft capsule shells may also contain colorants, opaquants, preservatives, and other agents.

the clean tray and, using the spatula, counts and sweeps the dosage units into the trough until the desired number is reached. Then the pharmacist closes the trough cover, picks up the tray, returns the uncounted dosage units to the bulk container by means of the lip at the back of the tray, places the prescription container at the opening of the trough, and carefully transfers the capsules or tablets into the container. With this method, the dosage units remain untouched by the pharmacist. To prevent batch-to-batch contamination, the tray must be wiped clean after each use because powder, particularly from uncoated tablets, may remain. In some community and hospital pharmacies, small automated counting and filling machines may be used as shown in Figure 7.19. Computer-based automated dispensing systems are also available that will fill, label, and check the drug using bar code or video systems.

On the industrial scale, solid dosage forms are counted by large automated pieces of equipment that count and transfer the desired number of dosage units into bulk containers. The containers are then mechanically capped, inspected visually or electronically,

labeled, and inspected once more. Some filled containers are then placed in outer packaging cartons. An industrial counting and filling machine is shown in Figure 7.20. Capsules are packaged in glass or in plastic containers, some containing packets of a desiccant to prevent absorption of excessive moisture.

The unit-dose and strip packaging of solid dosage forms, particularly by pharmacies that service nursing homes and hospitals, provides sanitary handling of the medications, ease of identification, and security in accountability for medications. Typical small-scale strip packaging equipment and commercial unit-dose packages of capsules and tablets are presented in Figures 7.21 and 7.22, respectively. Capsules should be stored in tightly capped containers in a cool, dry place.

ORAL ADMINISTRATION OF SOLID DOSAGE FORMS

Solid dosage forms (capsules and tablets) for oral administration are best taken by placing the dose upon the tongue and swallowing it with a glassful of water or beverage, for example, milk, coffee, juice, and tea. Ingesting
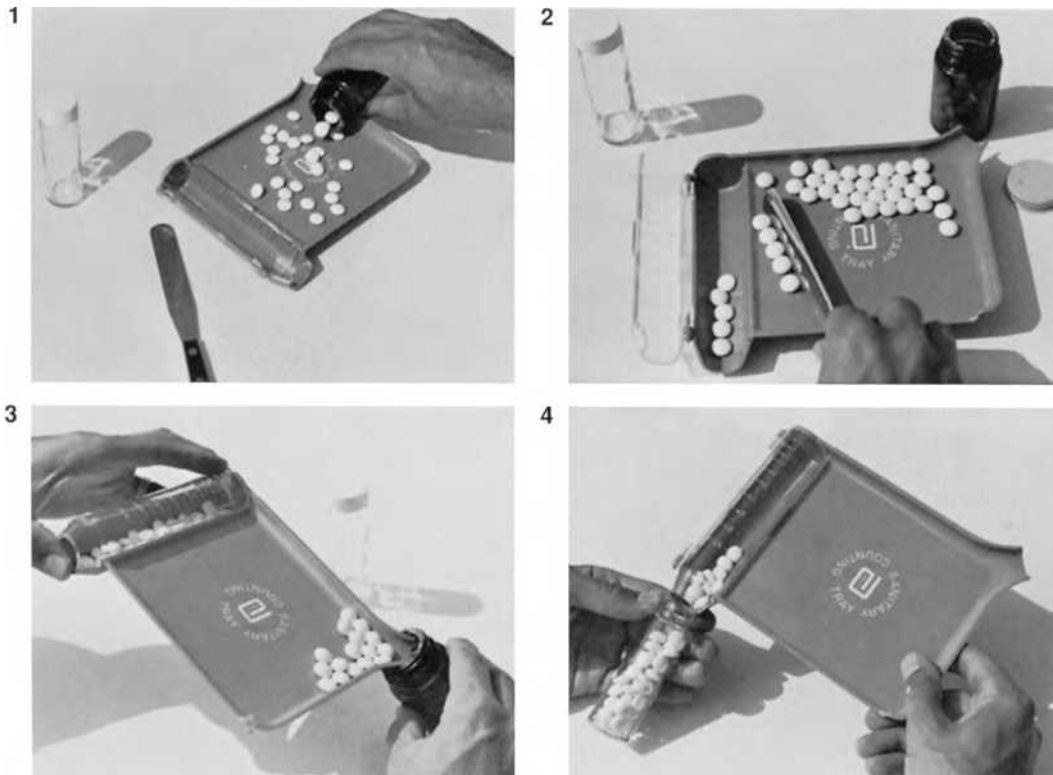
FIGURE 7.18 Steps in counting solid dosage units with the Abbott Sanitary Counting Tray. **1:** Transferring units from stock package to tray. **2:** Counting and transferring units to trough. **3:** Returning excess units to stock container. **4:** Placing the counted units in prescription container.

solid dosage forms with adequate amounts of fluid is important. Some patients attempt to swallow a tablet or capsule without water, but this can be dangerous because of the possibility that it will lodge in the esophagus. Esophageal ulceration can occur with dry ingestion of tablets and capsules, particularly taken just before bedtime. Among the drugs of greatest concern in this regard are alendronate sodium, aspirin, ferrous sulfate, any nonsteroidal anti-inflammatory drug, potassium chloride, and tetracycline antibiotics.

The proper administration of alendronate sodium tablets (Fosamax, Merck), for example, calls for the tablets to be taken with a full 6- or 8-ounce glass of plain water upon rising in the morning and at least half an hour before taking any food, beverage, or other medication to prevent local irritation of the esophagus and other upper gastrointestinal mucosa. The patient is also instructed not to recline for

at least 30 minutes and until after the first food of the day is eaten because of the possibility that the drug will reflux into the esophagus.

In general, patients with gastroesophageal reflux disease must take their medications with adequate amounts of water and avoid reclining for at least an hour to avoid reflux.

The administration of oral medication in relation to meals is very important because the bioavailability and efficacy of certain drugs may be severely affected by food and certain drinks. For example, atorvastatin should not be administered with grapefruit juice because the juice inhibits the CYP 3A4 isoenzyme resulting in a higher plasma concentration of atorvastatin. The pharmacist should know about such instances and counsel patients accordingly.

As mentioned earlier in this chapter, oral dosage forms with special coatings (e.g., enteric) or that are designed to provide controlled drug release, to preserve their drug-release

FIGURE 7.19 Versacount Model automatic tablet and capsule counting and filling apparatus. (Courtesy of Production Equipment Co.)

FIGURE 7.21 Strip packager for unit-dose dispensing of solid dosage forms. Drug information is imprinted on each package unit. This model has a fully automatic cutoff for 1 to 24 dosage units and is especially suited to unit-dose packaging and dispensing in hospitals, dispensaries, nursing homes, and clinics. (Courtesy of Lakso Company.)

features, must not be chewed, broken, or crushed.

When an ordinary tablet is crushed or a capsule opened to facilitate ease of administration, any unpleasant drug taste may be partially masked by mixing with custard, yogurt, rice pudding, other soft food, or fruit juice. The patient should be advised to consume the entire drug–food mixture to obtain the full dose,

and to maintain stability, the drug should not be premixed and allowed to set.

If a patient cannot swallow a solid dosage form, the pharmacist can suggest a chewable or liquid form of the drug. If these are not available, an extemporaneously compounded liquid form may be prepared. Extemporaneous compounding involves a pharmacist preparing a dosage form suitable for an individual patient. There are numerous resources available for this very important and expanding part of pharmacy practice (15,16).

FIGURE 7.20 Large Merrill filling machine that fills 16 bottles with 200 tablets each at one time. A flipper gate in the upper manifold directs the tablets into one row of bottles, while the other filled row is evacuated, and a new row of bottles is moved into position.

FIGURE 7.22 Unit-dose packaging of tablets and capsules. The drug name and other information are imprinted on the backing portion of each unit. (Courtesy of Eli Lilly and Company.)

PHARMACEUTICS ⬤ CASE STUDY

SUBJECTIVE INFORMATION

You have received the following prescription:

Rx

Diphenhydramine hydrochloride	25 mg
Phenyltoloxamine citrate	30 mg
Acetaminophen	325 mg

Make No. 30

Sig: Caps i to ii po HS prn sleep

You need to determine the amounts of the ingredients and of lactose to use to make 30 capsules each of size 3, 1, or 0.

OBJECTIVE INFORMATION

Volume capacity of capsules

3: 0.3 mL
1: 0.5 mL
0: 0.67 mL

Tapped density of ingredients, excipients

Lactose:	950 mg/mL
Diphenhydramine hydrochloride:	800 mg/mL
Phenyltoloxamine citrate:	750 mg/mL
Acetaminophen:	850 mg/mL

ASSESSMENT

For each active ingredient, the amount required to make 30 capsules is

Diphenhydramine HCl	750 mg
Phenyltoloxamine citrate	900 mg
Acetaminophen	9.75 g

DETERMINING THE AMOUNT OF LACTOSE REQUIRED: METHOD 1 USING NO. 1 CAPSULES

Weight of five empty No. 1 capsules: 400 mg

Weight of five No. 1 capsules full of lactose: 2.775 g

Weight of five No. 1 capsules full of diphenhydramine HCl: 2.4 g

Weight of five No. 1 capsules full of phenyltoloxamine citrate: 2.275 g

Weight of five No. 1 capsules full of acetaminophen: 2.525 g

Now average

Lactose: $(2{,}775 - 400)/5 = 475$ mg per capsule

Diphenhydramine HCl: $(2{,}400 - 400)/5 = 400$ mg per capsule

Phenyltoloxamine citrate: $(2{,}275 - 400)/5 = 375$ mg per capsule

Acetaminophen: $(2{,}525 - 400)/5 = 425$ mg per capsule

Percent of capsule filled by the required amounts of active ingredient

Diphenhydramine HCl: $25/400 \times 100 = 6.25\%$

Phenyltoloxamine citrate: $30/375 \times 100 = 8\%$

Acetaminophen: $325/425 \times 100 = 76.47\%$

Total = 90.72%, so the remaining 9.28% of each capsule will be lactose. Therefore, we require a total of $0.0928 \times 475 \times 30 = 1.3$ g approximately of lactose to make 30 No. 1 capsules. This calculation can be done in the same way for the No. 0 capsules, resulting in 6.15 g approximately of lactose required to make 30 No. 0 capsules. We cannot use No. 3 capsules for this prescription as only 255 mg of acetaminophen (and nothing else) will fit into a No. 3 capsule.

DETERMINING THE AMOUNT OF LACTOSE REQUIRED: METHOD 2

Calculate the percentage of the volume of a No. 1 capsule that each active ingredient will occupy:

Diphenhydramine HCl: $25 \text{ mg}/(800 \text{ mg/mL})/0.5 \text{ mL} \times 100 = 6.25\%$

Phenyltoloxamine citrate: $30 \text{ mg}/(750 \text{ mg/mL})/0.5 \text{ mL} \times 100 = 8\%$

Acetaminophen: $325 \text{ mg}/(850 \text{ mg/mL})/0.5 \text{ mL} \times 100 = 76.47\%$

Total = 90.72%, so the remaining 9.28% of each capsule will be lactose. The total amount of lactose required is

Lactose: $9.28/100 \times 0.5 \text{ mL} \times (950 \text{ mg/mL}) = 1.3$ g approximately

PHARMACEUTICS CASE STUDY CONT.

PLAN

To make 30 No. 1 capsules, we will require

Diphenhydramine HCl:	750 mg
Phenyltoloxamine citrate:	900 mg
Acetaminophen:	9.75 g
Lactose:	1.3 g

To make 30 No. 0 capsules, we will require

Diphenhydramine HCl:	750 mg
Phenyltoloxamine citrate:	900 mg
Acetaminophen:	9.75 g
Lactose:	6.15 g

We cannot use No. 3 capsules for this prescription.

CLINICAL CASE STUDY

SUBJECTIVE INFORMATION

HPI: K.P. is a 12-year-old WF who is brought to the emergency department by her mother, who states that "she went unconscious for about a minute." Mother was teaching her to bake cookies when K.P. asked if there was something burning in the oven. She described the smell as being that of "gasoline." Mother did not pay much attention to the strange smell, at which time the patient started to "wiggle" both her hands and "smack her lips together." Mother also stated that she started to chew really hard without any food in her mouth. The episode of strange chewing and lip smacking lasted about a minute, after which K.P. appeared confused and disoriented for several minutes. Her mother recalls asking if something was wrong during the episode, but the patient was unable to respond. Immediately after the episode, mother anxiously drove her to the emergency department. Upon arrival, the patient was oriented to time, place, and people. She denies any nausea, vomiting, dizziness, or confusion. When asked about the episode, patient states that she does not recall what her mother described. Patient is otherwise well.

PMH: No hospitalizations since birth

Birth history: Mother was diagnosed with preeclampsia at 8.5 months. Mother denies any use of drugs and alcohol during pregnancy. K.P. was born at 39 weeks' gestational age. She was bottle-fed as an infant.

Developmental history: Not significant. Patient developed well according to age. Currently developmentally intact

Immunizations: Up-to-date

SH: (–) EtOH

            (–) Tobacco

            (–) Caffeine

            (–) Illicit drugs

No siblings, lives with parents in Bloomingdale

FH: Mother with gestational diabetes × 12 years

            Father with HTN × 2 years

Diet: Eats about five times a day, mostly snacks (i.e., fruit, granola bars). Does not like to eat breakfast or dinner. Lunch is her biggest meal of the day. Meals consist mostly of cooked vegetables and pasta. Does not like junk food. Does not follow any specific diet

All: NKDA

PTA: No meds

CLINICAL CASE STUDY CONT.

OBJECTIVE INFORMATION

Ht:	4'4"
Wt:	102 lb
T:	100.1
Na:	135 mmol/L
K:	4.5 mmol/L
Cl:	102 mmol/L
CO_2:	18 mmol/L
BUN:	3.0 mmol/L
SrCr:	65 mmol/L

Abnormal EEG findings consistent with complex partial seizures: pattern of spikes and slow waves with a frequency of two cycles per second.

ASSESSMENT

K.P. is a 12-year-old white girl diagnosed with complex partial seizure per EEG and description of episode.

PLAN

1. Recommend extended-release carbamazepine (Carbatrol) 200 mg capsule by mouth twice daily. However, mother states that K.P. is unable to swallow capsules or tablets. Counsel the mother on gently opening the capsule at the seal, being careful not to break the capsule. Tell the mother to sprinkle the contents of the capsule into a small amount of food (e.g., a tablespoon of yogurt or applesauce) to ensure that all of the food with the drug is consumed. If contents are sprinkled in a large amount of food, the patient may not finish it all, hence may not receive the full dose of medication. This may lead to the medication not managing her seizures properly. As an alternative, counsel the mother about the use of the PillGlide to enable the carbamazepine to be easily swallowed.

2. Teach the patient and the mother about the common side effects of carbamazepine (e.g., dizziness, fatigue, worsening of seizures, nausea, vomiting) that affect a small fraction of patients. Advise the patient and the mother to report any unusual side effects (e.g., unusual bleeding, bruising, jaundice, dark urine, sore throat, abdominal pain).

3. Teach the patient and the mother about signs and symptoms of seizures. Inform them that most complex seizures are followed by an aura, which may consist of a strange smell, taste, sound, or visual disturbance. For example, K.P. smelled something burning before she had the seizure. Other signs may include a feeling of fear or anxiety. Inform the patient and the mother of the tonic–clonic movements that usually follow the aura. Explain to the mother that loss of consciousness is common with this type of seizure. Also explain that the patient may appear confused for several minutes after the seizure.

4. Monitoring parameters: carbamazepine plasma levels, signs and symptoms of seizures, frequency of episodes, and side effects of the medication. Goals: Increased patient knowledge about the condition, no medication side effects, no second episode, and therapeutic carbamazepine levels (4 to 12 mg/mL). Make sure the patient and the mother understand the importance of follow-up physician visits and of exercising caution when purchasing nonprescription and herbal products (i.e., consult a pharmacist).

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Compare the advantages and disadvantages of unit-dose packaging versus capsules packaged in plastic bottle containers.
2. Create a listing of extemporaneous prescriptions that call for the creation of a capsule dosage form for a patient.
3. Create a listing of conceivable ways a consumer/patient may misuse a capsule dosage form.
4. List five counseling points for proper administration of solid dosage forms, for example, capsules.
5. Make a listing of factors that might make a patient apprehensive about taking a capsule dosage form. List the points of advice/counseling points and methods and devices that are available to overcome this apprehension.

6. Identify several patient populations who might have difficulty administering a solid dosage form, for example, capsules, and explain your examples.

Individual Activities

1. Create a listing of liquid, oral prescription products, including the concentration of active ingredient(s), available in hard or soft gelatin capsules.
2. Create a listing of liquid, oral nonprescription products, including the concentration of active ingredient(s), available in hard or soft gelatin capsules.
3. Generate a listing of drug products that utilize active ingredients in a micronized powder form.
4. Select one USP drug monograph for a capsule dosage form and identify and describe its main components.

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8 Tablets

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between the various types of tablet dosage forms
2. Compare and contrast advantages and disadvantages of the various types of tablet dosage forms
3. List categories of ingredients, with examples, which are employed in the manufacture of compressed tablets
4. State quality standards and USP compendial requirements for tablets
5. Define and differentiate weight variation from content uniformity
6. Describe appropriate techniques for inspecting, packaging, and storing tablets

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration, and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture. Most tablets are used in the oral administration of drugs. Many of these are prepared with colorants and coatings of various types. Other tablets, such as those administered sublingually, buccally, or vaginally, are prepared to have features most applicable to their particular route of administration.

Tablets are prepared primarily by compression, with a limited number prepared by molding. Compressed tablets are manufactured with tablet machines capable of exerting great pressure in compacting the powdered or granulated material (Fig. 8.1A and B). Their shape and dimensions are determined by the use of various shaped punches and dies (Fig. 8.2). Molded tablets are prepared on a large scale by tablet machinery or on a small scale by manually forcing dampened powder material into a mold from which the formed tablet is then ejected and allowed to dry.

Some tablets are *scored*, or grooved, which allows them to be easily broken into two or more parts. This enables the patient to swallow smaller portions as may be desired, or when prescribed, it allows the tablet to be taken in reduced or divided dosage. Some tablets that are not scored are not intended to be broken or cut by the patient since they may have special coatings and/or drug-release features that would be compromised by altering the tablet's physical integrity.

TYPES OF TABLETS

The various types of tablets are described as follows.

Compressed Tablets

In addition to the medicinal agent or agents, compressed tablets usually contain a number of pharmaceutical excipients, including the following:

Diluents or *fillers*, which add the necessary bulk to a formulation to prepare tablets of the desired size

FIGURE 8.1 A: MiniTAblet Press for development and small-scale production. (Courtesy of GlobePharma.) **B:** High-performance double rotary tablet press. The Korsch PharmapressR has a maximum output of 1 million tablets per hour, but for continuous operation, it is generally run to produce 600,000 to 800,000 tablets per hour. (Courtesy of Korsch Tableting.)

Binders or *adhesives*, which promote adhesion of the particles of the formulation, allowing a granulation to be prepared and maintaining the integrity of the final tablet

Disintegrants or *disintegrating agents*, which promote breakup of the tablets after administration to smaller particles for ready drug availability

Antiadherents, *glidants*, *lubricants*, or *lubricating agents*, which enhance the flow of the material into the tablet dies, minimize wear of the punches and dies, prevent fill material from sticking to the punches and dies, and produce tablets with a sheen

Miscellaneous adjuncts such as colorants and flavorants

After compression, tablets may be coated with various materials as described later. Tablets for oral, buccal, sublingual, or vaginal administration may be prepared by compression.

Multiple Compressed Tablets

Multiple compressed tablets are prepared by subjecting the fill material to more than a single compression. The result may be a multiple-layer tablet or a tablet within a tablet, the inner tablet being the *core* and the outer portion being the *shell* (Fig. 8.3). Layered tablets are prepared by initial compaction of a portion of fill material in a die followed by

FIGURE 8.2 Various punches and dies for the production of distinctive tablets. (Courtesy of Cemach Machineries Ltd.)
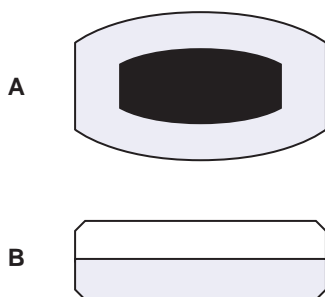
FIGURE 8.3 Multiple compressed tablets. **A:** A core of one drug and a shell of another. **B:** A layered tablet of two drugs.

FIGURE 8.4 Cutaway view of gelcaps dosage form, a gelatin-coated capsule-shaped tablet. Dosage form is more easily swallowed than a comparable tablet, smaller than an equivalent capsule, and tamper evident. (Courtesy of McNeil Consumer Products.)

additional fill material and compression to form two-layered or three-layered tablets, depending on the number of separate fills. Each layer may contain a different medicinal agent, separated for reasons of chemical or physical incompatibility, staged drug release, or simply the unique appearance of the layered tablet. Usually, each portion of fill is a different color to produce a distinctive-looking tablet. In preparation of tablets within tablets, special machines are required to place the preformed core tablet precisely within the die for application of surrounding fill material.

Sugarcoated Tablets

Compressed tablets may be coated with a colored or an uncolored sugar layer. The coating is water soluble and quickly dissolves after swallowing. The sugarcoat protects the enclosed drug from the environment and provides a barrier to objectionable taste or odor. The sugarcoat also enhances the appearance of the compressed tablet and permits imprinting of identifying manufacturer's information. Among the disadvantages to sugarcoating tablets are the time and expertise required in the coating process and the increase in size, weight, and shipping costs. Sugarcoating may add 50% to the weight and bulk of the uncoated tablet.

Film-Coated Tablets

Film-coated tablets are compressed tablets coated with a thin layer of a polymer capable of forming a skin-like film. The film is usuall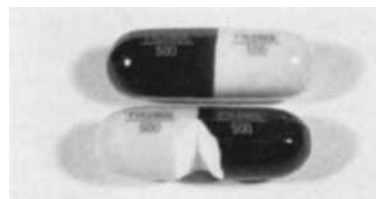y colored and has the advantage over sugarcoatings in that it is more durable, less bulky, and less time-consuming to apply. By its composition, the coating is designed to rupture and expose the core tablet at the desired location in the gastrointestinal tract.

Gelatin-Coated Tablets

A recent innovation is the gelatin-coated tablet. The innovator product, the gelcap, is a capsule-shaped compressed tablet (Fig. 8.4) that allows the coated product to be about one-third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilitates swallowing, and gelatin-coated tablets are more tamper evident than unsealed capsules. Examples include Tylenol Cold Multi-Symptom Daytime (McNeil Consumer).

Enteric-Coated Tablets

Enteric-coated tablets have delayed-release features. They are designed to pass unchanged through the stomach to the intestines, where the tablets disintegrate and allow drug dissolution and absorption and/or effect. Enteric coatings are employed when the drug substance is destroyed by gastric acid or is particularly irritating to the gastric mucosa or when bypass of the stomach substantially enhances drug absorption. Examples include Ecotrin tablets and caplets (GlaxoSmithKline Beecham).

Buccal and Sublingual Tablets

Buccal and sublingual tablets are flat, oval tablets intended to be dissolved in the buccal pouch (*buccal tablets*) or beneath the tongue (*sublingual tablets*) for absorption through the

oral mucosa. They enable oral absorption of drugs that are destroyed by the gastric juice and/or are poorly absorbed from the gastrointestinal tract. Buccal tablets are designed to erode slowly, whereas those for sublingual use (such as nitroglycerin [NTG]) dissolve promptly and provide rapid drug effects. *Lozenges* or *troches* are disc-shaped solid dosage forms containing a medicinal agent and generally a flavoring substance in a hard candy or sugar base. They are intended to be slowly dissolved in the oral cavity, usually for local effects, although some are formulated for systemic absorption. An example would be Mycelex troches (Bayer Consumer Care).

Chewable Tablets

Chewable tablets, which have a smooth, rapid disintegration when chewed or allowed to dissolve in the mouth, have a creamy base, usually of specially flavored and colored mannitol. Chewable tablets are especially useful for administration of large tablets to children and adults who have difficulty swallowing solid dosage forms. Examples include Pepcid AC chewable tablets (J&J Merck) and Rolaids chewable tablets (Pfizer Consumer Healthcare).

Effervescent Tablets

Effervescent tablets are prepared by compressing granular effervescent salts that release gas when in contact with water. These tablets generally contain medicinal substances that dissolve rapidly when added to water. The "bubble action" can assist in breaking up the tablets and enhancing the dissolution of the active drug. Examples include Alka-Seltzer Original tablets (Bayer Consumer Care) and Zantac EFFERdose (GlaxoSmithKline).

Molded Tablets

Certain tablets, such as tablet triturates, may be prepared by molding rather than by compression. The resultant tablets are very soft and soluble and are designed for rapid dissolution.

Tablet Triturates

Tablet triturates are small, usually cylindrical, molded, or compressed tablets containing small amounts of usually potent drugs. Today, only a few tablet triturate products are available commercially, with most of these produced by tablet compression. Since tablet triturates must be readily and completely soluble in water, only a minimal amount of pressure is applied during their manufacture. A combination of sucrose and lactose is usually the diluent. The few tablet triturates that remain are used sublingually, such as NTG tablets.

Pharmacists also employ tablet triturates in compounding. For example, triturates are inserted into capsules or dissolved in liquid to provide accurate amounts of potent drug substances.

Hypodermic Tablets

Hypodermic tablets are no longer available in the United States. They were originally used by physicians in extemporaneous preparation of parenteral solutions. The required number of tablets was dissolved in a suitable vehicle, sterility attained, and the injection performed. The tablets were a convenience, since they could be easily carried in the physician's medicine bag and injections prepared to meet the needs of the individual patients. However, the difficulty in achieving sterility and the availability of prefabricated injectable products, some in disposable syringes, have eliminated the need for hypodermic tablets.

Dispensing Tablets

Dispensing tablets are no longer in use. They might better have been termed *compounding tablets* because the pharmacist used them to compound prescriptions; they were *not* dispensed as such to the patient. The tablets contained large amounts of highly potent drug substances, so the pharmacist could rapidly obtain premeasured amounts for compounding multiple dosage units. These tablets had the dangerous potential of being inadvertently dispensed as such to patients.

Immediate-Release Tablets

Immediate-release tablets are designed to disintegrate and release their medication with no special rate-controlling features, such as special coatings and other techniques.

Rapidly Disintegrating or Dissolving Tablets

Rapid-release tablets (rapidly dissolving tablets or RDTs) are characterized by disintegrating or dissolving in the mouth within 1 minute, some within 10 seconds (e.g., Clarinex Reditabs [loratadine], Schering). Tablets of this type are designed for children and the elderly or for any patient who has difficulty in swallowing tablets. They liquefy on the tongue, and the patient swallows the liquid. A number of techniques are used to prepare these tablets, including lyophilization (e.g., Zydis, R.P. Scherer), soft direct compression (e.g., Wow-Tab, Yamanouchi Shaklee Pharma), and other methods (e.g., Quicksolv, Janssen). These tablets are prepared using very water-soluble excipients designed to wick water into the tablet for rapid disintegration or dissolution. They have the stability characteristics of other solid dosage forms.

The original fast-dissolving tablets were molded tablets for sublingual use. They generally consisted of active drug and lactose moistened with an alcohol–water mixture to form a paste. The tablets were then molded, dried, and packaged. For use, they were simply placed under the tongue to provide a rapid onset of action for drugs such as NTG. Also, they have been used for drugs that are destroyed in the gastrointestinal tract, such as testosterone, administered sublingually for absorption to minimize the first-pass effect.

These RDTs are more convenient to carry and administer than an oral liquid. They are generally packaged in cards or bubble-type packaging with each individual tablet in its own cavity. As these tablets are often soft, the backing is peeled back to reveal the tablet where it is then removed, as opposed to attempting to press the tablet through the backing material as is common with standard compressed tablets. There are no standards that define an RDT, but one possibility

is dissolution in the mouth within approximately 15 seconds; anything slower would not be categorized as rapidly dissolving.

Notwithstanding these advantages, there are a number of disadvantages and difficulties associated with formulating RDTs, including drug loading, taste masking, friability, manufacturing costs, and stability of the product.

Drug loading is incorporation of the drug into the dosage form. Some RDTs are made as blanks to which a drug is postloaded, or added after the blank is made. Generally, the drug is in solution, often in an organic solvent (alcohol), and is added to the tablet, after which the solvent evaporates. It is also possible for the drug to be added as a dry powder electrostatically at this stage. Most drugs, however, are incorporated into the tablets during manufacturing.

Taste masking poses numerous challenges for RDTs. Since the drug product dissolves in the mouth, any taste of the drug must be covered, either by a flavoring technique or by microencapsulation or nanoencapsulation. The product also should not be gritty, which necessitates very small particle sizes if microencapsulation is used.

Friability is an inherent problem in RDTs. For a product to dissolve instantly, it may be quite friable. Making it more firm and less friable may increase dissolution time. A balance generally must be achieved between friability and the speed of dissolution.

Lyophilized Foam

The first entry into the RDT field was the Zydis delivery system. The tablets are prepared by foaming a mixture of gelatin, sugar or sugars, drug, and any other components and by pouring the foam into a mold. The mold also serves as the unit dose-dispensing package. The foam is lyophilized (Fig. 8.5), and the tablets in the mold are packaged. This system is the fastest disintegrating system on the market, as the tablets will dissolve on the tongue in a matter of a few seconds. One disadvantage of this method is that taste masking can be a problem, since the drug is incorporated during the formation of the tablet itself. Another difficulty is that these

FIGURE 8.5 A large-scale lyophilizer. (Courtesy of Virtis.)

tablets are sometimes difficult to remove from the packaging, since they are soft and one should not press on the dosage unit to remove it but should peel off the material, exposing the tablet in its mold.

Claritin (loratadine) rapidly disintegrating tablets (Reditabs, Schering Corporation) contain 10 mg of micronized loratadine in a base containing citric acid, gelatin, mannitol, and mint flavor formed with the Zydis technology. It disintegrates within seconds after being placed on the tongue, with or without water. Claritin Reditabs have been shown to provide at least equivalent pharmacokinetic parameters to those of traditional tablets; in some cases, the Reditabs provided greater maximum concentration (C_{max}) and area under the curve values. Claritin Reditabs are blister-packaged tablets that should be stored in a dry place at 2°C to 25°C. They should be used within 6 months of opening the protective laminated foil pouch containing the blister cards; each foil pouch contains one blister card containing 10 individually sealed tablets (1). Other commercial products using this technology include the Maxalt-MLT (Merck), Zofran ODT (GlaxoSmithKline), Zyprexa Zydis (Eli Lilly) tablets, and Tylenol Meltaways Jr. (McNeil Consumer). It should be noted that the Clarinex Reditabs (desloratadine, Schering) use a different formulation principle, despite the same dosage form designation. The excipients consist of mannitol, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate, butylated methacrylate copolymer, crospovidone, aspartame, citric acid, sodium bicarbonate, colloidal silicon dioxide, ferric oxide red, and tutti-frutti flavoring (2).

Compression

Another method of preparation is using standard tableting technology with a composition that will enhance fluid uptake and tablet disintegration and dissolution. For example, superdisintegrants incorporated with a small quantity of effervescent material will lead to intermediately fast disintegration. The tablets are compressed a little thinner than standard tablets to allow for a larger surface area exposed to the saliva in the mouth. Upon placement in the mouth, the disintegrant starts wicking water into the tablet. The effervescent materials start dissolving and aid in the breakup. This continues until the tablet has disintegrated.

An example product is the Dimetapp ND orally disintegrating tablet (nondrowsy allergy tablets; Wyeth Consumer Healthcare).

These tablets contain loratadine 10 mg in a vehicle of artificial and natural flavor, aspartame, citric acid, colloidal silicon dioxide, corn syrup solids, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, modified food starch, and sodium bicarbonate (3).

One product using the DuraSolv and OraSolv technologies by Cima Labs is Tempra Quicklets containing acetaminophen 80 mg. These tablets also contain aspartame, citric acid, D&C Red No. 27 Lake, FD&C Blue No. 1 Lake, flavor, magnesium stearate, mannitol, potassium carbonate, silicon dioxide, and sodium bicarbonate. They are somewhat slower than the Zydis tablet, taking about 30 to 45 seconds, unless some tongue pressure is used. These tablets come in a firm molded plastic package to prevent breakage (4). Other commercial products using the same technology include the Alavert (Wyeth), NuLev FasTabs (Schwarz Pharma), Symax FasTabs (Capellon), Remeron SolTabs (Organon), Triaminic Softchews (Novartis Consumer Health), Abilify Discmelt (Otsuka America), Tylenol Meltaways (McNeil Consumer), and the Zomig ZMT (AstraZeneca).

The Flashtab technology by Ethypharm is used in Excedrin QuickTabs and an example of the Wowtab technology by Yamanouchi Pharma is the Benadryl Fastmelt.

Example Chewable Dispersible Tablets

Lamictal chewable dispersible tablets for oral administration contain 2, 5, or 25 mg of lamotrigine and the following inactive ingredients: black currant flavor, calcium carbonate, low-substituted hydroxypropyl cellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate (5).

Lamotrigine is also available as standard swallow tablets for oral administration in strengths of 25, 100, 150, and 200 mg, also containing lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, and various coloring agents for the different strengths. Lamotrigine is an antiepileptic drug chemically unrelated to existing drugs in this therapeutic class. The swallow tablets should be swallowed whole, as chewing may leave a bitter taste. The chewable tablets may be swallowed whole, chewed, or mixed in water or diluted fruit juice. If they are chewed, a small amount of water or diluted fruit juice will aid in swallowing. If the tablet is to be dispersed before it is taken, it can be added to a small amount of liquid (1 teaspoonful or sufficient to cover the medication in a glass or spoon), and approximately 1 minute later when the tablet is completely dispersed, it is mixed and administered immediately.

Didanosine (Videx) is available in three dosage forms: a chewable dispersible buffered tablet, buffered powder for oral solution, and a pediatric powder for oral solution (6). Videx is a synthetic purine nucleoside analog active against HIV. The chewable dispersible buffered tablets are for oral administration in strengths of 25, 50, 100, 150, and 200 mg. Each tablet is buffered with calcium carbonate and magnesium hydroxide. Also contained in the tablet matrix are aspartame, sorbitol, microcrystalline cellulose, Polyplasdone, mandarin orange flavor, and magnesium stearate.

Didanosine (2′,3′-dideoxyinosine) is unstable in acidic solutions; at a pH less than 3 at body temperature, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes. This is the reason for the buffering agents in the chewable tablets and in one of the oral solutions. It is also available as an enteric-coated formulation (Videx EC delayed-release capsules) to protect it from the acidic contents of the stomach.

Since these tablets tend to be more fragile than standard compressed tablets, they are generally packaged in more sturdy materials to prevent damage.

Extended-Release Tablets

Extended-release tablets (sometimes called controlled-release tablets) are designed to release their medication in a predetermined manner over an extended period. They are discussed in Chapter 9.

Vaginal Tablets

Vaginal tablets, also called *vaginal inserts*, are uncoated, bullet-shaped, or ovoid tablets

inserted into the vagina for local effects. They are prepared by compression and shaped to fit snugly on plastic inserter devices that accompany the product. They contain antibacterials for the treatment of nonspecific vaginitis caused by *Haemophilus vaginalis* or antifungals for the treatment of vulvovaginitis candidiasis caused by *Candida albicans* and related species.

COMPRESSED TABLETS

The physical features of compressed tablets are well known: round, oblong, or unique in shape; thick or thin; large or small in diameter; flat or convex; unscored or *scored* (Fig. 8.6) in halves, thirds, or quadrants; engraved or imprinted with an identifying symbol and/or code number; coated or uncoated; colored or uncolored; and one, two, or three layered.

Tablet diameters and shapes are determined by the die and punches used in compression. The less concave the punches, the flatter the tablets; conversely, the more concave the punches, the more convex the resulting tablets (Fig. 8.7). Punches with raised impressions produce recessed impressions on the tablets; punches with recessed etchings produce tablets with raised impressions or monograms. Monograms may be placed on one or on both sides of a tablet, depending on the punches.
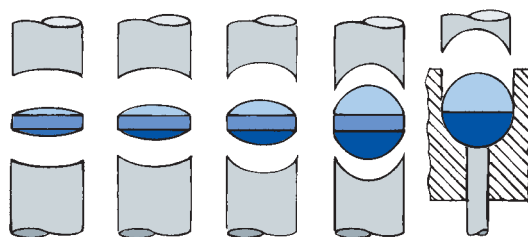

FIGURE 8.7 Contours of the punches determine the shape of the tablets. *From left to right*: flat face, shallow cup, standard cup, deep cup, and modified ball. (Courtesy of Cherry-Burrell Corporation.)

Quality Standards and Compendial Requirements

In addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards. These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. These factors must be controlled during production (in-process controls) and verified after the production of each batch to ensure that established product quality standards are met (Fig. 8.8).

FIGURE 8.6 Packages of a drug product of different tablet strengths.

FIGURE 8.8 Quality control in the manufacturing of tablets. (Courtesy of Eli Lilly and Company.)

FIGURE 8.9 Automatic balance that weighs product and prints statistics to determine compliance with USP weight variation requirements for tablets. (Courtesy of Mocon Modern Controls.)

Tablet Weight and USP Weight Variation Test

The quantity of fill in the die of a tablet press determines the weight of the tablet. The volume of fill is adjusted with the first few tablets to yield the *desired weight and content*. For example, if a tablet is to contain 20 mg of a drug substance and if 100,000 tablets are to be produced, 2,000 g of drug is included in the formula. After the addition of the pharmaceutical additives, such as the diluent, disintegrant, lubricant, and binder, the formulation may weigh 20 kg, which means that each tablet must weigh 200 mg for 20 mg of drug to be present. Thus, the depth of fill in the tablet die must be adjusted to hold a volume of granulation weighing 200 mg. During production, sample tablets are periodically removed for visual inspection and automated physical measurement (Fig. 8.9).

The USP contains a test for determination of dosage form uniformity by *weight variation* for uncoated tablets (5). In the test, 10 tablets are weighed individually, and the average weight is calculated. The tablets are assayed, and the content of active ingredient in each of the 10 tablets is calculated assuming homogeneous drug distribution.

Content Uniformity

By the USP method, 10 dosage units are individually assayed for their content according to the method described in the individual monograph. Unless otherwise stated in the monograph, the requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range of 85% to 115% of the label claim and the standard deviation is less than 6%. If one or more dosage units do not meet these criteria, additional tests as prescribed in the USP are required (7).

Tablet Thickness

The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compression.

To produce tablets of uniform thickness during and between batch productions for the same formulation, care must be exercised to employ the same factors of fill, die, and pressure. The degree of pressure affects not only thickness but also hardness of the tablet; hardness is perhaps the more important criterion since it can affect disintegration and dissolution. Thus, for tablets of uniform thickness and hardness, it is doubly important to control pressure. Tablet thickness may be measured by hand gauge during production or by automated equipment (Figs. 8.10 to 8.12).

Tablet Hardness and Friability

It is fairly common for a tablet press to exert as little as 3,000 and as much as 40,000 lb of force in the production of tablets. Generally, the greater the pressure applied, the harder the tablets, although the characteristics of the granulation also have a bearing on hardness. Certain tablets, such as lozenges and buccal tablets, that are intended to dissolve slowly are intentionally made hard; other tablets, such as those for immediate drug release, are made soft. In general, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing.

Special dedicated hardness testers (Fig. 8.13) or multifunctional systems (Fig. 8.12) are used to measure the degree of force (in kilograms, pounds, or in arbitrary units) required to break a tablet. A force of about 4 kg is considered the minimum requirement for a satisfactory

FIGURE 8.10 Tablet thickness gauge. (Courtesy of Eli Lilly and Company.)

tablet. Multifunctional automated equipment can determine weight, hardness, thickness, and diameter of the tablet.

A tablet's durability may be determined through the use of a *friabilator* (Fig. 8.14). This apparatus determines the tablet's *friability*, or tendency to crumble, by allowing it to roll and fall within the drum. The tablets are weighed before and after a specified number of rotations, and any weight loss is determined. Resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging, and shipment. A

maximum weight loss of not more than 1% generally is considered acceptable for most products.

Tablet Disintegration

For the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution. Tablet

FIGURE 8.12 Automatic weight, hardness, thickness, and tablet diameter test instrument for quality control. Using a microprocessor and monitor for visualization, the instrument can test up to 20 samples at a time. (Courtesy of JB Pharmatron.)
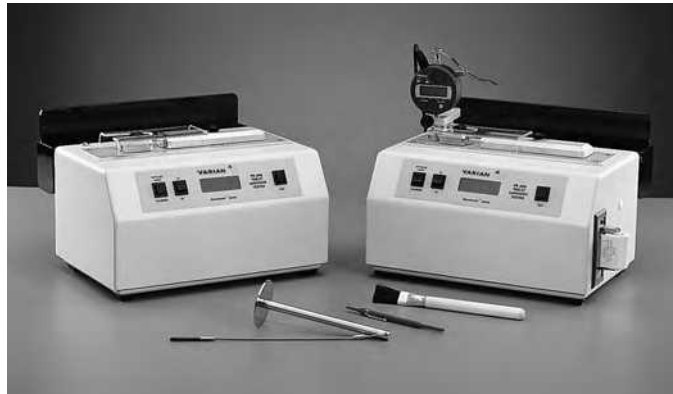

FIGURE 8.11 Tablet diameter testing instrument. (Courtesy of Shionogi Qualicaps.)

FIGURE 8.13 Tablet hardness tester. (Courtesy of Varian Inc.)

disintegration also is important for tablets containing medicinal agents (such as antacids and antidiarrheals) that are not intended to be absorbed but rather to act locally within the gastrointestinal tract. In these instances, tablet disintegration provides drug particles with an increased surface area for activity within the gastrointestinal tract.

FIGURE 8.14 Varian friabilator testing apparatus for rolling and impact durability. Tablets are weighed and placed in the acrylic drums, in which a curved baffle is mounted. When the motor is activated by setting the timer, the tablets roll and drop. If the free fall within the drum results in breakage or excessive abrasion of the tablets, they are considered not suited to withstand shipment. The motor makes 20 rpm. When the tablets have been tested, they are removed and weighed again. The difference in weight within a given time indicates the rate of abrasion. (Courtesy of Varian Inc.)

All USP tablets must pass a test for disintegration, which is conducted in vitro using a testing apparatus such as the one shown in Figure 8.15. The apparatus consists of a basket and rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen. During testing, a tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in the immersion fluid at 29 to 32 cycles per minute, the wire screen always below the level of the fluid. For uncoated tablets, buccal tablets, and

FIGURE 8.15 Tablet disintegration testing apparatus. (Courtesy of Varian Inc.)

sublingual tablets, water at about 37°C serves as the immersion fluid unless another fluid is specified in the individual monograph. For these tests, complete disintegration is defined as "that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core" (7). Tablets must disintegrate within the times set forth in the individual monograph, usually 30 minutes, but varying from about 2 minutes for NTG tablets to up to 4 hours for buccal tablets. If one or more tablets fail to disintegrate, additional tests prescribed by the USP must be performed.

Enteric-coated tablets are similarly tested, except that the tablets are tested in simulated gastric fluid for 1 hour, after which no sign of disintegration, cracking, or softening must be seen. They are then actively immersed in the simulated intestinal fluid for the time stated in the individual monograph, during which time the tablets disintegrate completely for a positive test.

Tablet Dissolution

In vitro dissolution testing of solid dosage forms is important for a number of reasons (8):

1. It guides formulation and product development toward product optimization. Dissolution studies in the early stages of a product's development allow differentiation between formulations and correlations identified with in vivo bioavailability data.
2. Manufacturing may be monitored by dissolution testing as a component of the overall quality assurance program. The conduct of such testing from early product development through approval and commercial production ensures control of any variables of materials and processes that could affect dissolution and quality standards.
3. Consistent in vitro dissolution testing ensures bioequivalence from batch to batch. In assessing such bioequivalence, the U.S. Food and Drug Administration (FDA) allows manufacturers to examine scale-up batches of 10% of the proposed size of the actual production batch or 100,000 dosage units, whichever is greater.

4. It is a requirement for regulatory approval of marketing for products registered with the FDA and regulatory agencies of other countries. New Drug Applications (NDAs) submitted to the FDA contain in vitro dissolution data generally obtained from batches used in pivotal clinical and/or bioavailability studies and from human studies conducted during product development (9). Once the specifications are established in an approved NDA, they become official (USP) specifications for all subsequent batches and bioequivalent products.

The goal of in vitro dissolution testing is to provide insofar as is possible a reasonable prediction of or correlation with the product's in vivo bioavailability. The system relates combinations of a drug's solubility (high or low) and its intestinal permeability (high or low) as a possible basis for predicting the likelihood of achieving a successful in vivo–in vitro correlation (IVIVC) (9,10). Using this system, drugs are placed into one of four categories as follows:

I	II
High solubility and high permeability	Low solubility and high permeability
III	IV
High solubility and low permeability	Low solubility and low permeability

For a high-solubility and high-permeability Category I drug, an IVIVC may be expected if the dissolution rate is slower than the rate of gastric emptying (the rate-limiting factor) (11). In the case of a low-solubility and high-permeability Category II drug, dissolution may be the rate-limiting step for absorption, and an IVIVC may be expected. In the case of a high-solubility and low-permeability Category III drug, permeability is the rate-controlling step, and only a limited IVIVC may be possible. In the case of a Category IV drug with low solubility and low permeability, significant problems are likely for oral drug delivery (9).

As noted previously, tablet disintegration is the important first step to the dissolution of the drug in a tablet. A number of formulation

and manufacturing factors can affect the disintegration and dissolution of a tablet, including particle size of the drug substance; solubility and hygroscopicity of the formulation; type and concentration of the disintegrant, binder, and lubricant; manufacturing method, particularly the compactness of the granulation and compression force used in tableting; and any in-process variables (12). Together, these factors present a set of complex interrelated conditions that have a bearing on a product's dissolution characteristics. Therefore, batch-to-batch consistency is vitally important to establish dissolution test standards and controls for both materials and processes and to implement them during production and in final testing.

In addition to formulation and manufacturing controls, the method of dissolution testing must be controlled to minimize important variables such as paddle rotational speed, vibration, and disturbances by sampling probes. Dissolution testing for oral dosage forms has been a component of evaluating product quality in the USP since 1970, when only 12 monographs contained such a requirement. Today, the requirement is standard for tablets and capsules.

The USP includes seven apparatus designs for drug release and dissolution testing of immediate-release oral dosage forms, extended-release products, enteric-coated products, and transdermal drug delivery devices. Of primary interest here are USP Apparatus 1 and USP Apparatus 2, used principally for immediate-release solid oral dosage forms.

The equipment consists of (*a*) a variable-speed stirrer motor; (*b*) a cylindrical stainless steel basket on a stirrer shaft (USP Apparatus 1) or a paddle as the stirring element (USP Apparatus 2); (*c*) a 1,000-mL vessel of glass or other inert transparent material fitted with a cover having a center port for the shaft of the stirrer and three additional ports, two for removal of samples and one for a thermometer; and (*d*) a water bath to maintain the temperature of the dissolution medium in the vessel. For use of USP Apparatus 1, the dosage unit is placed inside the basket. For use of USP Apparatus 2, the dosage unit is placed in the vessel.

In each test, a volume of the dissolution medium (as stated in the individual monograph) is placed in the vessel and allowed to come to 37°C ± 0.5°C. Then, the stirrer is rotated at the speed specified, and at stated intervals, samples of the medium are withdrawn for chemical analysis of the proportion of drug dissolved. The tablet or capsule must meet the stated monograph requirement for rate of dissolution, for example, "not less than 85% of the labeled amount is dissolved in 30 minutes."

There is growing recognition that where inconsistencies in dissolution occur, they occur not between dosage units from the same production batch but rather between batches or between products from different manufacturers, most likely because of the many factors of formulation, materials, and manufacturing pointed out earlier. However, since dosage units within a batch are generally not the problem, pooled dissolution testing has emerged. This process recognizes batch characteristics and allows pooled specimens to be tested. The pooled specimens may be sampled from the individual dissolution vessels in the apparatus or from multiple dosage units dissolved in a single vessel (13).

Sophisticated and highly automated equipment is continually being developed to provide high levels of quality assurance and control to dissolution testing (Figs. 8.16 and 8.17).

FIGURE 8.16 Hanson Automated Dissolution Test System. It features microprocessor and templates to create, edit, store, and validate dissolution protocols; graphical displays with menus; and icon-based program controls. (Courtesy of Hanson Research.)

FIGURE 8.17   A modern computer laboratory dedicated to studies of drug dissolution from solid dosage forms. Included are Erweka dissolution baths, Hewlett-Packard computers, and Hewlett-Packard diode assay spectrophotometers. (Courtesy of Elan Corporation, plc.)

Compressed Tablet Manufacture

Compressed tablets may be made by three basic methods: *wet granulation*, *dry granulation*, and *direct compression*. Figure 8.18 presents schematic drawings of each method.

Most powdered medicinal agents require addition of excipients such as diluents, binders, disintegrants, and lubricants to provide the desired characteristics for tablet manufacture and efficacious use. One important requirement in tablet manufacture is that the drug mixture flows freely from the hopper of the tablet press into the dies to enable high-speed compression of the powder mix into tablets. Granulations of powders provide this free flow. Granulations also increase material density, improving powder compressibility during tablet formation.

Wet Granulation

Wet granulation is a widely employed method for the production of compressed tablets. The steps required are (*a*) weighing and blending the ingredients, (*b*) preparing a dampened powder or a damp mass, (*c*) screening the dampened powder or damp mass into pellets or granules, (*d*) drying the granulation, (*e*) sizing the granulation by dry screening, (*f*) adding lubricant and blending, and (*g*) forming tablets by compression.

Weighing and Blending

Specified quantities of active ingredient, diluent or filler, and disintegrating agent are mixed by mechanical powder blender or mixer until uniform.

Fillers include lactose, microcrystalline cellulose, starch, powdered sucrose, and calcium phosphate. The choice of filler usually is based on the experience of the manufacturer with the material, its relative cost, and its compatibility with the other formulation ingredients. For example, calcium salts must not be used as fillers with tetracycline antibiotics because of an interaction between the two agents that results in reduced tetracycline absorption from the gastrointestinal tract. Among the fillers most preferred are lactose, because of its solubility and compatibility, and microcrystalline cellulose, because of its easy compaction, compatibility, and consistent uniformity of supply (14).

Disintegrating agents include croscarmellose, corn and potato starches, sodium starch glycolate, sodium carboxymethylcellulose, polyvinylpyrrolidone (PVP), crospovidone, cation exchange resins, alginic acid, and other materials that swell or expand on exposure to moisture and effect the rupture or breakup of the tablet in the gastrointestinal tract. Croscarmellose (2%) and sodium starch glycolate (5%) are often preferred because of their high water uptake and rapid action. One commercial brand of sodium starch glycolate is reported to swell up to 300% of its volume in water (15). When starch is employed, 5% to 10% is usually suitable, but up to about 20% may be used to promote more rapid tablet disintegration. The total amount of disintegrant used is not always added in preparing the granulation. Often a portion (sometimes half) is reserved and added to the finished granulation prior to tablet formation. This results in double disintegration of the tablet.
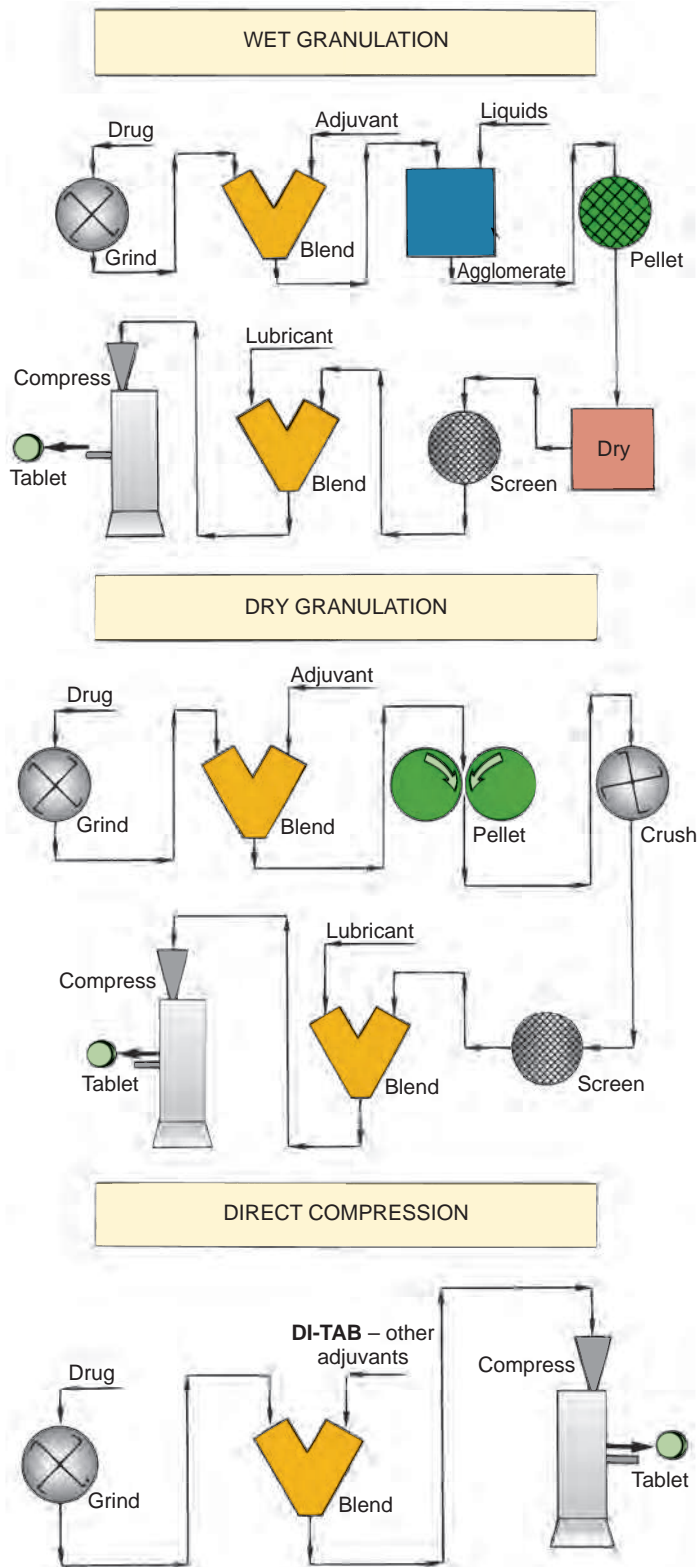
FIGURE 8.18 The three main methods for the preparation of tablets. (Courtesy of Stauffer Chemical Co.)

One portion assists in the breakup of the tablet into pieces, and the other portion assists in the breakup of the pieces into fine particles.

Preparing the Damp Mass

A liquid binder is added to the powder mixture to facilitate adhesion of the powder particles. Either a dampened powder formed into granules or a damp mass resembling dough is formed and used to prepare the granulation. A good binder results in appropriate tablet hardness and does not hinder the release of the drug from the tablet.

Among binding agents are solutions of povidone, an aqueous preparation of cornstarch (10% to 20%), glucose solution (25% to 50%), molasses, methylcellulose (3%), carboxymethylcellulose, and microcrystalline cellulose. If the drug substance is adversely affected by an aqueous binder, a nonaqueous solution, or dry binder, may be used. The amount of binding agent used is part of the operator's art; however, the resulting binder–powder mixture should compact when squeezed in the hand. The binding agent contributes to adhesion of the granules to one another and maintains the integrity of the tablet after compression. However, care must be exercised not to overwet or underwet the powder. Overwetting can result in granules that are too hard for proper tablet formation, and underwetting can result in tablets that are too soft and tend to crumble. When desired, a colorant or flavorant may be added to the binding agent to prepare a granulation with an added feature.

Screening the Damp Mass into Pellets or Granules

The dampened powder granules are screened, or the wet mass is pressed through a screen (usually 6 or 8 meshes) to prepare the granules. This may be done by hand or with special equipment that prepares the granules by extrusion through perforations in the apparatus. The resultant granules are spread evenly on large lined trays and dried to consistent weight or constant moisture content.
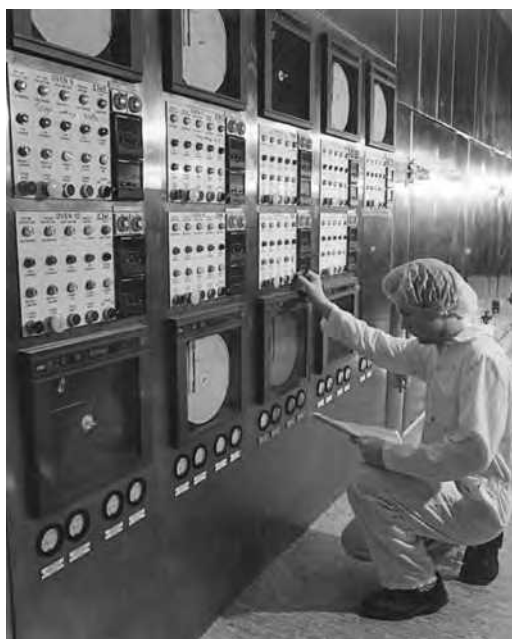

FIGURE 8.19 Temperature-controlled Casburt Drying Oven used in the preparation of granules and controlled-release beads. (Courtesy of Elan Corporation, plc.)

Drying the Granulation

Granules may be dried in thermostatically controlled ovens that constantly record the time, temperature, and humidity (Fig. 8.19).

Sizing the Granulation by Dry Screening

After drying, the granules are passed through a screen of a smaller mesh than that used to prepare the original granulation. The degree to which the granules are reduced depends on the size of the punches to be used. In general, the smaller the tablet to be produced, the smaller the granules. Screens of 12- to 20-mesh size are generally used for this purpose. Sizing of the granules is necessary so that the die cavities for tablet compression may be completely and rapidly filled by the free-flowing granulation. Voids or air spaces left by too large a granulation result in the production of uneven tablets.

Adding Lubricant and Blending

After dry screening, a dry lubricant is dusted over the spread-out granulation through a fine-mesh screen. Lubricants

contribute to the preparation of compressed tablets in several ways: They improve the flow of the granulation in the hopper to the die cavity. They prevent adhesion of the tablet formulation to the punches and dies during compression. They reduce friction between the tablet and the die wall during the ejection of the tablet from the machine. They give a sheen to the finished tablet. Among the more commonly used lubricants are magnesium stearate, calcium stearate, stearic acid, talc, and sodium stearyl fumarate. Magnesium stearate is most used (14). The quantity of lubricant used varies from one operation to another but usually ranges from about 0.1% to 5% of the weight of the granulation.

All-in-One Granulation Methods

Technologic advances now allow the entire process of granulation to be completed in a continuous *fluid bed process*, using a single piece of equipment, the fluid bed granulator (Figs. 8.20 and 8.21).

FIGURE 8.20 Fluid bed granulator. (Courtesy of Glatt Air Techniques, Inc.)

The fluid bed granulator performs the following steps: (*a*) preblending the formulation powder, including active ingredients, fillers, and disintegrants, in a bed with fluidized air; (*b*) granulating the mixture by spraying onto the fluidized powder bed, a suitable liquid binder, such as an aqueous solution of acacia, hydroxypropyl cellulose, or povidone; and (*c*) drying the granulated product to the desired moisture content.

Another method, microwave vacuum processing, also allows the powders to be mixed, wetted, agglomerated, and dried within the confines of a single piece of equipment (Fig. 8.22). The wet mass is dried by gentle mixing, vacuum, and microwave. The use of the microwave reduces the drying time considerably, often by one fourth. The total batch production time is usually in the range of 90 minutes. After adding lubricants and screening, the batch is ready for tablet formation or capsule filling.

Dry Granulation

By the dry granulation method, the powder mixture is compacted in large pieces and subsequently broken down or sized into granules (Fig. 8.18). For this method, either the active ingredient or the diluent must have cohesive properties. Dry granulation is especially applicable to materials that cannot be prepared by wet granulation because they degrade in moisture or the elevated temperatures required for drying the granules.

Slugging

After weighing and mixing the ingredients, the powder mixture is slugged, or compressed, into large flat tablets or pellets about 1 inch in diameter. The slugs are broken up by hand or by a mill (Fig. 8.23) and passed through a screen of desired mesh for sizing. Lubricant is added in the usual manner, and tablets are prepared by compression. Aspirin, which is hydrolyzed on exposure to moisture, may be prepared into tablets after slugging.

Roller Compaction

Instead of slugging, powder compactors may be used to increase the density of a powder by pressing it between rollers at 1 to 6 tons of pressure. The compacted material is broken
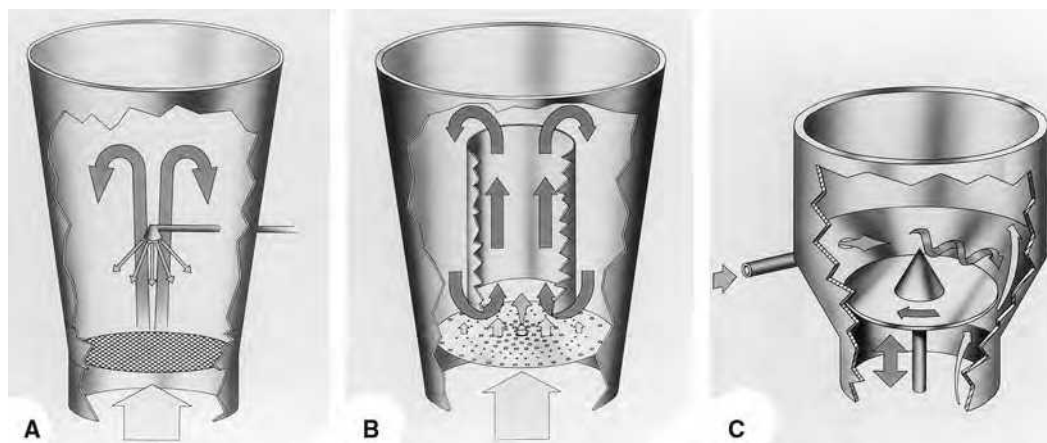
FIGURE 8.21 Fluid bed coating of solid particles. **A:** Top spray. **B:** Bottom spray (Wurster). **C:** Tangential spray. (Courtesy of Glatt Air Techniques.)

up, sized, and lubricated, and tablets are prepared by compression in the usual manner. The *roller compaction* method is often preferred to slugging. Binding agents used in roller compaction formulations include methylcellulose or hydroxy methylcellulose (6% to 12%), which can produce good tablet hardness and friability (16).

Tableting of Granulation

There are a number of types of tablet presses or tableting machines, each varying in productivity but similar in basic function and operation. They all compress a tablet formulation within a steel die cavity by the pressure exerted by the movement of two steel

FIGURE 8.22 Microwave vacuum processing in which tablet ingredients are dry mixed, wetted with a binding liquid, and dried by vacuum and microwave in a single piece of equipment. (Courtesy of GEI Processing.)

FIGURE 8.23 Frewitt Oscillator or Fitz Mill used to pulverize or granulate. (Courtesy of Eli Lilly and Company.)
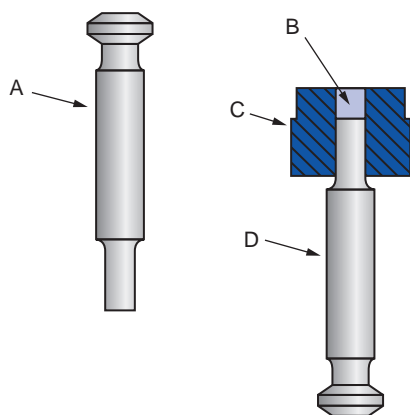
FIGURE 8.24 Punch and die set. *A*: Upper punch. *B*: Die cavity. *C*: Die. *D*: Lower punch. (Courtesy of Cherry-Burrell Corporation.)

punches, a lower punch and an upper punch (Fig. 8.24).

The operation of a single-punch tablet press describes the basic mechanical process. As the lower punch drops, the feed shoe filled with granulation from the hopper is positioned over and fills the die cavity. The feed shoe retracts, scrapes away the excessive granulation, and levels the fill in the die cavity. The upper punch lowers and compresses the fill, forming the tablet. The upper punch retracts as the lower punch rises with the formed tablet to the precise level of the stage. The feed shoe moves over the die cavity, shoves the tablet aside, and once again fills the cavity with granulation to repeat the process. The tablets fall into a collection container. Samples of tablets are assayed and tested for the various quality standards described earlier.

Rotary tablet machines equipped with multiple punches and dies operate via continuous rotating movement of the punches. A single rotary press with 16 stations (16 sets of punches and dies) may produce up to 1,150 tablets per minute. Double rotary tablet presses with 27, 33, 37, 41, or 49 sets of punches and dies are capable of producing two tablets for each die. Some of these machines can produce 10,000 or more tablets per minute of operation (Fig. 8.25). For such high-speed production, induced die feeders are required to force the fill material into the dies to keep up with the rapidly moving punches (Fig. 8.26).

FIGURE 8.25 Manesty Rotapress rotary compression machine. Tablets leaving the machine run over a tablet duster to screen, where they are inspected. Material to be compressed is fed from the overhead hopper through yoke to the two compressing machine hoppers. Hardness of tablet is monitored electronically by oscilloscope at right. (Courtesy of Upjohn Company.)

A consequence of high-speed production is the increased occurrence of *lamination* (horizontal striations) and tablet *capping*, in which the top of the tablet separates from the whole because the fill material does not have enough time to bond after compression. Reduced speed remedies the problem (17).

Multiple-layer tablets are produced by multiple feed and multiple compression of fill material within a single die. Tablets with an inner core are prepared by machines with a special feed apparatus that places the core tablet precisely within the die for compression with surrounding fill.

Direct Compression Tableting

Some granular chemicals, like potassium chloride, possess free-flowing and cohesive properties that enable them to be compressed directly in a tablet machine without any need of granulation. For chemicals lacking this quality, special pharmaceutical
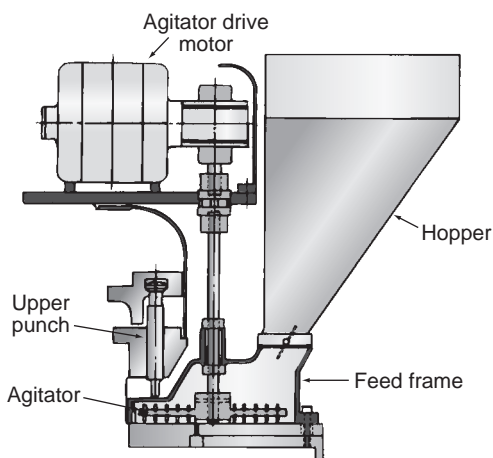
FIGURE 8.26 Induced die feeder. The standard gravity-fed open feed frame can be replaced with an induced die feeder, with which granulation is forced into the die by the rotary action of the agitator. (Courtesy of Cherry-Burrell Corporation.)

FIGURE 8.27 Tablets that have split on aging because of conditions of manufacture or storage.

excipients may be used to impart the necessary qualities for the production of tablets by direct compression. These excipients include *fillers*, such as spray-dried lactose, microcrystals of alpha-monohydrate lactose, sucrose–invert sugar–corn starch mixtures, microcrystalline cellulose, crystalline maltose, and dicalcium phosphate; *disintegrating agents*, such as direct compression starch, sodium carboxymethyl starch, cross-linked carboxymethylcellulose fibers, and cross-linked PVP; *lubricants*, such as magnesium stearate and talc; and *glidants*, such as fumed silicon dioxide.

The capping, splitting, or laminating of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tableting is released, resulting in splits or layers in the tablets. Forced or induced feeders can reduce air entrapment, making the fill powder more dense and amenable to compaction.

Capping also may be caused by punches that are not immaculately clean and perfectly smooth or by a granulation with too much fines or fine powder. Fine powder, which results when a dried granulation is sized, is generally 10% to 20% of the weight of the granulation. Some fine powder is desired to fill the die cavity properly. However, an excess can lead to tablet softness and capping.
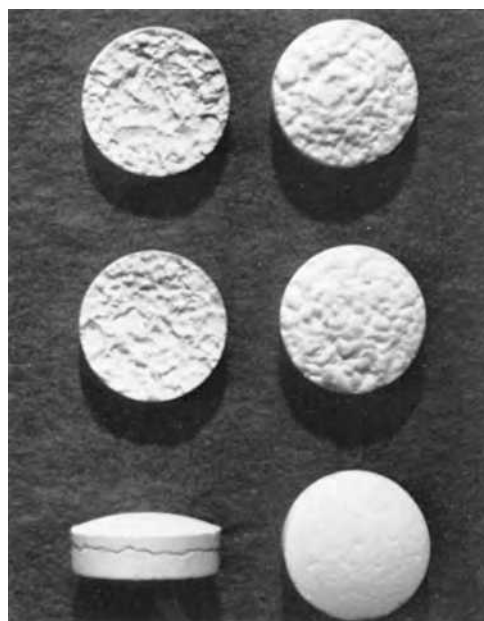
Tablets that have aged or been stored improperly also may exhibit splitting or other physical deformations (Fig. 8.27).

Tablet Dedusting

To remove traces of loose powder adhering to tablets following compression, the tablets are conveyed directly from the tableting machine to a deduster (Fig. 8.28). The compressed tablets may then be coated.

CHEWABLE TABLETS

Chewable tablets are pleasant-tasting tablets formulated to disintegrate smoothly in the mouth with or without chewing. They are prepared by wet granulation and compression, using only minimal degrees of pressure to produce a soft tablet. Generally, chewable tablets do not contain disintegrants, so patients must be counseled to chew the tablets thoroughly and not swallow them whole.

Mannitol, a white crystalline hexahydric alcohol, is used as the excipient in most chewable tablets. Mannitol is about 70% as sweet as sucrose, with a cool feel in the mouth resulting from its negative heat of solution. Mannitol accounts for 50% or more of the

weight of many chewable tablet formulations. Sometimes, other sweetening agents, such as sorbitol, lactose, dextrose, crystalline maltose, and glucose, may be substituted for part or all of the mannitol. Xylitol may be used in the preparation of sugar-free chewable tablets. Xylitol is sweeter than mannitol and has the desirable negative heat of solution that provides the cool mouth feel upon dissolution.

Lubricants and binders that do not detract from the texture or desired hardness of the tablet may be used. Colorants and tart or fruity flavorants are commonly employed to enhance the appeal of the tablets. Among the types of products prepared as chewable tablets are antacids (e.g., calcium carbonate), antibiotics (e.g., erythromycin), anti-infective agents (e.g., didanosine), anticonvulsants (e.g., carbamazepine), vasodilators (e.g., isosorbide dinitrate), analgesics (e.g., acetaminophen), various vitamins, and cold–allergy combination tablets. Chewable tablets are particularly useful for children and adults who have difficulty swallowing other solid dosage forms.

The following is a formula for a typical chewable antacid tablet (18):

Per Tablet

Aluminum hydroxide	325.0 mg
Mannitol	812.0 mg
Sodium saccharin	0.4 mg
Sorbitol (10% w/v solution)	32.5 mg
Magnesium stearate	35.0 mg
Mint flavor concentrate	4.0 mg

Preparation: Blend the aluminum hydroxide, mannitol, and sodium saccharin. Prepare a wet granulation with the sorbitol solution. Dry at 49°C (120°F), and screen through a 12-mesh screen. Add the flavor and magnesium stearate, blend, and compress into tablets.

MOLDED TABLETS

Commercial preparation of tablets by molding has been replaced by tablet compression. However, molded tablets, or *tablet triturates*, may be prepared on a small laboratory scale as follows.

The mold is made of hard rubber, hard plastic, or metal. It has two parts, the upper part, or *die* portion, and the lower part, containing squat, flat *punches*. The die portion is a flat plate with the thickness of the tablets to be produced, with 50 to 200 uniformly drilled and evenly spaced circular holes (Fig. 8.29). The lower part of the mold has corresponding punches that fit the holes precisely. When the die is filled with material and placed atop the punches, the punches gently lift the

FIGURE 8.29 Laboratory mold for preparation of tablet triturates.

fill material from the holes to rest upon the punches for drying.

The base for molded tablets is generally a mixture of finely powdered lactose with or without a portion of powdered sucrose (5% to 20%). The addition of sucrose results in less brittle tablets. In preparing the fill, the drug is mixed uniformly with the base by geometric dilution when potent drugs are used. The powder mixture is wetted with a 50% mixture of water and alcohol sufficient only to dampen the powder so that it may be compacted. The solvent action of the water on a portion of the lactose or lactose–sucrose base binds the powder mixture upon drying. The alcohol portion hastens drying.

The upper mold is placed on a clean flat glass surface and the damp mass added by a rubbing motion. When each opening is filled completely and smoothed, top and bottom, the mold is fitted on the punch portion of the mold and pressed down, leaving the tablets raised on the pegs to dry.

Before use, the mold should be calibrated for the fill material used since the densities of different formulas result in tablets of different weights. This may be done by preparing a test batch of the formula and weighing and recording the weight of the dry tablets. This weight is used in calculations for production quantities.

Molded tablets are intended to dissolve rapidly in the mouth. They do not contain disintegrants, lubricants, or coatings to slow their rate of dissolution. (A more complete discussion of the preparation of molded tablets and the standardization of laboratory molds may be found on this book's companion Web site.)

TABLET COATING

Tablets are coated for a number of reasons, including to protect the medicinal agent against destructive exposure to air and/or humidity, to mask the taste of the drug, to provide special characteristics of drug release (e.g., enteric coatings), and to provide aesthetics or distinction to the product.

In a limited number of instances, tablets are coated to prevent inadvertent contact with the drug substance and the effects of drug absorption. For example, Proscar tablets (finasteride, Merck) are coated for just this reason. The drug is used by men in the treatment of benign prostatic hyperplasia. The labeling instructions warn that women who are pregnant or who may become pregnant should not come into contact with it. Drug contact can occur through handling broken tablets. If finasteride is absorbed by a woman who is pregnant with a male baby, the drug has the potential to adversely affect the developing male fetus.

The general methods involved in coating tablets are as follows.

Sugarcoating Tablets

The sugarcoating of tablets may be divided into the following steps: (*a*) waterproofing and sealing if needed, (*b*) subcoating, (*c*) smoothing and final rounding, (*d*) finishing and coloring if desired, and (*e*) polishing. The entire coating process is conducted in a series of mechanically operated acorn-shaped coating pans of galvanized iron, stainless steel, or copper. The pans, which are partially open in the front, have diameters ranging from about 1 to 4 feet and various capacities (Figs. 8.30 and 8.31). The smaller pans are used for experimental, developmental, and pilot plant operations and the larger pans for industrial production. The pans operate at about a 40-degree angle to contain the tablets while allowing the operator visual and manual

FIGURE 8.30 Tablet coating, an old-style coating pan, showing the warm air supply and the exhaust. (Courtesy of Wyeth Laboratories.)

FIGURE 8.31 Modern tablet-coating facility. Air and exhaust ducts to assist drying are automatically operated from central board. (Courtesy of Eli Lilly and Company.)

FIGURE 8.32 Gauge used to measure coated tablets. (Courtesy of Eli Lilly and Company.)

access. During operation, the pan is mechanically rotated at moderate speeds, allowing the tablets to tumble over each other while making contact with the coating solutions, which are gently poured or sprayed onto the tablets. To allow gradual buildup of the coatings, the solutions are added in portions, with warm air blown in to hasten drying. Each coat is applied only after the previous coat has dried. Tablets intended to be coated are manufactured to be thin edged and highly convex to allow the coatings to form rounded rather than angular edges.

Waterproofing and Sealing Coats

For tablets containing components that may be adversely affected by moisture, one or more coats of a waterproofing substance, such as pharmaceutical shellac or a polymer, are applied to the compressed tablets before the subcoating application. The waterproofing solution (usually alcoholic) is gently poured or sprayed on the compressed tablets rotating in the coating pans. Warm air is blown into the pan during the coating to hasten the drying and to prevent tablets from sticking together.

Subcoating

After the tablets are waterproofed if needed, three to five subcoats of a sugar-based syrup are applied. This bonds the sugar coating to the tablet and provides rounding. The sucrose and water syrup also contains gelatin, acacia, or PVP to enhance coating. When the tablets are partially dry, they are sprinkled with a dusting powder, usually a mixture of powdered sugar and starch but sometimes talc, acacia, or precipitated chalk as well. Warm air is applied to the rolling tablets, and when they are dry, the process is repeated until the tablets are of the desired shape and size (Fig. 8.32). The subcoated tablets are then scooped out of the coating pan, and the excess powder is removed by gently shaking the tablets on a cloth screen.

Smoothing and Final Rounding

After the tablets are subcoated, 5 to 10 additional coatings of a thick syrup are applied to complete the rounding and smooth the coatings. This syrup is sucrose based, with or without additional components such as starch and calcium carbonate. As the syrup is applied, the operator moves his or her hand through the rolling tablets to distribute the syrup and to prevent the tablets from sticking to one another. A dusting powder is often used between syrup applications. Warm air is applied to hasten the drying time of each coat.

Finishing and Coloring

To attain final smoothness and the appropriate color to the tablets, several coats of a

thin syrup containing the desired colorant are applied in the usual manner. This step is performed in a clean pan, free from previous coating materials.

Imprinting

Solid dosage forms may be passed through a special imprinting machine (Fig. 8.33) to impart identification codes and other distinctive symbols. By FDA regulation, effective in 1995, all solid dosage forms for human consumption, including both prescription-only and over-the-counter drug products, must be imprinted with product-specific identification codes. Some exemptions to this requirement are allowed: those used in clinical investigations, those that are extemporaneously compounded in the course of pharmacy practice, radiopharmaceutical drug products, and products that, because of their size, shape, texture, or other physical characteristics, make imprinting technologically not feasible.

Technically, the imprint may be *debossed*, *embossed*, *engraved*, or printed on the surface with ink. *Debossed* means imprinted with a mark below the surface, *embossed* means imprinted with a mark raised above the surface, and *engraved* means imprinted with a code that is cut into the surface during production.

Polishing

Coated tablets may be polished in several ways. Special drum-shaped pans or ordinary coating pans lined with canvas or other cloth impregnated with carnauba wax and/or beeswax may be used to polish tablets as they tumble in the pan. Or, pieces of wax may be placed in a polishing pan, and the tablets allowed to tumble over the wax until the desired sheen is attained. A third method is light spraying of the tablets with wax dissolved in a nonaqueous solvent. Two or three coats of wax may be applied, depending upon the desired gloss. After each coat has been applied, the addition of a small amount of talc to the tumbling tablets contributes to their high luster (Fig. 8.34).

FIGURE 8.33 Branding of coated compression tablets on a Hartnett branding machine. (Courtesy of Pfizer, Inc.)

FIGURE 8.34 Coated, polished, and monogrammed tablets. (Courtesy of Wyeth-Ayerst Laboratories.)

Film-Coating Tablets

The sugarcoating process, as described, not only is tedious, time-consuming, and specialized, requiring the expertise of highly skilled technicians, but also results in coated tablets that may be twice the size and weight of the original uncoated tablets. Also, sugarcoated tablets may vary slightly in size from batch to batch and within a batch. All of these factors are important considerations for a manufacturer. From a patient's point of view, large tablets are not as easily swallowed as are small tablets.

The film-coating process, which places a thin, skin-tight coating of a plastic-like material over the compressed tablet, was developed to produce coated tablets having essentially the same weight, shape, and size as the originally compressed tablet. Also, the coating is thin enough to reveal any identifying monograms embossed in the tablet during compression by the tablet punches. Film-coated tablets also are far more resistant to destruction by abrasion than are sugarcoated tablets. However, like sugarcoated tablets, the coating may be colored to make the tablets attractive and distinctive.

Film-coating solutions may be nonaqueous or aqueous. The nonaqueous solutions contain the following types of materials to provide the desired coating to the tablets:

1. A *film former* capable of producing smooth, thin films reproducible under conventional coating conditions and applicable to a variety of tablet shapes. Example: cellulose acetate phthalate
2. An *alloying substance* providing water solubility or permeability to the film to ensure penetration by body fluids and therapeutic availability of the drug. Example: polyethylene glycol
3. A *plasticizer* to produce flexibility and elasticity of the coating and thus provide durability. Example: castor oil
4. A *surfactant* to enhance spreadability of the film during application. Example: polyoxyethylene sorbitan derivatives
5. *Opaquants* and *colorants* to make the appearance of the coated tablets handsome and distinctive. Examples: opaquant, titanium dioxide; colorant, FD&C or D&C dyes
6. *Sweeteners*, *flavors*, and *aromas* to enhance the acceptability of the tablet by the patient. Examples: sweeteners, saccharin; flavors and aromas, vanillin
7. A *glossant* to provide luster to the tablets without a separate polishing operation. Example: beeswax
8. A *volatile solvent* to allow the spread of the other components over the tablets while allowing rapid evaporation to permit an effective yet speedy operation. Example: alcohol mixed with acetone

Tablets are film coated by application or spraying of the coating solution on the tablets in ordinary coating pans. The volatility of the solvent enables the film to adhere quickly to the surface of the tablets.

Because of both the expense of the volatile solvents used in the film-coating process and the environmental problem of the release of solvents, pharmaceutical manufacturers generally favor the use of aqueous solutions. One of the problems attendant to these, however, is slow evaporation of the water base compared to the volatile organic solvent–based solutions. One commercial water-based colloidal coating dispersion called Aquacoat (FMC Corporation) contains a 30% ethyl cellulose pseudolatex. Pseudolatex dispersions have a high solid content for greater coating ability and a relatively low viscosity. The low viscosity allows less water to be used in the coating dispersion, requiring less evaporation and reducing the likelihood that water will interfere with tablet formulation. In addition, the low viscosity permits greater coat penetration into the crevices of monogrammed or scored tablets. A plasticizer may be added to assist in the production of a dense, relatively impermeable film with high gloss and mechanical strength. Other aqueous film-coating products use cellulosic materials such as methylcellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose as the film-forming polymer.

A typical aqueous film-coating formulation contains the following (19):

1. *Film-forming polymer* (7% to 18%). Examples: cellulose ether polymers such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and methylcellulose
2. *Plasticizer* (0.5% to 2.0%). Examples: glycerin, propylene glycol, polyethylene glycol, diethyl phthalate, and dibutyl subacetate
3. *Colorant and opacifier* (2.5% to 8%). Examples: FD&C or D&C lakes and iron oxide pigments
4. *Vehicle* (water, to make 100%)

There are some problems attendant on aqueous film coating, including the appearance of small amounts (*picking*) or larger amounts (*peeling*) of film fragments flaking from the tablet surface, roughness of the tablet surface due to failure of spray droplets to coalesce (*orange peel effect*), an uneven distribution of color on the tablet surface (*mottling*), filling-in of the score line or indented logo on the tablet by the film (*bridging*), and disfiguration of the core tablet when subjected for too long to the coating solution (tablet *erosion*). The cause of each of these problems can be determined and the problem rectified through appropriate changes in formulation, equipment, technique, or process.

Enteric Coating

Enteric-coated solid dosage forms are intended to pass through the stomach intact to disintegrate and release their drug content for absorption along the intestines. The design of an enteric coating may be based on the transit time required for passage to the intestines and may be accomplished through coatings of sufficient thickness. However, usually an enteric coating is based on factors of pH, resisting dissolution in the highly acid environment of the stomach but yielding to the less acid environment of the intestine. Some enteric coatings are designed to dissolve at pH 4.8 and greater.

Enteric-coating materials may be applied either to whole compressed tablets or to drug particles or granules used in the fabrication of tablets or capsules. The coatings may be applied in multiple portions to build a thick coating or as a thin film coat. The coating system may be aqueous or organic solvent based and effective so long as the coating material resists breakdown in the gastric fluid. Among the materials used in enteric coatings are pharmaceutical shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, diethyl phthalate, and cellulose acetate phthalate.

Fluid Bed or Air Suspension Coating

Fluid bed coating, which uses equipment of the type shown in Figure 8.35, is spray coating of powders, granules, beads, pellets, or

FIGURE 8.35 Vector/Freund Flo-Coater production system. A fluid bed system used to apply coatings to beads, granules, powders, and tablets. Capacity of models ranges from 5 to 700 kg. (Courtesy of Vector Corporation.)

tablets held in suspension by a column of air. Fluid bed processing equipment is multifunctional and may also be used in preparing tablet granulations.

In the Wurster process, named after its developer, the items to be coated are fed into a vertical cylinder and are supported by a column of air that enters from the bottom of the cylinder. Within the air stream, the solids rotate both vertically and horizontally. As the coating solution enters the system from the bottom, it is rapidly applied to the suspended, rotating solids, with rounding coats being applied in less than an hour with the assistance of warm air blasts released in the chamber.

In another type of fluid bed system, the coating solution is sprayed downward onto the particles to be coated as they are suspended by air from below. This method is commonly referred to as the *top-spray* method. This method provides greater capacity, up to 1,500 kg, than the other air suspension coating methods (20). Both the top-spray and bottom-spray methods may be employed using a modified apparatus used for fluid bed granulation. A third method, the *tangential-spray technique*, is used in rotary fluid bed coaters. The bottom-spray, top-spray, and tangential-spray methods are depicted in Figure 8.21. Electron microscope images of the results of this process are shown in Figure 8.36.

The three systems are increasingly used for application of aqueous or organic solvent–based polymer film coatings. The top-spray coating method is particularly recommended for taste masking, enteric release, and barrier films on particles or tablets. It is most effective when coatings are applied from aqueous solutions, latexes, or hot melts (17,18). The bottom-spray method is recommended for sustained-release and enteric-release products; the tangential method is used for layering coatings and for sustained-release and enteric-coated products (18).

Among the variables requiring control to produce the desired and consistent quality are equipment and the method of spraying (e.g., top, bottom, tangential), spray nozzle distance from spraying bed, droplet size, spray rate, spray pressure, volume of the air column, batch size, method and time for drying, and air temperature and moisture content in the processing compartment (18).

Compression Coating

In a manner similar to the preparation of multiple compressed tablets having an inner core and an outer shell of drug material, core tablets may be sugarcoated by compression. The coating material, in the form of a granulation or powder, is compressed onto a tablet core of drug with a special tablet press. Compression coating is an anhydrous operation and thus may be safely employed in the coating of tablets containing a drug that is labile to moisture. Compared to sugarcoating using pans, compression coating is
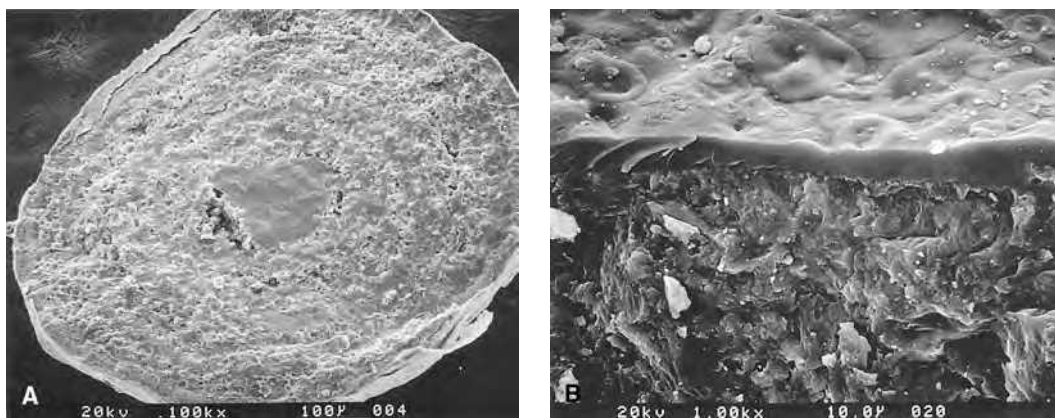

FIGURE 8.36 Scanning electron microscope images of pharmaceutical granules coated through fluid bed technology: **A:** Layered and coated granule. **B:** Cross section of top-spray enteric-coated granule. (Courtesy of Glatt Air Techniques.)

FIGURE 8.37 Checking for physical imperfections in coated tablets. (Courtesy of Smith, Kline & French.)

more uniform and uses less coating material, resulting in tablets that are lighter, smaller, and easier to swallow and less expensive to package and ship.

Irrespective of the method used in coating, all tablets are visually or electronically inspected for physical imperfections (Fig. 8.37).

IMPACT OF MANUFACTURING CHANGES ON SOLID DOSAGE FORMS

The quality and performance of a solid dosage form may be altered by changes in formulation or by changes in the method of manufacture.

The changes in formulation may arise from (*a*) the use of starting raw materials, including both the active ingredient and pharmaceutical excipients, that have different chemical or physical characteristics (e.g., solubility or particle size) than the standards set for the original components; (*b*) the use of different pharmaceutical excipients (e.g.,

magnesium stearate instead of calcium stearate as the lubricant); (*c*) the use of different quantities of the same excipients in a formulation (e.g., use of a more concentrated wet tablet binder); or (*d*) the addition of a new excipient to a formulation (e.g., a revised tablet-coating formula).

The changes in the method of manufacture may be (*a*) use of processing or manufacturing equipment of a different design; (*b*) a change in the steps or order in the process or method of manufacture (e.g., different mixing times); (*c*) different in-process controls, quality tests, or assay methods; (*d*) production of different batch sizes; (*e*) employment of different product reprocessing procedures; or (*f*) employment of a different manufacturing site.

Changes such as these may be proposed or implemented during the product development stage, during scale-up of product manufacture before NDA approval, or after NDA approval and product marketing. In all instances, it is critical to assess any effects of the change in meeting the proposed or established standards for product quality (e.g., dissolution rate and bioavailability). It is necessary for a manufacturer to document the change, validate its effect, and provide the necessary information to the FDA. Some changes are considered minor (e.g., a change in tablet color) and do not affect product quality; they do not require prior FDA approval. Other changes that may affect product quality and performance (e.g., use of a substantially different quantity or grade of an excipient or use of a piece of manufacturing equipment that changes the methodology of manufacture) require prior FDA approval (21).

OFFICIAL AND COMMERCIALLY AVAILABLE TABLETS

There are hundreds of tablets recognized by the USP and literally thousands of commercially available tablet products from virtually all pharmaceutical manufacturers, in most therapeutic categories and in various dosage strengths. Examples of a limited number of these are presented in Table 8.1.

Table 8.1 EXAMPLES OF OFFICIAL TABLETS

OFFICIAL TABLET	REPRESENTATIVE COMMERCIAL PRODUCTS	STRENGTH	CATEGORY
Acetaminophen	Tylenol (McNeil)	325, 500 mg	Analgesic, antipyretic
Acyclovir	Zovirax (Valeant)	400, 800 mg	Antiviral
Allopurinol	Zyloprim (Faro Pharmaceuticals)	100, 300 mg	Antigout and antiurolithic
Amitriptyline HCl	Endep (Roche)	10, 25, 50, 75, 100, 150 mg	Antidepressant
Carbamazepine	Tegretol (Novartis)	200 mg	Anticonvulsant
Chlorambucil	Leukeran (GlaxoSmithKline)	2 mg	Antineoplastic
Cimetidine	Tagamet (GlaxoSmithKline)	200, 300, 400, 800 mg	Histamine H_2 receptor antagonist
Ciprofloxacin	Cipro (Schering-Plough)	100, 250, 500, 750 mg	Antibacterial
Conjugated estrogens	Premarin (Wyeth-Ayerst)	0.3, 0.45, 0.625, 0.9, 1.25, 2.5 mg	Estrogen
Diazepam	Valium (Roche)	2, 5, 10 mg	Sedative, skeletal muscle relaxant
Digoxin	Lanoxin (GlaxoSmithKline)	0.125, 0.25 mg	Cardiotonic
Enalapril	Vasotec (Biovail)	2.5, 5, 10, 20 mg	Antihypertensive
Furosemide	Lasix (Aventis)	20, 40, 80 mg	Diuretic, antihypertensive
Griseofulvin	Various	250, 500 mg	Antifungal
Haloperidol	Haldol (McNeil)	0.5, 1, 2, 5, 10, 20 mg	Tranquilizer
Ibuprofen	Motrin (McNeil Consumer Healthcare)	400, 600, 800 mg	Analgesic and antipyretic
Levothyroxine sodium	Synthroid (Abbott)	0.025, 0.05, 0.075, 0.088, 0.1, 0.122, 0.125, 0.137, 0.15, 0.2, 0.3 mg	Thyroid hormone
Loratadine	Claritin (Schering-Plough)	10 mg	Antihistamine
Meperidine HCl	Demerol (Sanofi-Synthelabo)	50, 100 mg	Narcotic analgesic
Methyldopa	Aldomet (Merck)	125, 250, 500 mg	Antihypertensive
Nitroglycerin	Nitrostat (Parke-Davis)	0.3, 0.4, 0.6 mg	Antianginal
Penicillin V	Pen-Vee-K (Wyeth)	250, 500 mg	Anti-infective
Propranolol	Inderal (Wyeth–Ayerst)	10, 20, 40, 60, 80 mg	Antianginal, antiarrhythmic, antihypertensive
Terbutaline sulfate	Various	2.5, 5 mg	Antiasthmatic
Verapamil HCl	Calan (Searle)	40, 80, 120 mg	Antihypertensive
Warfarin sodium	Coumadin (Bristol-Myers Squibb)	1, 2, 2.5, 4, 5, 6, 7.5, 10 mg	Anticoagulant

PACKAGING AND STORING TABLETS

Tablets are stored in tight containers, in places of low humidity, and protected from extremes in temperature. Products that are prone to decomposition by moisture generally are packaged with a desiccant packet. Drugs that are adversely affected by light are packaged in light-resistant containers. With a few exceptions, tablets that are properly stored will remain stable for several years or more.

In dispensing tablets, the pharmacist is well advised to use a similar type of container as provided by the manufacturer of the product. The patient is well advised to keep the drug in the container dispensed. Storage conditions, as recommended for the particular product, should be maintained by the pharmacist and patient alike and expiration dates observed.

The pharmacist should be aware also that the hardness of certain tablets may change upon aging, usually resulting in a decrease in the disintegration and dissolution rates of the product. The increase in tablet hardness can frequently be attributed to the increased adhesion of the binding agent and other formulative components within the tablet. Examples of increased tablet hardening with age have been reported for a number of drugs, including aluminum hydroxide, sodium salicylate, and phenylbutazone (22).

In tablets containing volatile drugs, such as NTG, the drug may migrate between tablets in the container, resulting in a lack of uniformity among the tablets (23). Also, packing materials, such as cotton and rayon, in contact with NTG tablets may absorb varying amounts of NTG, reducing potency of the tablets (24). The USP directs that NTG tablets be preserved in tight containers, preferably of glass, at controlled room temperature. Also, migration within tablets can occur resulting in unequal distribution within a single tablet; this can be problematic if the tablet is scored and designed to be broken in half where the two halves may not contain equal portions of the drug. Storage of a container next to a heat source may result

in greater loss or movement of the volatile drug in the portion of the bottle closest to the heat. Some third party payors require the dispensing of higher strength tablets with the patient to divide them prior to administration to decrease costs. In addition to the difficulties just mentioned, it is troublesome for many patients to split tablets into two equal halves.

The USP further directs that NTG tablets be dispensed in the original unopened container, labeled with the following statement directed to the patient. "Warning: to prevent loss of potency, keep these tablets in the original container or in a supplemental NTG container specifically labeled as being suitable for NTG tablets. Close tightly immediately after use" (4).

The pharmacist also should caution patients about handling medication when it poses a risk. For example, as noted earlier, finasteride tablets are taken by men to treat benign prostatic hyperplasia. Finasteride has the potential to harm a male fetus if absorbed by a pregnant woman either through direct contact with finasteride or possibly through semen. Therefore, a woman who is pregnant or who may become pregnant should not handle finasteride tablets or come into contact with finasteride powder. In addition, when the male patient's sexual partner is pregnant or may become pregnant, the patient should avoid exposure of his partner to semen or should discontinue the use of this drug.

Finally, rapidly dissolving tablets tend to be softer than regular compressed immediate-release tablets and require special packaging. An example is shown in Figure 8.38.

OTHER SOLID DOSAGE FORMS FOR ORAL ADMINISTRATION

Lozenges (Troches)

Lozenges (troches) are solid oral dosage forms that are designed to dissolve or disintegrate slowly in the mouth. They contain one or more active drugs that are slowly released from the flavored and sweetened base. They are used for both local and systemic action.

FIGURE 8.38 Rapidly dissolving/melting tablet. (Loratadine Orally Disintegrating Tablets-Dimetapp ND).

Typically, the active drugs include antiseptics, analgesics, decongestants, antitussives, and antibiotics. Some molded lozenges may also be called cough drops or pastilles.

Lozenges can be made by compression or molding. Compressed lozenges are made using a tablet machine and large, flat punches. The machine is operated at a high degree of compression to produce lozenges that are harder than ordinary tablets so that they dissolve or disintegrate slowly in the mouth. Medicinal substances that are heat stable may be molded into hard sugar candy lozenges by candy-making machines that process a warm, highly concentrated, flavored syrup as the base and form the lozenges by molding and drying.

Lozenges can be made using sugars such as sucrose and dextrose or can be "sugar-free" in a formulation generally based on sorbitol or mannitol. To slow the rate of dissolution, polyethylene glycols and hypromellose are sometimes added. Compressed lozenges are made with excipients that may include a filler, binder, sweetening agent, flavoring agent, and lubricant and are prepared similar to conventional tablets. They can also be prepared by formulating a paste, cutting or stamping and drying. Also, they can be prepared by forcing dampened powders under low pressure into mold cavities, ejecting them, and allowing them to dry.

Lollipops

Fentanyl Actiq (Cephalon) is a raspberry lollipop that is a sugar-based lozenge on a stick and contains fentanyl citrate. It has an off-white color, and the stick bears a large Rx mark. Actiq is the first product specifically designed to aid in controlling breakthrough pain in cancer patients. It is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already taking and are tolerant to opioids. Breakthrough cancer pain occurs in about 50% of cancer pain patients and is a component of chronic cancer pain that is particularly difficult to treat because of its severity, rapid onset, and frequent unpredictability. The lollipop provides almost immediate relief as the drug starts being absorbed in the mouth and starts to work within minutes; its effects last for only about 15 minutes, but that is usually long enough to relieve the breakthrough pain. The concern about this product being accidentally used by children is addressed by special packaging that requires scissors to open (1).

Pellets

Pellets are dosage forms that are composed of small, solid particles of uniform shape sometimes called beads. Typically, pellets are nearly spherical, but that is not a requirement. They may be administered orally or parenterally. They can be used to provide physical separation for chemically or physically incompatible materials, extended release of an active pharmaceutical ingredient (API), or delayed release to protect an acid-labile API from degradation in the stomach or to protect stomach tissues from irritation. Pellet dosage forms can be formulated as single or multiple entities. Oral pellets are usually placed within hard gelatin capsules for administration. The size range of the pellets is governed by the constraints of the volume of commonly used capsules (typically

size #1 or #0). Typically, pellets for oral use fall within a size range of 710 μm to 2.36 mm.

For delayed release, pellets are prepared by applying a coating in various numbers of layers.

Pellets are typically manufactured by wet extrusion processes followed by spheronization, by wet or dry coating processes, or by compression. Pellets prepared by wet coating involves the application of successive coatings onto nonpareil seeds; this process may be carried out in a fluid bed processing equipment. The manufacture of pellets by compression is largely restricted to the production for subcutaneous implantation as it can be done in an aseptic processing environment. Coacervation techniques can be used for coating and will generally produce coated particles that are smaller than those produced by other techniques.

Bolus Tablets

Bolus tablets are large, usually elongated tablets intended for administration to large animals. Conventional tableting processes can be used to manufacture bolus tablets, but higher compression forces may be necessary due to their larger size.

Pills

By definition, pills are small, round solid dosage forms containing a medicinal agent and intended to be administered orally. Although the manufacture and administration of pills were at one time quite prevalent, today pills have been replaced by compressed tablets and capsules. Pills are distinguished from tablets as they are usually prepared by a wet massing and molding technique, while tablets are typically formed by compression.

Excipients are selected for pills based on their ability to produce a firm and plastic mass. The API is triturated with powdered excipients in geometrically to obtain a uniform mixture. Liquid excipients are added to bind and provide plasticity to the mass, which is formed by kneading. The firmness and plasticity are required for the mass to be worked and retain the produced shape. A cylindrical pill pipe is produced and then cut into individual lengths corresponding to the intended size/dose. These short cylinders are then rolled to form the final spherical shape. Small machines/devices are available that can automate this process.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

A pharmaceutical manufacturer has developed a formula for an antihistamine compressed tablet. During the initial run, the tablets were found to be too friable. What can be done?

OBJECTIVE INFORMATION

The formula for the tablet is as follows:

Antihistamine	50 mg
Directly compressible lactose	150 mg
Magnesium stearate	10 mg
Starch	100 mg
Talc	25 mg

The tablet is to be compressed, so it has the following characteristics:

Description	8-mm white biconvex bisected tablet
Weight	335 mg
Hardness	8 kg
Dissolution	Medium: 0.01 N Hydrochloric acid, 500 mL Apparatus 2: 50 rpm Time: 30 minutes

Following the initial run, hardness testing reveals that the tablet's hardness is only 6.5 kg.

PHARMACEUTICS CASE STUDY CONT.

ASSESSMENT

The tablet's hardness must be increased to meet specifications. There are a couple of different approaches to accomplishing this:

1. Increase the pressure of the upper punch of the tableting machine.
2. Add a tablet binder such as pregelatinized starch, acacia, or methylcellulose. Some or all of the starch in the tablet formula could be replaced by pregelatinized starch, as it will serve all of the functions of regular starch (diluent, dissolution enhancer, etc.) plus serve as a tablet binder.

PLAN

Adjust the tableting machine, and increase the pressure of the upper punch. Sometimes, the simplest solutions are the best.

CLINICAL   CASE STUDY

SUBJECTIVE INFORMATION

HPI: F.L. is a 46-year-old AAM brought to the emergency department (ER) by his wife with chief complaint of "chest pain." His spouse states that F.L. began to feel constant pain in his chest while watching television. The pain radiated to his left arm and back. Spouse noticed excessive sweating on his forehead as he started to "gasp for breath." Immediately, she brought him to the ER. At the ER, F.L. describes pain as the "worst pain of his life" and feels like "an elephant's foot is pressuring into my chest." The patient was brought into the ER within an hour of onset of symptoms. F.L. denies any previous episodes of chest pain, sweating, weakness, shortness of breath, syncope, nausea, or vomiting. The patient denies any previous episodes of pain on exertion. He rates pain intensity as 10/10.

PMH: HTN × 12 years

Type II diabetes × 2 years

PSH: Lasik eye surgery, 2002

SH: (–) EtOH: quit drinking in 1996

(–) Tobacco: quit smoking in 1996

(–) Caffeine

(–) Illicit drugs: "none, never"

Patient lives in Hanover Park with wife and 1 daughter and 1 son, no pets

Has own business, works at home

FH: Father died of an asthma attack at 67 y/o

Mother died of a myocardial infarction (MI) at 59 y/o

Sister: Asthma

Diet: Eats 3 times a day and 2 or 3 snacks a day. Denies following any low-fat, low-cholesterol, or low-salt diet. On a low-sugar diet and states that he follows it. Eats fast food at least twice a week. Snacks consist mostly of chips, cookies, and salsa.

<div align="center">**CLINICAL CASE STUDY CONT.**</div>

Exer: Pt states, "I don't have time to exercise. I've got a business and a family to handle." The extent of patient's exercise is walking up and down the stairs when he needs to get around the house.

All: NKDA

PTA: Lisinopril (Zestril) 40 mg po qhs for HTN

Felodipine (Plendil) 10 mg po qd for HTN

Glyburide/metformin (Glucovance)—2.5/500 mg po tid for type II diabetes

ADHERENCE

The patient states that he adheres to all his medications. He uses a pillbox to help remind him. He checks his blood glucose levels three times a day, alternating before and after meals.

OBJECTIVE INFORMATION

Ht:	5'8"	Wt:	185 lb
Pain:	10/10	BP:	112/80
Na:	140 mmol/L	K:	4.0 mmol/L
Cl:	100 mmol/L	CO_2:	24 mmol/L
BUN:	4.0 mmol/L	SrCr:	70 mmol/L
HgA_{1c}:	7	CK:	30

Last Accu-Checks: After breakfast, 9:30 AM: 151
After lunch, 1:00 PM: 155
After dinner, 7:00 PM: 141

ASSESSMENT

The patient is a 46-year-old AAM with a PMH of controlled HTN and type II diabetes who has had his first MI. The patient is at increased risk for MI due to HTN, diabetes, and significant family history. Though the patient adheres to his medication regimen, he does not adhere to a healthy diet and exercise plan, which may increase his chances of experiencing a similar episode in the future.

PLAN

1. Recommend sustained-release NTG Nitro-Bid 2.5-mg capsules once a day on an empty stomach with a full glass of water, either 30 minutes before or an hour after meals. Instruct the patient to take the medication the same time each day and to swallow the capsule whole. If the patient misses a dose, he should take it as soon as he remembers unless the next scheduled dose is within 2 hours; in that case, he should skip the missed dose and take only the next dose.

2. Recommend sublingual NTG NitroQuick 0.30-mg (1/200 gr) tablets. Instruct the patient to use the sublingual tablet at the first sign of attack. Instruct the patient to wet the tablet with saliva and place under the tongue or between the gums or in cheek until the tablet dissolves. Do not swallow the tablet. Effects of NTG should be felt within 2 minutes, lasting for up to 30 minutes. If symptoms do not resolve within 5 minutes of the first dose, repeat with a second sublingual tablet. Again, wait 5 minutes, and use a third sublingual tablet if symptoms persist. Call for emergency assistance (911) if symptoms continue after three doses of NTG. Inform the patient to keep and store sublingual tablets in original glass container, keep them away from heat or light, and keep the bottle tightly closed after use.

3. Counsel the patient on common side effects of NTG, such as headache, dizziness, drowsiness, and low blood pressure. Recommend acetaminophen (e.g., Tylenol) for relief of headache. Tell the patient to avoid alcoholic beverages and medications containing alcohol while using NTG, as their concurrent use may cause severe hypotension and

CLINICAL CASE STUDY CONT.

cardiovascular difficulties. Inform the patient that the use of sildenafil (Viagra) is dangerous and should be avoided while using this medication as it may increase the blood pressure–lowering effect of NTG. Instruct the patient to check expiration dates of tablets regularly because therapeutic effectiveness of NTG may decrease in tablets older than 6 months. Consult physician before stopping the use of NTG because abrupt discontinuation may cause severe chest pain.

4. Educate the spouse and the patient to recognize the signs and symptoms of a heart attack (e.g., excessive sweating, chest pain, jaw or back pain). Explain that a "silent" MI can occur without any symptoms. Further education on the condition and how it may be managed and prevented may benefit this patient. Stress the importance of lifestyle changes such as exercise and dietary modifications (e.g., low-fat, low-salt, low-cholesterol diet). Have the patient consult physician before embarking on an exercise regimen. An exercise regimen may include exercising at least 3 or 4 times a week for 15 to 30 minutes or as tolerated by the patient.

5. Monitoring parameters: BP, signs and symptoms of heart attack, frequency of episodes, and side effects of the medication. Goal: Increased patient knowledge of the condition, improved adherence to diet and exercise regimen, no medication side effects, and no second episode. Make sure the patient understands the importance of follow-up physician visits and exercising caution when purchasing nonprescription and herbal products (i.e., consult a pharmacist).

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Compare the advantages and disadvantages of unit dose packaging *versus* tablets packaged in plastic bottle containers.
2. Create a listing of extemporaneous prescriptions that provide the pharmacist an opportunity to use a tablet dosage form in its preparation.
3. Create a listing of conceivable ways a consumer/patient may misuse a tablet dosage form.
4. List five counseling points for proper administration of solid dosage forms, for example, tablets.
5. Make a listing of factors that might make a patient apprehensive about taking a tablet dosage form. List points of advice/counseling points to overcome this apprehension.
6. Identify several patient populations who might have difficulty administering a tablet dosage form, and explain your reasoning.

Individual Activities

1. Create a table of oral, chewable tablets, including amount of active ingredient(s), indication, contraindication, adverse effects/precautions, and dosage.
2. Create a listing of trademarked tablet dosage forms that have unique characteristics, for example, size, shape, and color, and describe/detail those features.
3. Generate a listing of tablet drug products that utilize (an) active ingredient(s) in a micronized powder form.
4. From the primary literature, find a clinical study demonstrating a comparison between a sustained-release tablet product and a compressed tablet for clinical effectiveness, and determine which one would be preferred in terms of patient acceptance, patient adherence, bioequivalence, and cost. Explain the rationale for your decision.
5. Select one USP drug monograph for an official tablet dosage form, and identify and describe its main components.

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9 Solid Oral Modified-Release Dosage Forms and Drug Delivery Systems

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between the various types of modified-release dosage forms
2. Compare and contrast advantages and disadvantages of the various types of modified-release dosage forms
3. List physical–chemical characteristics of drugs that make them candidates for an extended-release dosage form
4. Explain microencapsulation, embedding, ion exchange, and osmotic pump as these apply to modified-release dosage forms
5. Describe how the in vitro and in vivo drug release from an extended-release/delayed-release oral dosage form will differ from an oral, film-coated tablet
6. List applicable criteria to the development of in vitro–in vivo correlations to the development of oral, extended-release products

This chapter describes solid oral dosage forms and drug delivery systems that, by virtue of formulation and product design, have modified drug-release features. US prescription drug sales rose to 300.3 billion in 2009, an increase of 1.8% over the previous year (1). There are two primary driving forces behind this market, namely, patient-related factors and market-driven factors (2). The patient-related factors are discussed later in the chapter. The life cycle of a drug includes introduction of the new molecular entity, initial product introduction, and, later, possibly a new patent or patents obtained by the introduction of controlled-release formulations of the existing immediate-release products. This and the addition of new therapeutic indications for these products provide an attractive financial option for pharmaceutical companies. Example products include Augmentin XR (GlaxoSmithKline) and Cipro XR (Bayer) (2).

In contrast to conventional (immediate-release) forms, modified-release products provide either delayed release or extended release (ER) of drug. Most *delayed-release* products are enteric-coated tablets or capsules designed to pass through the stomach unaltered, later to release their medication within the intestinal tract. As noted in the previous chapter, enteric coatings are used either to protect a substance from destruction by gastric fluids or to reduce stomach distress caused by irritating drugs. *Extended-release* products are designed to release their medication in a *controlled* manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug.

Most modified-release products are orally administered tablets and capsules, and

therefore, these dosage forms are emphasized in this chapter. However, some other modified-release dosage forms and drug delivery systems are also described, including ocular, parenteral, subdermal, and vaginal products. Transdermal patches, which provide rate-controlled drug delivery, are touched on here and discussed at length in Chapter 11.

THE RATIONALE FOR EXTENDED-RELEASE PHARMACEUTICALS

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate-release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results.

Multiple daily dosing is inconvenient for the patient and can result in missed doses, made-up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose (Fig. 9.1). However, when doses are *not* administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of subtherapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient.

Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig. 9.2). The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well (3–5). For nonoral rate-controlled drug delivery systems, the drug-release pattern ranges in duration from 24 hours for most transdermal patches to 3 months for the estradiol vaginal ring insert (Estring, Pharmacia).

Some advantages of extended-release systems are given in Table 9.1. Some disadvantages are the loss of flexibility in adjusting the drug dose and/or dosage regimen and a risk of sudden and total drug release, or dose dumping, due to a failure of technology.
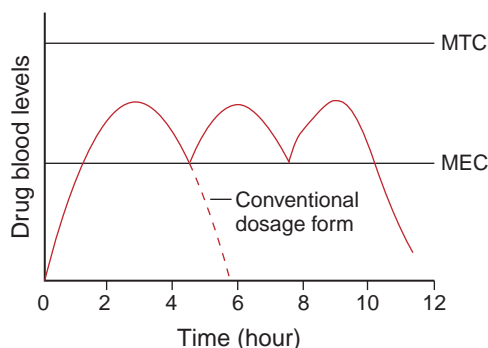

FIGURE 9.1 Hypothetical drug blood level–time curves for a conventional solid dosage form and a multiple-action product.
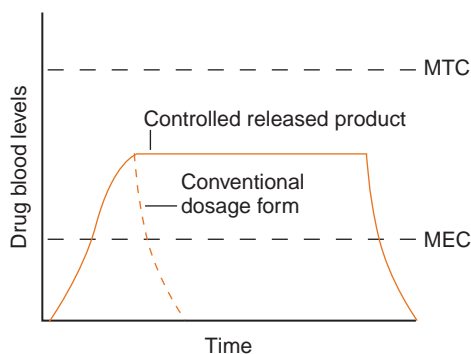

FIGURE 9.2 Hypothetical drug blood level–time curves for a conventional solid dosage form and a controlled-release product.

Table 9.1	ADVANTAGES OF EXTENDED-RELEASE DOSAGE FORMS OVER CONVENTIONAL FORMS	
ADVANTAGE	**EXPLANATION**
Less fluctuation in drug blood levels	Controlling rate of release eliminates peaks and valleys of blood levels.
Frequency reduction in dosing	Extended-release products frequently deliver more than a single dose, hence may be taken less often than conventional forms.
Enhanced convenience and compliance	With less frequency of dosing, a patient is less apt to neglect taking a dose; also greater convenience with day and night administration
Reduction in adverse side effects	Because of fewer blood level peaks outside therapeutic range and into toxic range, adverse side effects are less frequent.
Reduction in overall health care costs	Although initial cost of extended-release dosage forms may be greater than for conventional forms, overall cost of treatment may be less because of enhanced therapeutic benefit, fewer side effects, and reduced time for health care personnel to dispense and administer drugs and monitor patients.

TERMINOLOGY

Drug products that provide extended or sustained release (SR) first appeared as a major new class of dosage form in the late 1940s and early 1950s (6). Over the years, many terms (and abbreviations), such as *sustained release* (*SR*), *sustained action* (*SA*), *prolonged action* (*PA*), *controlled release* (*CR*), *extended release* (*ER*), *timed release* (*TR*), *and long acting* (*LA*), have been used by manufacturers to describe product types and features. Although these terms often have been used interchangeably, individual products bearing these descriptions may differ in design and performance and must be examined individually to ascertain their respective features. For the most part, these terms are used to describe orally administered dosage forms, whereas the term *rate-controlled delivery* is applied to certain types of drug delivery systems in which the rate of delivery is controlled by features of the device rather than by physiologic or environmental conditions like gastrointestinal pH or drug transit time through the gastrointestinal tract.

Modified Release

In recent years, *modified release* has come into general use to describe dosage forms having drug-release features based on time, course, and/or location that are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate-release forms (4,7). The *US Pharmacopeia* (USP) differentiates modified-release forms as *extended release* and *delayed release* (8).

Extended Release

The US Food and Drug Administration (FDA) defines an extended-release dosage form as one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate-release dosage form (4,9).

Delayed Release

A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

Repeat Action

Repeat-action forms usually contain two single doses of medication, one for immediate release and the second for delayed release. Two-layer tablets, for example, may be prepared with one layer of drug for immediate release with the second layer designed to

release drug later as either a second dose or in an extended-release manner.

Targeted Release

Targeted release describes drug release directed toward isolating or concentrating a drug in a body region, tissue, or site for absorption or for drug action.

EXTENDED-RELEASE ORAL DOSAGE FORMS

Not all drugs are suited for formulation into extended-release products, and not all medical conditions require treatment with such a product. The drug and the therapeutic indication must be considered jointly in determining whether or not to develop an extended-release dosage form.

Drug Candidates for Extended-Release Products

To be a successful extended-release product, the drug must be released from the dosage form at a predetermined rate, dissolved in the gastrointestinal fluids, maintained at sufficient gastrointestinal residence time, and absorbed at a rate that will replace the amount of drug being metabolized and excreted.

In general, the drugs best suited for incorporation into an extended-release product have the following characteristics:

- *They exhibit neither very slow nor very fast rates of absorption and excretion.* Drugs with slow rates of absorption and excretion are usually inherently long acting, and it is not necessary to prepare them in extended-release forms. Drugs with very short half-lives, that is, less than 2 hours, are poor candidates for ER because of the large quantities of drug required for such a formulation. Also, drugs that act by affecting enzyme systems may be longer acting than indicated by their quantitative half-lives because of residual effects and recovery of the diminished biosystem (10).
- *They are uniformly absorbed from the gastrointestinal tract.* Drugs prepared in

extended-release forms must have good aqueous solubility and maintain adequate residence time in the gastrointestinal tract. Drugs absorbed poorly or at varying and unpredictable rates are not good candidates for extended-release products.
- *They are administered in relatively small doses.* Drugs with large single doses frequently are not suitable for ER because the tablet or capsule needed to maintain a sustained therapeutic blood level of the drug would be too large for the patient to swallow easily.
- *They possess a good margin of safety.* The most widely used measure of the margin of a drug's safety is its therapeutic index, that is, the median toxic dose divided by the median effective dose. For very potent drugs, the therapeutic index may be narrow or very small. The larger the therapeutic index, the safer the drug. Drugs that are administered in very small doses or possess very narrow therapeutic indices are poor candidates for formulation into extended-release formulations because of technologic limitations of precise control over release rates and the risk of dose dumping due to a product defect. Patient misuse (e.g., chewing dosage unit) also could result in toxic drug levels.
- *They are used in the treatment of chronic rather than acute conditions.* Drugs for acute conditions require greater adjustment of the dosage by the physician than that provided by extended-release products.

Extended-Release Technology for Oral Dosage Forms

For orally administered dosage forms, extended drug action is achieved by affecting the rate at which the drug is released from the dosage form and/or by slowing the transit time of the dosage form through the gastrointestinal tract (4).

The rate of drug release from solid dosage forms may be modified by the technologies described next, which in general are based on (*a*) modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings, (*b*) controlling

drug diffusion rates from dosage forms, and (*c*) chemical reaction or interaction between the drug substance or its pharmaceutical barrier and site-specific biologic fluids.

Coated Beads, Granules, and Microspheres

In these systems, the drug is distributed onto beads, pellets, granules, or other particulate systems. Using conventional pan coating or air suspension coating, a solution of the drug substance is placed on small inert nonpareil seeds or beads made of sugar and starch or on microcrystalline cellulose spheres. The nonpareil seeds are most often in the range of 425 to 850 mm, whereas the microcrystalline cellulose spheres range from 170 to 600 mm. The microcrystalline spheres are considered more durable during production than sugar-based cores (11).

If the dose of the drug is large, the starting granules of material may be composed of the drug itself. Some of these granules may remain uncoated to provide immediate drug release. Other granules (about two-thirds to three-fourths) receive varying coats of a lipid material like beeswax, carnauba wax, glyceryl monostearate, or cetyl alcohol or a cellulosic material like ethylcellulose. Then, granules of different coating thicknesses are blended to achieve a mix having the desired drug-release characteristics. The coating material may be colored to distinguish granules or beads of different coating thicknesses (by depth of color) and to provide distinctiveness to the product. When properly blended, the granules may be placed in capsules or formed into tablets. Various commercial aqueous coating systems use ethylcellulose and plasticizer as the coating material (e.g., Aquacoat [FMC Corporation] and Surelease [Colorcon]) (12,13). Aqueous coating systems eliminate the hazards and environmental concerns associated with organic solvent–based systems.

The variation in the thickness of the coats and in the type of coating material used affects the rate at which body fluids penetrate the coating to dissolve the drug. Naturally, the thicker the coat, the more resistant to penetration and the more delayed will be drug release and dissolution. Typically, the coated beads are about 1 mm in diameter. They are combined to have three or four release groups among the more than 100 beads contained in the dosing unit (10). This provides the different desired rates of sustained or extended release and the targeting of the coated beads to the desired segments of the gastrointestinal tract. An example of this type of dosage form is the Spansule (SmithKline Beecham) capsule shown in Figure 9.3.

Multitablet System

Small spheroid compressed tablets 3 to 4 mm in diameter may be prepared to have varying drug-release characteristics. They then may be placed in gelatin capsule shells to provide the desired pattern of drug release (14). Each capsule may contain 8 to 10 minitablets, some uncoated for immediate release and others coated for extended drug release.
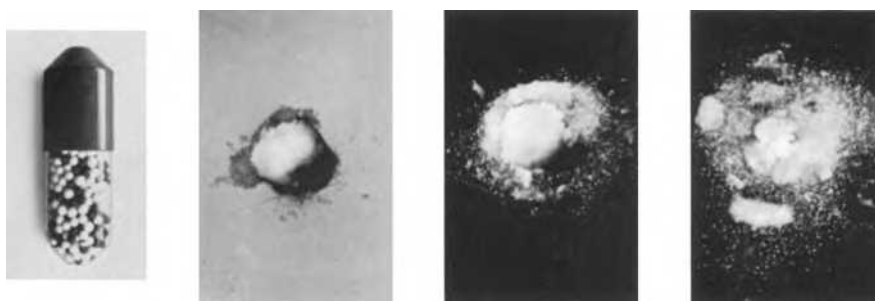

FIGURE 9.3 The Spansule capsule showing the hard gelatin capsule containing hundreds of tiny pellets for sustained drug release and rupture of one of the pellets as occurs in the gastric fluid. (Courtesy of SmithKline Beecham.)

Microencapsulated Drug

Microencapsulation is a process by which solids, liquids, or even gases may be enclosed in microscopic particles by formation of thin coatings of wall material around the substance. The process had its origin in the late 1930s as a cleaner substitute for carbon paper and carbon ribbons as sought by the business machine industry. The ultimate development in the 1950s of reproduction paper and ribbons that contained dyes in tiny gelatin capsules released on impact by a typewriter key or the pressure of a pen or pencil was the stimulus for the development of a host of microencapsulated materials, including drugs. Gelatin is a common wall-forming material, and synthetic polymers, such as polyvinyl alcohol, ethylcellulose, polyvinyl chloride, and other materials, also may be used.

The typical encapsulation process usually begins with dissolving the wall material, say gelatin, in water. The material to be encapsulated is added and the two-phase mixture thoroughly stirred. With the material to be encapsulated broken up to the desired particle size, a solution of a second material, usually acacia, is added. This additive material concentrates the gelatin (polymer) into tiny liquid droplets. These droplets (the *coacervate*) form a film or coat around the particles of the substance to be encapsulated as a consequence of the extremely low interfacial tension of the residual water or solvent in the wall material so that a continuous tight film coating remains on the particle (Fig. 9.4). The final dry microcapsules are free-flowing discrete particles of coated material. The wall material usually constitutes 2% to 20% of the total particle weight. Different rates of drug release may be obtained by changing the ratio of core to wall, the polymer used for the coating, and the method of microencapsulation (15).

One of the advantages of microencapsulation is that the administered dose of a drug is subdivided into small units that are spread over a large area of the gastrointestinal tract, which may enhance absorption by diminishing local drug concentration (15). An example
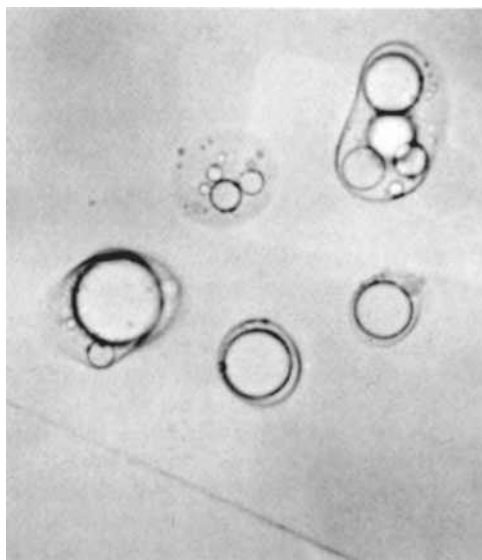

FIGURE 9.4 Microcapsules of mineral oil in a gelatin–acacia coacervate. (Courtesy of James C. Price, PhD, College of Pharmacy, University of Georgia.)

of a drug commercially available in a microencapsulated extended-release dosage form is potassium chloride (Micro-K Extencaps, Wyeth).

Embedding Drug in Slowly Eroding or Hydrophilic Matrix System

The drug substance is combined and made into granules with an excipient material that slowly erodes in body fluids, progressively releasing the drug for absorption. When these granules are mixed with granules of drug prepared without the excipient, the uncombined granules provide the immediate effect, and the drug–excipient granules provide extended action. The granule mix may be formulated as tablets or capsules for oral delivery.

Hydrophilic cellulose polymers are commonly used as the excipient base in tablet matrix systems. The effectiveness of these hydrophilic matrix systems is based on the successive processes of hydration of the cellulosic polymer, gel formation on the polymer's surface, tablet erosion, and the subsequent and continuous release of drug. Hydroxypropyl methylcellulose (HPMC), a free-flowing powder, is commonly used to provide the

hydrophilic matrix. Tablets are prepared by thoroughly distributing HPMC in the formulation, preparing the granules by wet granulation or roller compaction, and manufacturing the tablets by compression (16).

After ingestion, the tablet is wetted by gastric fluid, and the polymer begins to hydrate. A gel layer forms around surface of the tablet, and an initial quantity of drug is exposed and released. As water permeates further into the tablet, the thickness of the gel layer increases, and soluble drug diffuses through the gel layer. As the outer layer becomes fully hydrated, it erodes from the tablet core. If the drug is insoluble, it is released as such with the eroding gel layer. Thus, the rate of drug release is controlled by diffusion and tablet erosion (17).

For a successful hydrophilic matrix system, the polymer must form a gelatinous layer rapidly enough to protect the inner core of the tablet from disintegrating too rapidly after ingestion. As the proportion of polymer in a formulation increases, so does the viscosity of the gel, with a resultant decrease in the rate of drug diffusion and drug release (17). In general, 20% of HPMC results in satisfactory rates of release for an extended-release tablet formulation. However, as with all formulations, consideration must be given to the possible effects of other formulation ingredients, including fillers, tablet binders, and disintegrants. An example of a proprietary product using a hydrophilic matrix base of HPMC for extended drug release is Oramorph SR Tablets (AllPharma), which contains morphine sulfate.

When hydrophilic matrix formulations are used in the preparation of extended-release capsules, the same concept applies. When the capsule is ingested, water penetrates the capsule shell, comes in contact with the fill, hydrates the outer layer of powder, and forms a gelatinous plug from which the drug content diffuses gradually over time as hydration continues and the gelatinous plug dissolves.

Manufacturers may prepare two-layer tablets, with one layer containing the uncombined drug for immediate release and the other layer having the drug embedded in a hydrophilic matrix for ER. Three-layer tablets may be similarly prepared, with both outer layers containing the drug for immediate release. Some commercial tablets are prepared with an inner core containing the extended-release portion of drug and an outer shell enclosing the core and containing drug for immediate release.

Embedding Drug in Inert Plastic Matrix

The drug is granulated with an inert plastic material such as polyethylene, polyvinyl acetate, or polymethacrylate, and the granulation is compressed into tablets. The drug is slowly released from the inert plastic matrix by diffusion. The compression creates the matrix or plastic form that retains its shape during leaching of the drug and during its passage through the alimentary tract. An immediate-release portion of drug may be compressed onto the surface of the tablet. The inert tablet matrix, expended of drug, is excreted with the feces. The historical example of a dosage form of this type is the Gradumet (Abbott).

Complex Formation

Some drug substances, when chemically combined with certain other chemical agents, form complexes that may be only slowly soluble in body fluids, depending on the pH of the environment. This slow dissolution rate provides the ER of the drug. Salts of tannic acid, tannates, provide this quality in a variety of proprietary products by the trade name Rynatan (Wallace) (10).

Ion-Exchange Resins

A solution of a cationic drug may be passed through a column containing an ion-exchange resin, forming a complex by the replacement of hydrogen atoms. The resin–drug complex is washed and may be tableted, encapsulated, or suspended in an aqueous vehicle. The release of the drug depends on the pH and electrolyte concentration in the gastrointestinal tract. Release is greater in the acidity of the stomach than in the less acidic environment of the small intestine. Examples of drug

products of this type include hydrocodone polistirex and chlorpheniramine polistirex suspension (Tussionex Pennkinetic extended-release suspension [CellTech]) and phentermine resin capsules (Ionamin capsules [CellTech]).

The mechanism of action of drug release from ion-exchange resins may be depicted as follows:

In the Stomach.

1. Drug resinate + HCl ⇌ acidic resin + drug hydrochloride

2. Resin salt + HCl ⇌ resin chloride + acidic drug

In the Intestine.

1. Drug resinate + NaCl ⇌ sodium resinate + drug hydrochloride

2. Resin salt + NaCl ⇌ resin chloride + sodium salt of drug

This system incorporates a polymer barrier coating and bead technology in addition to the ion-exchange mechanism. The initial dose comes from an uncoated portion and the remainder from the coated beads. The coating does not dissolve, and release is extended over 12 hours by ionic exchange. The drug-containing polymer particles are minute and may be suspended to produce a liquid with extended-release characteristics as well as solid dosage forms.

Osmotic Pump

The pioneer *oral osmotic* pump drug delivery system is the *OROS* system developed by Alza. The system is composed of a core tablet surrounded by a semipermeable membrane coating having a 0.4-mm-diameter hole produced by laser beam (Fig. 9.5). The core tablet has two layers, one containing the drug (the active layer) and the other containing a polymeric osmotic agent (the push layer). The system operates on the principle of osmotic pressure.

When the tablet is swallowed, the semipermeable membrane permits water to enter from the patient's stomach into the core tablet, dissolving or suspending the drug. As pressure increases in the osmotic layer, it pumps the drug solution out of the delivery orifice on the side of the tablet. Only the drug solution (not the undissolved drug) is capable of passing through the hole in the tablet. The system is designed such that only a few drops of water are drawn into the tablet each hour. The rate of inflow of water and the function of the tablet depend on an osmotic gradient between the contents of the two-layer core and the fluid in the gastrointestinal tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant. The drug-release rate may be altered by changing the surface area, thickness or composition of the membrane, and/or diameter of the drug-release orifice. The drug-release rate is not affected by gastrointestinal acidity, alkalinity, fed conditions, or gastrointestinal motility. The biologically inert components
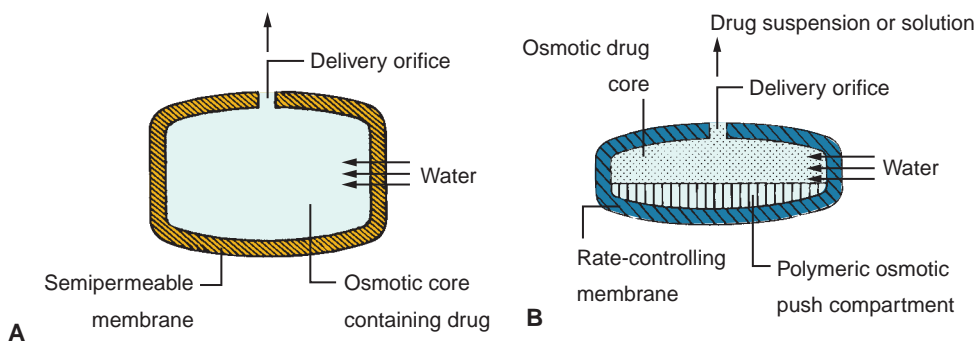

FIGURE 9.5 **A:** Elementary OROS (oral release osmotic system) osmotic pump drug delivery system. **B:** Push–pull osmotic system.

of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

This type of osmotic system, termed the *gastrointestinal therapeutic system* (GITS [Pfizer]), is employed in the manufacture of Glucotrol XL ER tablets and Procardia XL ER tablets. Another example of the osmotic system is the *controlled-onset extended release* (COER [Searle]) system used in Covera-HS tablets, in which initial drug is released 4 to 5 hours after tablet ingestion. The delay in drug release is effected by a slowly solubilized coated layer between the active drug core and the outer semipermeable membrane.

Repeat-Action Tablets

Repeat-action tablets are prepared so that an initial dose of drug is released immediately and a second dose follows later. The tablets may be prepared with the immediate-release dose in the tablet's outer shell or coating and the second dose in the tablet's inner core, separated by a slowly permeable barrier coating. In general, the drug from the inner core is exposed to body fluids and released 4 to 6 hours after administration. An example of this type of product is Repetabs (Schering). Repeat-action dosage forms are best suited for treatment of chronic conditions requiring repeated dosing. The drugs should have low dosage and fairly rapid rates of absorption and excretion.

DELAYED-RELEASE ORAL DOSAGE FORMS

The release of a drug from an oral dosage form may be intentionally delayed until it reaches the intestines for several reasons. The purpose may be to protect a drug destroyed by gastric fluids, to reduce gastric distress caused by drugs particularly irritating to the stomach, or to facilitate gastrointestinal transit for drugs that are better absorbed from the intestines. As stated previously, capsules and tablets specially coated to remain intact in the stomach and to yield their ingredients in the intestines are termed *enteric coated*. The enteric coating may be pH dependent, breaking down in the less acidic environment of the intestine; time dependent, eroding by moisture over time during gastrointestinal transit; or enzyme dependent, deteriorating as a result of the hydrolysis-catalyzing action of intestinal enzymes. Among the many agents used for enteric coating of tablets and capsules are fats, fatty acids, waxes, shellac, and cellulose acetate phthalate.

Examples of modified-release tablets and capsules official in the USP are presented in Table 9.2, and examples of proprietary modified-release oral dosage forms are presented in Table 9.3.

Table 9.2	MODIFIED-RELEASE TABLETS AND CAPSULES OFFICIAL IN THE USP

Delayed release
  Aspirin delayed-release tablets
  Dirithromycin delayed-release tablets
  Doxycycline hyclate delayed-release capsules
  Erythromycin delayed-release capsules
  Oxybutynin chloride extended-release tablets
  Oxtriphylline delayed-release tablets
Extended release
  Aspirin extended-release tablets
  Bupropion hydrochloride extended-release tablets
  Diltiazem hydrochloride extended-release capsules
  Disopyramide phosphate extended-release capsules
  Indomethacin extended-release capsules
  Isosorbide dinitrate extended-release tablets and capsules
  Lithium carbonate extended-release tablets
  Oxtriphylline extended-release tablets
  Potassium chloride extended-release tablets
  Phenytoin sodium extended-release capsules
  Procainamide hydrochloride extended-release tablets
  Propranolol hydrochloride extended-release capsules
  Quinidine gluconate extended-release tablets
  Theophylline extended-release capsules

Table 9.3	PROPRIETARY MODIFIED-RELEASE ORAL DOSAGE FORMS
DRUG PRODUCT AND MANUFACTURER	**DOSAGE FORM CHARACTERISTICS**
Delayed release	
E-Mycin (erythromycin) delayed-release tablets (Knoll)	Tablets enteric-coated with cellulose acetate phthalate, carnauba wax, and cellulose polymers. Use: antibiotic
Erythromycin delayed-release capsules (Abbott)	Capsules contain enteric-coated pellets of erythromycin base. Use: antibiotic
Asacol (mesalamine) delayed-release tablets (Procter & Gamble)	Tablets coated with Eudragit S (methacrylic acid copolymer B), a resin that bypasses the stomach and dissolves in the ileum and beyond. Use: treat ulcerative colitis
Prilosec (omeprazole) delayed-release capsules (AstraZeneca)	Enteric-coated granules of omeprazole placed in capsules. Omeprazole is acid labile and is degraded by gastric acid. Use: treatment of duodenal ulcer
Extended-release coated particles and beads	
Toprol-XL (metoprolol succinate) tablets (AstraZeneca)	Drug pellets coated with cellulose polymers compressed into tablets. Use: treatment of hypertension
Indocin SR (indomethacin) capsules (Merck)	Coated pellets for SR. Formulation includes polyvinyl acetate–crotonic acid copolymer and HPMC. Use: analgesic, anti-inflammatory
Compazine (prochlorperazine) Spansule capsules (SmithKline Beecham)	Coated pellets in capsule formulated to release initial dose promptly with additional drug for prolonged release. Use: antinausea, antivomiting
Adderall XR (amphetamines) capsules (Shire US Inc)	Encapsulated sugar spheres coated with drug and HPMC and methacrylic acid copolymer providing a double-pulsed delivery. Use: attention deficit disorder
Extended-release inert matrix	
Procanbid (procainamide HCl) tablets (Monarch)	Extended-release tablets with a core tablet of a nonerodible wax matrix coated with cellulose polymers. Use: an antiarrhythmic
Extended-release hydrophilic/eroding matrix	
Depakote ER (divalproex sodium) extended-release tablets (Abbott)	Drug is dispersed and compressed in a hypromellose and microcrystalline cellulose matrix. Use: antiepileptic
Quinidex (quinidine sulfate) tablets (Robins)	Extended-release provided by hydrophilic matrix that swells and slowly erodes. Use: antiarrhythmic
Oramorph SR (morphine sulfate) tablets (AllPharma)	Sustained-release hydrophilic matrix system, based on polymer HPMC. Use: analgesic for severe pain
Extended-release microencapsulated	
K-Dur microburst release system (potassium chloride) tablets (Key)	Immediately dispersing drug microencapsulated with ethylcellulose and hydroxypropyl cellulose. Use: potassium depletion
Effexor XR (venlafaxine hydrochloride) capsules cellulose, ethylcellulose, and hypromellose resulting in once a day	Drug dispersed in spheroids and coated. Polymers used include (Wyeth) administration that is not pH dependent. Use: antidepressant
Extended-release osmotic	
Glucotrol XL (glipizide) tablets (Pfizer)	Controlled-release GITS[a] osmotic system. Ingredients include polyethylene oxide, hydroxypropyl cellulose, cellulose acetate. Use: antihyperglycemic
Covera-HS (verapamil HCl) tablets (Searle)	A COER[b] osmotic system. Use: antihypertensive, antianginal

[a]Gastrointestinal therapeutic system.
[b]Controlled onset, ER.

USP REQUIREMENTS AND FDA GUIDANCE FOR MODIFIED-RELEASE DOSAGE FORMS

The USP contains general chapters and specific tests to determine the drug-release capabilities of extended-release and delayed-release tablets and capsules (8).

Drug Release

The USP test for drug release for extended-release and delayed-release articles is based on drug dissolution from the dosage unit against elapsed test time (Fig. 9.6). Descriptions of the various test apparatus and procedures may be found in the USP Chapter <724> (8). The individual monographs contain specific criteria for compliance with the test and the apparatus and test procedures to be used. For example, for aspirin extended-release tablets, the USP requires the following aspirin dissolution rate to meet the stated drug-release test:

Time (Hours)	Amount Dissolved
1.0	15%–40%
2.0	25%–60%
4.0	35%–75%
8.0	Not less than 70%

Uniformity of Dosage Units

Modified-release tablets and capsules must meet the USP standard for uniformity as described in Chapter 8 for conventional dosage units. Uniformity of dosage units may be demonstrated by either of two methods, weight variation or content uniformity, as described in USP Chapter <905> (8).

In Vitro–In Vivo Correlations

In vitro–in vivo relationships or in vitro–in vivo correlations (IVIVCs) are critical to the development of oral extended-release products. Assessing IVICRs is important throughout product development, clinical evaluation, submission of an application for FDA approval for marketing, and during postapproval for any proposed formulation or manufacturing changes (18).

In 1997, the FDA published a guidance document, *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of* In Vitro/In Vivo *Correlations* (9). It provides guidance to sponsors of new drug applications and abbreviated new drug applications for extended-release oral products. The guidance provides methods of (*a*) developing an IVIVC and evaluating its predictability, (*b*) using an IVIVC to establish dissolution specifications, and (*c*) applying an IVIVC as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence during the approval process or during postapproval for certain formulation or manufacturing changes.

Three categories of IVIVCs are included in the document:

- *Level A*: A predictive mathematical model for the relationship between the entire in vitro dissolution and release time course and the entire in vivo response time course, for example, the time course of

FIGURE 9.6 Varian Biodis Dissolution Apparatus for determining dissolution characteristics of modified-release products. (Courtesy of Varian Inc.)

plasma drug concentration or amount of drug absorbed. This is the most common type of correlation submitted.

- *Level B*: A predictive mathematical model of the relationship between summary parameters that characterize the in vitro and in vivo time courses, for example, models that relate the mean in vitro dissolution time to the mean in vivo dissolution time, the mean in vitro dissolution time to the mean residence time in vivo, or the in vitro dissolution rate constant to the absorption rate constant
- *Level C*: A predictive mathematical model of the relationship between the amount dissolved in vitro at a particular time (or the time required for in vitro dissolution of a fixed percent of the dose, e.g., T_{50}) and a summary parameter that characterizes the in vivo time course (e.g., maximum concentration [C_{max}] or area under the curve). The level of IVIVCs may be useful in the early stages of formulation development when pilot formulations are being selected.

The most common process for developing an IVIVC model (level A) is to (*a*) develop formulations with different release rates (e.g., slow, fast, and intermediate) or a single-release rate if dissolution is independent of condition, (*b*) obtain in vitro dissolution profiles and in vivo plasma concentration profiles for these formulations, and (*c*) estimate the in vivo absorption or dissolution time course for each formulation and subject using appropriate mathematical approaches.

Among the criteria applicable to the development of IVIVCs are the following (9):

- In determining in vitro dissolution, USP dissolution apparatus, type I (basket) or type II (paddle), is preferred, although type III (reciprocating cylinder) or type IV (flow-through cell) may be applicable in some instances.
- An aqueous medium with a pH not exceeding 6.8 is preferred as the medium for dissolution studies. For poorly soluble drugs, a surfactant (e.g., 1% sodium lauryl sulfate) may be added.
- The dissolution profiles of at least 12 individual dosage units from each lot should be determined.

- For in vivo studies, human subjects are used in the fasted state unless the drug is not well tolerated, in which case the studies may be conducted in the fed state. Acceptable data sets have been shown to be generated with use of 6 to 36 human subjects.
- Crossover studies are preferred, but parallel studies or cross-study analysis may be acceptable using a common reference treatment product, such as an intravenous solution, an aqueous oral solution, or an immediate-release product.

Labeling

The USP indicates labeling requirements for modified-release dosage form articles in addition to general labeling requirements. The requirements are specific to the monograph article. For example, the label of aspirin delayed-release tablets must state that *the tablets are enteric coated*, whereas the labeling for theophylline extended-release capsules must indicate *whether the product is intended for dosing every 12 or 24 hours and state with which* in vitro *drug-release test the product complies* (seven tests are described in the monograph, each with different drug-release times and tolerances).

CLINICAL CONSIDERATIONS IN THE USE OF ORAL MODIFIED-RELEASE DOSAGE FORMS

Patients should be advised of the dose and dosing frequency of modified drug-release products and instructed not to use them interchangeably or concomitantly with immediate-release forms of the same drug. Patients stabilized on a modified-release product should not be changed to an immediate-release product without consideration of any existing blood level concentrations of the drug. Also, once stabilized, patients should not be changed to another extended-release product unless there is assurance of equivalent bioavailability. A different product can result in a marked shift in the patient's drug blood level because of differences in drug-release characteristics.

Patients should be advised that modified-release tablets and capsules should not be crushed or chewed, since such action

compromises their drug-release features (19). Patients being fed by enteral nutrition through a nasogastric tube may receive conventional or modified-release medication. For example, coated pellets from inside capsules simply may be mixed with water and poured down the feeding tube (20). Similarly, modified-release tablets and capsules should not generally be used as the source of a drug to prepare other dosage forms, that is, pediatric oral liquids.

Patients and caregivers should be advised that nonerodible plastic matrix shells and osmotic tablets remain intact throughout gastrointestinal transit and the empty shells or ghosts from osmotic tablets may be seen in the stool. The patient should be assured of the normalcy of this event and that drug absorption has taken place (4).

PACKAGING AND STORING MODIFIED-RELEASE TABLETS AND CAPSULES

Modified-release tablets and capsules are packaged and stored in the same manner as conventional products as discussed in Chapters 7 and 8.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

You work in a small but growing pharmaceutical company producing extended-release tablets. Sales have been good, and the pressure is on to increase production by 20% per day. The only way you can accomplish this is to increase the speed at which your rotary machines work, since you are running three shifts of 8 hours each. When you increase the speed of your machine and start production, you start getting reports that the tablets do not produce the proper extended-release dissolution profile and they are not of the proper hardness. Also, the tablets are less potent and weigh less than that specified. No other adjustments have been made to the machine other than to increase the speed. What will you do?

OBJECTIVE INFORMATION

Your machines are 36-station rotary tablet presses using gravity feed. You produce the tablets, which are oblong, with a hydrophilic matrix system and an oblong punch and die. The optimal speed was established during the scale-up phase of product development and has been used for the past 18 months with no problems.

ASSESSMENT

The production of tablets must follow a well-defined set of conditions. If not, the final product may not have the desired characteristics of hardness, disintegration, dissolution, friability, and appearance. It appears that the increase in speed is not allowing the powder blend sufficient time to flow by gravity into the tablet dies, as the increased speed causes the die to pass under the powder feed apparatus faster than before. This results in less powder per tablet in the die, and when they are compressed, the resulting tablets are not as firm; when subjected to a dissolution test, the result is a more rapid release of the drug. This also explains the lighter tablets and the lower quantity of active drug per tablet.

PLAN

There are two options here: first, decrease the rate of speed to that at which the production was validated, and second, consider a force-feed system to move the powder into the dies faster. The latter option requires validation of the equipment under the new conditions. A third option may be the most reasonable, and that is to purchase additional machines.

CLINICAL CASE STUDY

SUBJECTIVE INFORMATION

CC: K.F. is a 9-year-old WM who arrives at the pediatric clinic with his mother. The mother states that K.F. talks excessively, interrupts others when they speak, rarely follows her directions, and frequently runs around the house. The mother also states that she has heard from the teacher that he leaves the classroom in the middle of the class, often blurts out answers before questions have been completed, has a difficult time waiting his turn (e.g., in the lunchroom), is "fidgety," rarely follows directions or pays attention, and turns in incomplete homework assignments. His teacher has also told the mother that he frequently distracts the other students at school. The mother states, "I would like your help. But I do not want him to be put on a medicine where he has to take it more than once a day because I might forget to give it to him. Also, I do not want him taking any medicine to school."

HPI: The mother states that K.F. has been "this way" since he was 6 years old. However, it is now at the point where he does not complete any of his tasks (e.g., making his bed, doing his homework) and his grades are "slipping." His latest report card showed "many Cs and Ds."

PMH: Otitis media, 4 weeks ago

Meds: Zithromax suspension, finished it about 3 weeks ago

OTC Meds: K.F. and his mother deny K.F.'s use of vitamins, herbals, or any other supplements.

PSH: None

FH: Mother, DM type II since age 29

SH: (per K.F.)
  (−) Tobacco
  (−) EtOH
  (−) Illicit drugs
  (+) Caffeine: loves Mountain Dew, drinks a couple of cans (~2 to 3) per day

Exercise, daily activities: Goes to school from 8 AM to 3 PM; after school, likes to watch TV, in-line skate, and play basketball

Timing of meals: Breakfast at 7:30 AM, lunch at noon, snack at 3:30 PM, and dinner at 6:30 PM

Diet: Chips, candy, peanut butter and jelly sandwiches, pasta, and two or three cans of Mountain Dew per day

Bedtime: 9:30 to 10:30 PM

Siblings: None

Mother and father are both accountants, and each works approximately 40 hours per week. They have been married for 11 years.

ALL: NKDA

OBJECTIVE INFORMATION

9-year-old WM

Ht: 4'2"   **Wt:** 71 lb
BP: 119/75 **P:** 70   **T:** 98.6°F **RR:** 15
Pain: None

The mother presents K.F.'s last report card with grades Cs and Ds along with notes from K.F.'s teacher about his behavior.

ASSESSMENT

ADHD: Combined type

PLAN

Recommend extended-release methylphenidate HCl (i.e., Concerta) 18 mg by mouth once a day with breakfast and a full glass of water, milk, or juice at 7:30 AM (to aid with adherence). Inform the mother that the prescription has to be dispensed to her within 7 days after the date it is issued. Concerta has a rapid onset of action to help K.F. focus in the morning at school and a long duration of action, which will be useful during and after school for homework.

Counsel the mother on possible side effects, such as insomnia, loss of appetite, and weight loss. Inform K.F.'s mother also about a possible decrease in rate of height growth (not final height). Advise

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CLINICAL CASE STUDY CONT.

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her not to administer it after school if her son misses a dose of the drug in the morning. Wait until the next morning for the next dose. Do not double the dose the next day. Inform the mother that this product is prepared in a nonabsorbable shell, which means that the empty shell may or may not be observed in the stool. So if K.F. notices something that resembles a tablet in the stool and mentions it to his mother, she can tell him not to worry; the medicine is working. As methylphenidate is a class II drug, the mother should understand the necessity to secure a new prescription from the physician for every cycle of therapy. This can be done when K.F. returns to the physician's office for routine monitoring (e.g., blood pressure, pulse, height, weight, encountered side effects).

Counsel K.F. and his mother that he should take the tablet with a full glass of water or juice. He should swallow the tablet whole and not to chew it. Discuss the change in medication dosage forms for children when they convert from liquid dosage forms to solid dosage forms and the apprehension that may be involved. K.F. and his mother should know that there is no conclusive evidence regarding sugar dietary intake and its effect on ADHD. However, if K.F.'s mother believes that K.F.'s symptoms are worse with sugary foods or drinks, these should be minimized and decreased from his diet. It is given that the caffeinated soft drink (i.e., Mountain Dew) should be changed for a caffeine-free soft drink. No caffeinated beverages should be ingested by K.F. after 6 PM.

Goal: Resolution of symptoms (e.g., improved attention, less fidgeting), improvement in grades, and no side effects from Concerta. Also, K.F.'s mother should be referred to a child psychologist who can provide K.F.'s needed behavioral therapy.

www.concerta.net
www.add.org
www.adhd.com

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APPLYING THE PRINCIPLES AND CONCEPTS

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Group Activities

1. Compare the advantages and disadvantages of modified-release dosage forms to conventional oral dosage forms.
2. Create a listing of conceivable ways a consumer/patient might misuse a modified-release dosage form.
3. List five counseling points for proper administration of solid modified-release dosage forms, and provide a rationale for each counseling point.
4. Referring to the USP <724>, select three individual drug monographs containing specific criteria for compliance with the test and the apparatus and test procedures to be used, and state the reasons for any differences that exist among the three monographs.
5. Create a listing, including active ingredient(s), of 10 modified-release dosage form products whose names imply a modified-release product.

Individual Activities

1. Create a table of modified-release dosage form products including amount of active ingredient(s), indication, contraindication, adverse effects/precautions, and dosage.
2. Create a listing of trademarked modified-release dosage forms that possess unique characteristics, for example, size, shape, and color, and describe/detail those features.

APPLYING THE PRINCIPLES AND CONCEPTS Cont.

3. Generate a listing of drugs whose physical–chemical characteristics make them a candidate for incorporation into a modified-release dosage form.

4. From the primary literature, find a clinical study demonstrating a comparison between a modified-release tablet product and a compressed tablet for clinical effectiveness, and determine which one would be preferred in terms of patient acceptance, patient adherence, bioequivalence, and cost. Explain the rationale for your decision.

5. Select one USP drug monograph for an official modified-release tablet dosage form, and identify and describe its main components.

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SEMISOLID DOSAGE FORMS AND TRANSDERMAL SYSTEMS

10 Ointments, Creams, and Gels

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between the various types of semisolid bases on the basis of physical and chemical properties
2. List the criteria for the selection of a semisolid base to treat a topical affliction
3. Describe the methods to incorporate (an) active ingredient(s) into a semisolid base
4. Explain the difference between an ointment, a cream, and a gel
5. Compare and contrast an ophthalmic ointment base and a topical ointment base for application to the skin
6. List advantages and disadvantages of administering drugs rectally and vaginally
7. List counseling points the pharmacist should share with the patient for each of the routes of administration used for topical product application

Ointments, creams, and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, placed on the surface of the eye, or used nasally, vaginally, or rectally. Most of these preparations are used for the effects of the therapeutic agents they contain. The unmedicated ones are used for their physical effects as protectants or lubricants.

Topical preparations are used for both local and systemic effects. Systemic drug absorption should always be considered when using topical products if the patient is pregnant or nursing, because drugs can enter the fetal blood supply and breast milk and be transferred to the fetus or nursing infant.

Topical applications can be designed for either local effects or systemic absorption. The following distinction is an important one with regard to dermatologic applications. A *topical dermatological* product is designed to deliver drug *into* the skin in treating dermal disorders, *with the skin as the target organ*. A *transdermal* product is designed to deliver drugs *through* the skin (*percutaneous absorption*) to the general circulation for systemic effects, *with the skin not being the target organ* (1).

OINTMENTS

Ointments are semisolid preparations intended for external application to the skin or mucous membranes. Ointments may be medicated or not. Unmedicated ointments are used for the physical effects they provide as protectants, emollients, or lubricants. *Ointment bases*, as described, may be used for their physical effects or as vehicles for medicated ointments.

Ointment Bases

Ointment bases are generally classified by the USP (2) into four groups: (*a*) oleaginous bases, (*b*) absorption bases, (*c*) water-removable bases, and (*d*) water-soluble bases.

Oleaginous Bases

Oleaginous bases are also termed *hydrocarbon bases*. On application to the skin, they have an emollient effect, protect against the escape of moisture, are effective as occlusive dressings, can remain on the skin for long periods without drying out, and because of their immiscibility with water, are difficult to wash off. Water and aqueous preparations may be incorporated, but only in small amounts and with some difficulty. Petrolatum, white petrolatum, white ointment, and yellow ointment are examples of hydrocarbon ointment bases.

When powdered substances are to be incorporated into hydrocarbon bases, liquid petrolatum (mineral oil) may be used as the levigating agent.

Petrolatum, USP, is a purified mixture of semisolid hydrocarbons obtained from petroleum. It is an unctuous mass, varying in color from yellowish to light amber. It melts at 38°C to 60°C and may be used alone or in combination with other agents as an ointment base. Petrolatum is also known as yellow petrolatum and petroleum jelly. A commercial product is Vaseline (Chesebrough-Ponds).

White Petrolatum, USP, is a purified mixture of semisolid hydrocarbons from petroleum that has been wholly or nearly decolorized. It is used for the same purpose as petrolatum, but because of its lighter color, it is considered more esthetically pleasing by some pharmacists and patients. White petrolatum is also known as white petroleum jelly. A commercial product is White Vaseline (Chesebrough-Ponds).

Yellow Ointment, USP. This ointment has the following formula for the preparation of 1,000 g:

Yellow wax:	50 g
Petrolatum:	950 g

Yellow wax is the purified wax obtained from the honeycomb of the bee *Apis mellifera*. The ointment is prepared by melting the yellow wax on a water bath, adding the petrolatum until the mixture is uniform, then cooling and stirring until congealed. Also called simple ointment, it has a slightly greater viscosity than plain petrolatum.

White Ointment, USP. This ointment differs from yellow ointment by substitution of white wax (bleached and purified yellow wax) and white petrolatum in the formula.

Absorption Bases

Absorption bases are of two types: (*a*) those that *permit* the incorporation of aqueous solutions resulting in the formation of water-in-oil (W/O) emulsions (e.g., *hydrophilic petrolatum*) and (*b*) those that *are* W/O emulsions (syn: *emulsion bases*) that permit the incorporation of additional quantities of aqueous solutions (e.g., lanolin). These bases may be used as emollients, although they do not provide the degree of occlusion afforded by the oleaginous bases. Absorption bases are not easily removed from the skin with water washing, because the external phase of the emulsion is oleaginous. Absorption bases are useful as pharmaceutical adjuncts to incorporate small volumes of aqueous solutions into hydrocarbon bases. This is accomplished by incorporating the aqueous solution into the absorption base and then incorporating this mixture into the hydrocarbon base.

Hydrophilic Petrolatum, USP, has the following formula for the preparation of 1,000 g: It is prepared by melting the stearyl alco-

Cholesterol:	30 g
Stearyl alcohol:	30 g
White wax:	80 g
White petrolatum:	860 g

hol and white wax on a steam bath, adding the cholesterol with stirring until dissolved, adding the white petrolatum, and allowing the mixture to cool while stirring until congealed.

Commercial products, Aquaphor and Aquabase, variations of hydrophilic petrolatum, have the capacity to absorb up to three times their weight in water and are useful to help incorporate a water-soluble drug, for example, tobramycin sulfate, into

an oleaginous ointment base. This concept is used in the preparation of ophthalmic ointments. Eucerin is a 50% W/O emulsion.

Lanolin, USP, (anhydrous lanolin) obtained from the wool of sheep (*Ovis aries*), is a purified waxlike substance that has been cleaned, deodorized, and decolorized. It contains not more than 0.25% water. Additional water may be incorporated into lanolin by mixing. *Modified Lanolin*, *USP*, is lanolin processed to reduce the contents of free lanolin alcohols and any detergent and pesticide residues.

Water-Removable Bases

Water-removable bases are oil-in-water emulsions commonly called creams. Because the external phase of the emulsion is aqueous, they are easily washed from skin and are often called water-washable bases. They may be diluted with water or aqueous solutions. They can absorb serous discharges. Hydrophilic Ointment, USP, is an example of this type of base.

Hydrophilic Ointment, USP, has the following formula for 1,000 g:

Ingredient	Amount (grams)
Methylparaben:	0.25
Propylparaben:	0.15
Sodium lauryl sulfate:	10.00
Propylene glycol:	120.00
Stearyl alcohol:	250.00
White petrolatum:	250.00
Purified water:	370.00

The stearyl alcohol and white petrolatum are melted together at about 75°C. The other agents, dissolved in the purified water, are added with stirring until the mixture congeals. Sodium lauryl sulfate is the emulsifying agent, with the stearyl alcohol and white petrolatum constituting the oleaginous phase of the emulsion and the other ingredients the aqueous phase. Methylparaben and propylparaben are antimicrobial preservatives.

Water-Soluble Bases

Water-soluble bases do not contain oleaginous components. They are completely water washable and often referred to as greaseless. Because they soften greatly with the addition of water, large amounts of aqueous solutions are not effectively incorporated into these bases. They mostly are used for incorporation of solid substances. Polyethylene glycol (PEG) ointment, NF, is the prototype example of a water-soluble base.

Polyethylene Glycol Ointment, NF, PEG is a polymer of ethylene oxide and water represented by the formula $H(OCH_2CH_2)nOH$, in which *n* represents the average number of oxyethylene groups. The numeric designations associated with PEGs refer to the average molecular weight of the polymer. PEGs having average molecular weight below 600 are clear, colorless liquids; those with molecular weight above 1,000 are waxlike white materials; and those with molecular weight in between are semisolids. The greater the molecular weight, the greater the viscosity. The NF lists the viscosity of PEGs ranging from average molecular weight of 200 to 8,000.

The general formula for preparation of 1,000 g of PEG ointment is

PEG 3350:	400 g
PEG 400:	600 g

Combining PEG 3350, a solid, with PEG 400, a liquid, results in a very pliable semisolid ointment. If a firmer ointment is desired, the formula may be altered to contain up to equal parts of the two ingredients. When aqueous solutions are to be incorporated into the base, substitution of 50 g of PEG 3350 with an equal amount of stearyl alcohol is advantageous in rendering the final product firmer.

Selection of the Appropriate Base

Selection of the base to use in the formulation of an ointment depends on careful assessment of a number of factors, including the following:

- Desired release rate of the drug substance from the ointment base
- Desirability of topical or percutaneous drug absorption
- Desirability of occlusion of moisture from the skin

- Stability of the drug in the ointment base
- Effect, if any, of the drug on the consistency or other features of the ointment base
- Desire for a base easily removed by washing with water
- Characteristics of the surface to which it is applied

For example, an ointment is generally applied to dry, scaly skin; a cream is applied to weeping or oozing surfaces; and a lotion is applied to intertriginous areas or where friction may occur, as between the thighs or under the armpit. The base that provides the best combination of the most desired attributes should be selected.

Preparation of Ointments

Ointments are prepared by two general methods, (*a*) incorporation and (*b*) fusion, depending primarily on the nature of the ingredients.

Incorporation

The components are mixed until a uniform preparation is attained (Fig. 10.1). On a small scale, as in extemporaneous compounding, the pharmacist may mix the components using a mortar and pestle, or a spatula may be used to rub the ingredients together on an ointment slab (a large glass or porcelain plate or pill tile). Some pharmacists use nonabsorbent parchment paper to cover the working surface; being disposable, the paper eliminates cleaning the ointment slab. If using an ointment parchment pad, it is best to not allow too long a contact of the ointment with the parchment, as it may soften and tear.

Others will use an ointment mill, an electronic mortar and pestle, or a device called an "Unguator," which allows a pharmacist to place the ingredients in a plastic ointment jar with a special lid that allows for a mixing blade to be used to mix the ingredients in the dispensing container. These devices can be controlled manually or via computer software. See Figures 10.2 to 10.4.

Incorporation of Solids. When preparing an ointment by spatulation, the pharmacist works the ointment with a stainless steel spatula having a long, broad blade and

FIGURE 10.1 Creams and ointments in batch sizes up to 1,500 kg are manufactured in this stainless steel tank, which has counter sweep agitation and a built-in homogenizer. (Courtesy of Lederle Laboratories.)

periodically removes the accumulation of ointment on the large spatula with a smaller one. If the components of an ointment react with metal (as does iodine), hard rubber or silicone spatulas may be used. The ointment is prepared by thoroughly rubbing and working the components together on the hard surface until the product is smooth and uniform. The ointment base is placed on one side of the working surface and the powdered components, previously reduced to fine powders and thoroughly blended in a mortar, on the other side. A small portion of the powder is mixed with a portion of the base until uniform. Geometric dilution is continued until all portions of the powder and base are combined and thoroughly and uniformly blended.

It often is desirable to reduce the particle size of a powder or crystalline material before incorporation into the ointment base so the final product will not be gritty. This may be done by *levigating*, or mixing the solid material in a vehicle in which it is insoluble to make a smooth dispersion. The levigating
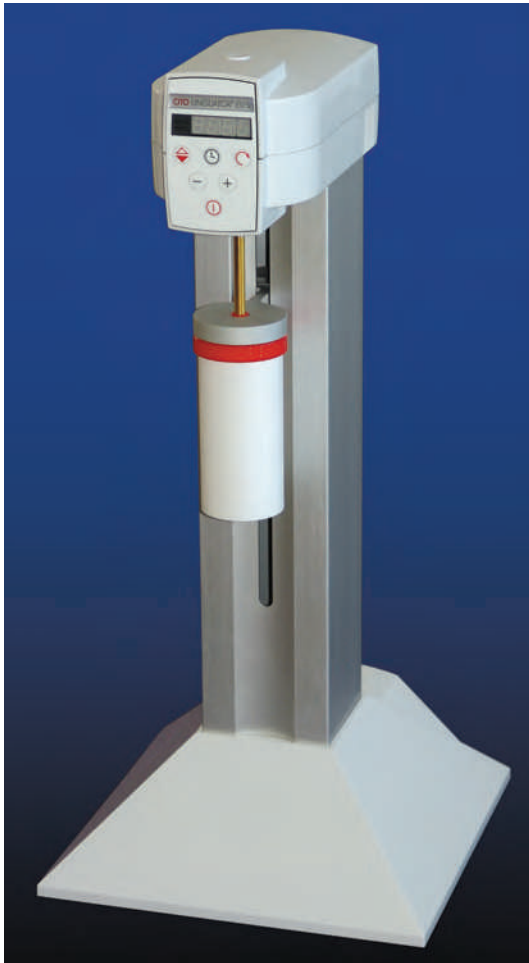
FIGURE 10.2 Unguator Model B-R Electronic mortar and pestle. (Courtesy of Health Engineering Systems.)

FIGURE 10.3 Example mixing spindles for use with the Unguator electronic mortar and pestle. (Courtesy of Health Engineering Systems.)

and the solution added to the ointment base by spatulation or in a mortar and pestle. The mortar and pestle method is preferred when large volumes of liquid are added, because the liquid is more captive than on an ointment slab.

For incorporating a gummy material, such as camphor, pulverization by intervention can be used. The material is dissolved in a solvent and spread out on the pill tile. The solvent is allowed to evaporate, leaving a thin film of the material onto which the other ingredient or ingredients are spread. The material is then worked into the ingredients by trituration with a spatula.

Incorporation of Liquids. Liquid substances or solutions of drugs, as described above, are added to an ointment only after due consideration of an ointment base's capacity to accept the volume required. For example,

FIGURE 10.4 Containers for use with the Unguator electronic mortar and pestle system. The mixing actually occurs within the container that is also used as the dispensing container. They have a "push-up" bottom, and the cap is removed to allow the material to be delivered. (Courtesy of Health Engineering Systems.)

agent (e.g., mineral oil for bases in which oils are the external phase or glycerin for bases in which water is the external phase) should be physically and chemically compatible with the drug and base. The levigating agent should be about equal in volume to the solid material. A mortar and pestle are used for levigation. This allows both reduction of particle size and dispersion of the substance in the vehicle. After levigation, the dispersion is incorporated into the ointment base by spatulation or with the mortar and pestle until the product is uniform.

Solids soluble in a common solvent that will affect neither the stability of the drug nor the efficacy of the product may first be dissolved in that solvent (e.g., water or alcohol)

as noted previously, only very small amounts of an aqueous solution may be incorporated into an oleaginous ointment, whereas hydrophilic ointment bases readily accept aqueous solutions. When it is necessary to add an aqueous preparation to a hydro*phobic* base, the solution first may be incorporated into a minimum amount of a hydro*philic* base and then that mixture added to the hydrophobic base. However, all bases, even if hydrophilic, have their limits to retain liquids, beyond which they become too soft or semiliquid.

Alcoholic solutions of small volume may be added easily to oleaginous vehicles or emulsion bases. Natural balsams, such as Peru balsam, are usually mixed with an equal portion of castor oil before incorporation into a base. This reduces the surface tension of the balsam and allows even distribution of the balsam throughout the base.

Ointment or roller mills can be used to force coarsely formed ointments through stainless steel or ceramic rollers to produce ointments uniform in composition and smooth in texture (Fig. 10.5). Small ointment mills also find use in product development laboratories and in small-batch manufacture or compounding.

Fusion

By the fusion method, all or some of the components of an ointment are combined by being melted together and cooled with constant stirring until congealed. Components not melted are added to the congealing mixture as it is being cooled and stirred. Naturally, heat-labile substances and any volatile components are added last, when the temperature of the mixture is low enough not to cause decomposition or volatilization of the components. Substances may be added to the congealing mixture as solutions or as insoluble powders levigated with a portion of the base. On a small scale, fusion may be conducted in a porcelain dish or glass beaker. On a large scale, it is carried out in large steam-jacketed kettles. Once congealed, the ointment may be passed through an ointment mill (in large-scale manufacture) or rubbed with a spatula or in a mortar to ensure a uniform texture.

FIGURE 10.5 Day ointment roller mill. Standards of fineness and smoothness require that no grains of material be visible under a 10-power microscope after passage through this machine. (Courtesy of Eli Lilly and Company.)

Medicated ointments and ointment bases containing components such as beeswax, paraffin, stearyl alcohol, and high molecular weight PEGs, which do not lend themselves well to mixture by incorporation, are prepared by fusion. By this general process, the materials with the highest melting points are heated to the lowest required temperature to produce a melt. The additional materials are added with constant stirring during cooling of the melt until the mixture is congealed. In this way, not all of the components are subjected to the highest temperature. Alternative methods entail melting the component with the lowest melting point first and adding the remaining components in order of their melting points or simply melting all of the components together under slowly increasing temperature. By these methods, a lower temperature is usually sufficient to achieve fusion because of the solvent action exerted by the first melted components on the others.

In preparation of ointments having an emulsion base, the method of manufacture

often involves both melting and emulsification. The water-immiscible components such as the oil and waxes are melted together in a steam bath to about 70°C to 75°C. Meantime, an aqueous solution of the heat-stable, water-soluble components is prepared and heated to the same temperature as the oleaginous components. Then the aqueous solution is slowly added, with mechanical stirring, to the melted oleaginous mixture. The temperature is maintained for 5 to 10 minutes, and the mixture is slowly cooled and stirred until congealed. If the aqueous solution is not at the same temperature as the oleaginous melt, some of the waxes will solidify on addition of the colder aqueous solution to the melted mixture.

COMPENDIAL REQUIREMENTS FOR OINTMENTS

Ointments and other semisolid dosage forms must meet USP tests for *microbial content*, *minimum fill*, *packaging*, *storage*, *and labeling* (2). As discussed later in this chapter, ophthalmic ointments must also meet tests for *sterility* and *metal particles* content.

Microbial Content

With the exception of ophthalmic preparations, topical applications are not required to be sterile. They must, however, meet acceptable standards for microbial content, and preparations prone to microbial growth must contain antimicrobial preservatives. Preparations that contain water tend to support microbial growth to a greater extent than water-free preparations. Among the antimicrobial preservatives used to inhibit microbial growth in topical preparations are methylparaben, propylparaben, phenols, benzoic acid, sorbic acid, and quaternary ammonium salts.

Microbial limits are stated for certain articles in the USP. For example, Betamethasone Valerate Ointment, USP, must *meet the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa*. These particular microbes have special importance in dermatologic preparations because of their capacity to infect the skin, which for patients being treated for a skin condition, is already compromised.

In the USP chapter titled "Microbiological Attributes of Nonsterile Pharmaceutical Products," emphasis is placed on strict adherence to environmental control and application of good manufacturing practices to minimize both the type and the number of microorganisms in unsterilized pharmaceutical products (2). This involves the testing of raw materials, use of acceptable water, in-process controls, and final product testing. The USP states certain products should be routinely tested for microorganisms because of the way they are used. Thus, dermatologic products should be examined for *P. aeruginosa* and *S. aureus*, and those intended for rectal, urethral, or vaginal use should be tested for yeasts and molds, common offenders at these sites of application.

Minimum Fill

The USP's *minimum fill* test is determination of the net weight or volume of the contents of filled containers to ensure proper contents compared with the labeled amount.

Packaging, Storage, and Labeling

Ointments and other semisolid preparations are packaged either in large-mouth ointment jars or in metal or plastic tubes. Semisolid preparations must be stored in well-closed containers to protect against contamination and in a cool place to protect against product separation in heat. When required, light-sensitive preparations are packaged in opaque or light-resistant containers.

In addition to the usual labeling requirements for pharmaceutical products, the USP directs the labeling for certain ointments and creams including proper storage conditions, dosing and administration.

Additional Standards

In addition to the USP requirements, manufacturers often examine semisolid preparations for viscosity and for in vitro drug release to ensure within-lot and lot-to-lot uniformity

(3,4). In vitro drug release tests include diffusion cell studies to determine the drug's release profile from the semisolid product.

CREAMS

Pharmaceutical *creams* are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either a water-in-oil (W/O) emulsion or an oil-in-water (O/W) emulsion or in another type of water-washable base. The so-called vanishing creams are oil-in-water emulsions containing large percentages of water and stearic acid or other oleaginous components. After application of the cream, the water evaporates, leaving behind a thin residue film of the stearic acid or other oleaginous component. Chapter 14 discusses the types of emulsions, their physical characteristics, and the method of manufacture.

Creams find primary application in topical skin products and in products used on mucous membranes, such as rectally and vaginally. Many patients and physicians prefer creams to ointments because they are easier to spread and remove. Pharmaceutical manufacturers frequently manufacture topical preparations of a drug in both cream and ointment bases to satisfy the preference of the patient and physician.

Creams have a relatively soft, spreadable consistency; an example of a W/O cream is cold cream and an example of an O/W cream is hydrophilic ointment. Creams are generally described as either nonwashable or washable, reflecting that an emulsion with an aqueous external continuous phase (O/W) is more easily removed than one with a nonaqueous external phase (W/O emulsion). When the term "cream" is used without further qualification, a water-washable formulation is generally inferred.

Preparation of Creams

Creams may be formulated from a variety of oils, both mineral and vegetable, and from fatty alcohols, fatty acids, and fatty esters. The solid excipients are melted at the time of preparation. Emulsifying agents include nonionic surfactants, detergents, and soaps. Soaps are usually formed from a fatty acid in the oil phase hydrolyzed by a base dissolved in the aqueous phase in situ during the preparation of creams.

Preparation usually involves separating the formula components into two portions: lipid and aqueous. The lipid portion contains all water-insoluble components and the aqueous portion the water-soluble components. Both phases are heated to a temperature above the melting point of the highest melting component. The phases then are mixed, and the mixture is stirred until reaching ambient temperature or the mixture has congealed. Mixing generally is continued during the cooling process to promote uniformity. Traditionally, the aqueous phase is added to the lipid phase, but comparable results have been obtained with the reverse procedure. High-shear homogenization may be employed to reduce particle or droplet size and improve the physical stability of the resultant dosage form.

The active pharmaceutical ingredients (APIs) can be added to the phase in which it is soluble at the beginning of the process, or it can be added after the cream is prepared by a suitable dispersion process such as levigation or milling with a roller mill. Creams usually require the addition of a preservative(s) unless they are compounded immediately prior to use and intended to be consumed in a relatively short period of time.

GELS

Gels (sometimes called jellies) are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jellylike by the addition of a *gelling agent*. Among the gelling agents used are synthetic macromolecules, such as carbomer 934; cellulose derivatives, such as carboxymethylcellulose or hydroxypropyl methylcellulose; and natural gums, such as tragacanth. Carbomers are high molecular weight water-soluble polymers of acrylic acid cross-linked with allyl ethers of sucrose and/or pentaerythritol. Their viscosity depends on their polymeric composition. The NF contains monographs for six such polymers,

carbomers 910, 934, 934P, 940, 941, and 1342. They are used as gelling agents at concentrations of 0.5% to 2.0% in water. Carbomer 940 yields the highest viscosity, between 40,000 and 60,000 centipoises as a 0.5% aqueous dispersion.

Single-phase gels are gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid. A gel mass consisting of floccules of small distinct particles is termed a *two-phase* system, often referred to as a *magma*. Milk of magnesia (or magnesia magma), which consists of a gelatinous precipitate of magnesium hydroxide, is such a system. Gels may thicken on standing, forming a thixotrope, and must be shaken before use to liquefy the gel and enable pouring.

In addition to the gelling agent and water, gels may be formulated to contain a drug substance, solvents, such as alcohol and/or propylene glycol; antimicrobial preservatives, such as methylparaben and propylparaben or chlorhexidine gluconate; and stabilizers, such as edetate disodium. Medicated gels may be prepared for administration by various routes, including the skin, the eye, the nose, the vagina, and the rectum.

Androgel 1.62% for topical use is a clear, colorless gel containing testosterone; it also contains Carbopol 980, ethyl alcohol, isopropyl myristate, purified water, and sodium hydroxide. It is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. It delivers about 20 mg of testosterone per pump actuation applied topically once daily in the morning to the shoulders and upper arms (5).

Gels can be administered by the topical oromucosal routes. Antibiotic-containing gels can be administered by teat infusion in veterinary medicine to treat mastitis.

Preparation of Gels

Gels formed with large organic molecules may be formed by dispersing the molecule in the continuous phase (e.g., by heating starch), by cross-linking the dispersed molecules by changing the pH (as for carbomers), or by reducing the continuous phase (as for jellies formed with sucrose).

Care should be taken to ensure uniformity of the APIs by dispersing them by vigorous mixing or milling or by shaking if the preparation is less viscous.

Packaging and Storage

Gels should be stored in tight containers to prevent water loss. Avoid freezing gels.

TRANSDERMAL PREPARATIONS

Recent years have seen an increase in the number of topical ointments, creams, and gels designed to deliver a drug systemically. This is often accomplished by addition of penetration enhancers to the topical vehicle. Penetration enhancers include dimethyl sulfoxide, ethanol, propylene glycol, glycerin, PEG, urea, dimethylacetamide, sodium lauryl sulfate, poloxamers, Spans, Tweens, lecithin, terpenes, and many others.

A transdermal preparation commonly compounded is Pluronic lecithin organogel. It consists of a Pluronic (poloxamer) F127 gel (usually 20% or 30% concentration) mixed at a ratio of approximately 1:5 with a mixture of equal parts of isopropyl palmitate and lecithin. This gel vehicle aids in rapid penetration of many active drugs through the skin.

MISCELLANEOUS SEMISOLID PREPARATIONS: PASTES, PLASTERS, AND GLYCEROGELATINS

Pastes

Pastes are semisolid preparations intended for application to the skin. They generally contain a larger proportion of solid material (such as 25%) than ointments and therefore are stiffer.

Pastes can be prepared in the same manner as ointments, by direct mixing or the use of heat to soften the base prior to incorporating the solids, which have been comminuted and sieved. However, when a levigating agent is to be used to render the powdered component smooth, a portion of the base is

often used rather than a liquid, which would soften the paste.

Because of the stiffness of pastes, they remain in place after application and are effectively employed to absorb serous secretions. Because of their stiffness and impenetrability, pastes are not suited for application to hairy parts of the body.

Among the few pastes in use today is zinc oxide paste (Lassar's Plain Zinc Paste), which is prepared by mixing 25% each of zinc oxide and starch with white petrolatum. The product is very firm and is better able to protect the skin and absorb secretions than is zinc oxide ointment.

Plasters

Plasters are solid or semisolid adhesive masses spread on a backing of paper, fabric, moleskin, or plastic. The adhesive material is a rubber base or a synthetic resin. Plasters are applied to the skin to provide prolonged contact at the site. Unmedicated plasters provide protection or mechanical support at the site of application. Adhesive tape used to be official under the title adhesive plaster, the use of this material being well known.

Medicated plasters provide effects at the site of application. They may be cut to size to conform to the surface to be covered. Among the few plasters in use today is salicylic acid plaster used on the toes for the removal of corns. The horny layers of skin are removed by the keratolytic action of salicylic acid. The concentration of salicylic acid used in commercial corn plasters ranges from 10% to 40%.

Glycerogelatins

Glycerogelatins are plastic masses containing gelatin (15%), glycerin (40%), water (35%), and an added medicinal substance (10%), such as zinc oxide. They are prepared by first softening the gelatin in the water for about 10 minutes, heating on a steam bath until the gelatin is dissolved, adding the medicinal substance mixed with the glycerin, and allowing the mixture to cool with stirring until congealed.

Glycerogelatins are applied to the skin for the long term. They are melted before application, cooled to slightly above body temperature, and applied to the affected area with a fine brush. Following application, the glycerogelatin hardens, is usually covered with a bandage, and is allowed to remain in place for weeks. The most recent official glycerogelatin was zinc gelatin, used in the treatment of varicose ulcers. It was also known as zinc gelatin boot because of its ability to form a pressure bandage.

Packaging Semisolid Preparations

Topical dermatologic products are packaged in either jars, tubes, or syringes, whereas ophthalmic, nasal, vaginal, and rectal semisolid products are almost always packaged in tubes or syringes.

Ointment jars are made of clear or opaque glass or plastic. Some are colored green, amber, or blue. Opaque jars, used for light-sensitive products, are porcelain white, dark green, or amber. Commercially available empty ointment jars vary in size from about 0.5 oz to 1 lb.

In commercial manufacture and packaging of topical products, the jars and tubes are first tested for compatibility and stability for the intended product. This includes stability testing of filled containers at room temperatures (e.g., 20°C) as well as under accelerated stability testing conditions (e.g., 40°C and 50°C).

Tubes used to package topical pharmaceutical products are gaining in popularity. They are light in weight, relatively inexpensive, convenient for use, and compatible with most formulative components, and they provide greater protection against external contamination and environmental conditions than jars (6).

Ointment tubes are made of aluminum or plastic. When the ointment is to be used for ophthalmic, rectal, vaginal, aural, or nasal application, they are packaged with special applicator tips. Tubes of aluminum generally are coated with an epoxy resin, vinyl, or lacquer to eliminate any interactions between the contents and the tube. Plastic tubes are made of high- or low-density polyethylene (HDPE or LDPE) or a blend of each, polypropylene

(PP), polyethylene terephthalate (PET), and various plastic, foil, and/or paper laminates, sometimes 10 layers thick.

Each type of plastic offers special features and advantages. For example, LDPE is soft and resilient, and it provides a good moisture barrier. HDPE provides a superior moisture barrier but is less resilient. PP has a high level of heat resistance, and PET offers transparency and a high degree of product chemical compatibility. Laminates provide an excellent moisture barrier because of the foil content, high durability, and product compatibility (5). These qualities and flexibility make plastic and plastic laminate tubes preferable to metal tubes for packaging of pharmaceuticals.

The cylindrical bodies of plastic tubes are made by extrusion and then joined to the shoulder, neck, and tip piece, which is made by molding. Most multiple-dose tubes used for pharmaceuticals have conventional, continuous thread closures. Single-dose tubes may be prepared with a tearaway tip. Metered-dose, tamper-evident, and child-resistant closures are available (6). Standard sizes of empty tubes have capacities of 1.5, 2, 3.5, 5, 15, 30, 45, 60, and 120 g (7). Ointments, creams, and gels are most frequently packaged in 5-, 15-, and 30-g tubes.

Ophthalmic ointments typically are packaged in small aluminum or collapsible plastic tubes holding 3.5 g (about 0.125 oz) of ointment, as shown in Figure 17.4. The tubes, which are sterilized before being aseptically filled, are fitted with narrow-gauge tips, which permit extrusion and placement of narrow bands of ointment on the inner margin of the eyelid, the usual site of application.

Either syringes for injection or syringes for oral use have been successfully used. The advantages include the exclusion of air from the system, and accurate quantities can be applied using the syringe to measure the amount needed.

Filling Ointment Jars

Ointment jars are filled on a small scale in the pharmacy by carefully transferring the weighed amount of ointment into the jar with a spatula. The ointment is packed on the

FIGURE 10.6 Arenco tube-filling machine automatically fills 125 tubes a minute with the proper amount, tightens the cap, orients each tube by electric eye so that the label faces forward, then closes and crimps the end. (Courtesy of Eli Lilly and Company.)

bottom and along the sides of the jar, avoiding entrapment of air. The jar size should allow the ointment to reach near the top of the jar but not so high as to touch the lid when closed. Ointments prepared by fusion may be poured directly into the ointment jar to congeal in it. This must be done cautiously to prevent stratification of the components. In large-scale manufacture of ointments, pressure fillers force the specified amount of ointment into the jars.

Filling Ointment Tubes

Tubes are filled from the open back end of the tube, opposite from the cap end (Fig. 10.6). Ointments prepared by fusion may be poured while still soft but viscous directly into the tubes with caution to prevent stratification of the components. On a small scale, as in the extemporaneous filling of an ointment in the pharmacy, the tube may be filled manually (Fig. 10.7) or with a small-scale filling machine (Fig. 10.8). The filled tube is closed and sealed. As depicted in Figure 10.7, manual filling of an ointment tube requires a number of steps: (*a*) The prepared ointment, placed on waxed or parchment paper and rolled into a cylindrical shape, is inserted into the open end of the tube and pushed forward as far as allowed. (*b*) With a spatula pressing against the lower portion of the tube and making a crease below the ointment fill, the paper is slowly removed, leaving the ointment in the tube. (*c*) The bottom of the tube is flattened,
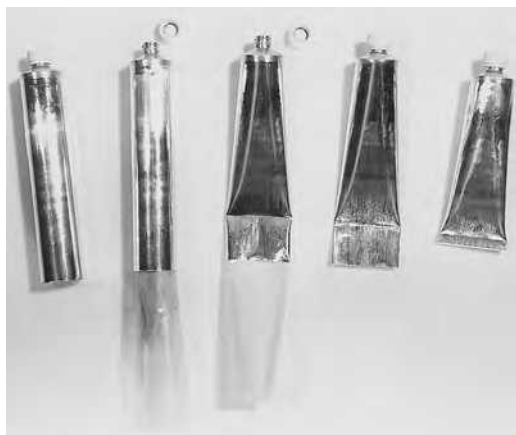
FIGURE 10.7 Steps in the manual filling of ointment tubes.

folded, and sealed with a crimping tool or clip.

Tubes can also be filled using a "caulking-gun" system where the semisolid is filled into the chamber and the product is delivered into the tube. The tubes can then be heat-sealed using a heat-sealing crimper for a nice, professional appearance.

FIGURE 10.8 A small-scale fully automatic filling and crimping machine for collapsible metal tubes. The capacity of the machine is up to 60 units per minute. (Courtesy of Chemical and Pharmaceutical Industry Co.)

Industrially, automatic filling, closing, crimping, and labeling machines are used for large-scale tube packaging of semisolid pharmaceuticals (Fig. 10.6). Depending on the model, machines have the capacity to fill about 1,000 to 6,000 tubes per hour (6–8). Rotary machines have four stations for tube feeding, cleaning, filling, and closing. Plastic and laminate tubes are closed and sealed by heat and crimping. Metal tubes are sealed by folding and crimping with or without a vinyl, latex, or lacquer sealant (6).

Electronic mortars and pestles can be used to prepare an ointment, cream, or gel in the dispensing container. The ingredients are placed in the container and the cap, which has a stirring rod and blade assembly, put in place. The unit can be programmed for thorough mixing using different speeds and up and down rates until the product is uniform. The rod is removed and the cap replaced with a dispensing cap. For administration, the bottom of the ointment jar is moved up, forcing the product out of the orifice in the dispensing cap. The small orifice cap is replaced for a tight seal.

Filling Syringes

Syringes can be filled either by drawing the semisolid into the barrel using the plunger (it may be necessary to soften the preparation by gentle heating first), or by removing the plunger and filling through the back end of the syringe. The plunger can then be reinserted. (This can be accomplished by placing a straightened paper clip down the inside of the barrel and inserting the plunger. The paper clip allows the escape of air until the plunger contacts the ointment. The paper clip can then be removed, and the seal formed by the plunger is reestablished.)

FEATURES AND USE OF DERMATOLOGIC PREPARATIONS

Among the dosage forms used in the topical treatment of conditions and diseases of the skin are ointments, creams, gels, pastes, and plasters. Other dosage forms include solutions, powders, and transdermal drug delivery systems, discussed elsewhere in this

text. Oral therapy also may be used for skin conditions, as in the treatment of poison ivy with prednisone.

In treating skin diseases, the drug in a medicated application should *penetrate* and be *retained* in the skin for a while. Drug penetration into the skin depends on a number of factors, including the physicochemical properties of the medicinal substance, the characteristics of the pharmaceutical vehicle, and the condition of skin itself. Normal unbroken skin acts as a natural barrier, limiting both the rate and degree of drug penetration.

The skin is divided histologically into the stratum corneum (the outer layer), the living epidermis, and the dermis, collectively a laminate of barriers protecting against permeation by external agents and loss of water from the body. Blood capillaries and nerve fibers rise from the subcutaneous fat into the dermis and up to the epidermis. Sebaceous glands, sweat glands, and hair follicles originating in the dermis and subcutaneous layers rise to the skin's surface (Fig. 10.9). The stratum corneum is the desquamating horny layer, a 10- to 15-mm-thick layer of flat,

partially desiccated, dead epidermal cells (9,10). The stratum corneum is composed of approximately 40% protein (mainly keratin) and 40% water, with the balance being lipid, principally as triglycerides, free fatty acids, cholesterol, and phospholipids. On the surface is a film of emulsified material composed of a complex mixture of sebum, sweat, and desquamating epidermal cells.

The film covering the stratum corneum varies in composition, thickness, and continuity as a result of differences in the proportion of sebum and sweat produced and the extent of their removal through washing and sweat evaporation. It offers little resistance to drug penetration. Hair follicles and gland ducts can provide entry for drug molecules, but because their relative surface area is so minute compared to the total epidermis, they are minor factors in drug absorption.

The stratum corneum, being keratinized tissue, behaves as a semipermeable membrane, and drug molecules can penetrate by passive diffusion. The rate of drug movement across this skin layer depends on the drug concentration in the vehicle, its aqueous
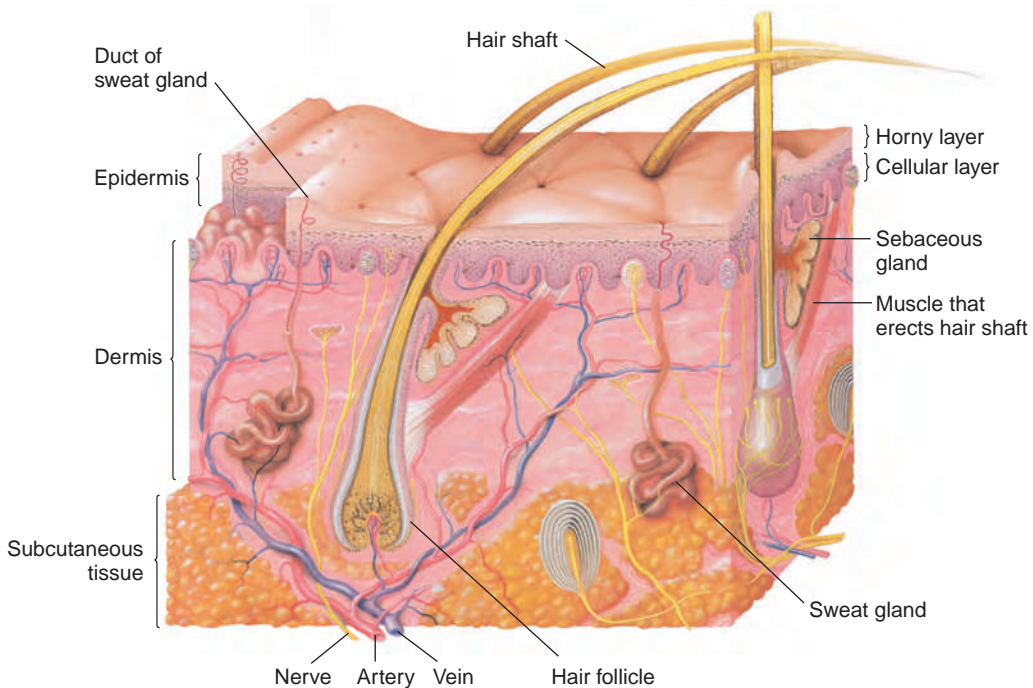

FIGURE 10.9 Stratified organization of the skin. (Reprinted with permission from Anatomical Chart Company.)

solubility, and the oil–water partition coefficient between the stratum corneum and the product's vehicle (11). Substances with both aqueous and lipid solubility characteristics are good candidates for diffusion through the stratum corneum. Once through the stratum corneum, drug molecules may pass through the deeper epidermal tissues and into the dermis. If the drug reaches the vascularized dermal layer, it becomes available for absorption into the general circulation.

Whereas drug blood levels achieved by transdermal delivery systems may be measured and equated against desired therapeutic effects, the same is not true for topical *non*systemic dermatologic products. For topical products, the therapeutically effective drug concentration in the skin is not known, so treatment is based on qualitative measures, with clinical efficacy often varying between patients and products.

Differences in emollient and occlusive effects and ease of application and removal between products are factors of the base used and product type. As noted earlier, oleaginous bases provide greater occlusion and emollient effects than do hydrophilic or water-washable bases. Pastes offer even greater occlusion and are more effective than ointments at absorbing serous discharge. Creams, usually oil-in-water emulsions, spread more easily than ointments and are easier to remove. Water-soluble bases are nongreasy and are easily removed.

Unless otherwise directed, before applying a dermatologic product, the patient should thoroughly clean the affected area with soap and water and dry by patting with a soft cloth. In most instances, a thin layer of medication should be applied to the affected area and spread evenly using gentle pressure with the fingertips. Typically, about 1 to 3 mg of ointment or cream is applied per square centimeter of skin (1). Unless there is a specified need for an occlusive dressing to protect the area from excessive contact or contaminants, a bandage should not be used. After application, the hands should be thoroughly washed.

Upon dispensing a prescription or over-the-counter (OTC) product, the pharmacist should be certain that the patient understands the proper method of administration, frequency and duration of use, special warnings (such as those related to pregnancy or nursing), therapeutic goals and anticipated outcomes, signs of adverse response, allergic sensitivity reactions or treatment failure, and reasons to discontinue treatment and seek further professional guidance.

The patient should be advised if symptoms persist or irritation develops, use of the product should be discontinued, and a physician or pharmacist consulted. It is fairly common for patients to have an allergic response, such as a skin rash, to a topical product as a result of sensitivity to the medicinal agent or pharmaceutic ingredient. An alternative product that does not contain the suspected offending agent may be substituted to solve the problem.

Examples of dermatologic ointments, creams, and gels are presented in Table 10.1 (ointments and creams by therapeutic categories) and Table 10.2 (gels by active ingredient).

FEATURES AND USE OF OPHTHALMIC OINTMENTS AND GELS

Among the dosage forms used in the topical treatment of conditions and diseases of the eye are ointments and gels. Other ophthalmic dosage forms used topically include solutions, suspensions, and inserts, discussed elsewhere in this text. Systemic therapy also may be undertaken, as in the use of diuretics in the adjunctive treatment of glaucoma.

The application of medication to the eye or conjunctival sac affects the surface of the eye and underlying tissues as the drug penetrates. The major route by which drugs enter the eye is simple diffusion via the cornea. For drugs that are poorly absorbed by the cornea, the conjunctiva and sclera provide an alternate route (12). The cornea is a three-layered structure with a lipophilic epithelial layer, a hydrophilic stromal layer, and a less lipophilic endothelial layer on the inside (12). Drug penetration depends on a drug's ability to traverse these three layers. Lipophilic

Table 10.1	DERMATOLOGIC OINTMENTS AND CREAMS BY THERAPEUTIC CATEGORY

PREPARATION	CORRESPONDING COMMERCIAL PRODUCT	USUAL STRENGTH OF ACTIVE INGREDIENT	USE
Adrenocortical Steroids			
Alclometasone dipropionate cream and ointment	Aclovate Cream and Ointment (Pharmaderm)	0.05% cream and ointment	Relief of inflammatory dermatoses
Fluocinolone acetonide cream, ointment	Fluonid (Allergan)	0.025% cream and ointment	Relief of inflammatory dermatoses
Hydrocortisone acetate cream, ointment	Cortaid Cream and Ointment (J&J Consumer)	0.5% and 1%	Relief of inflammatory dermatoses
Triamcinolone acetonide cream, ointment	Aristocort A Cream and Ointment (Fujisawa Healthcare)	0.1% ointment; 0.1%, 0.025%, 0.5% cream	Relief of inflammatory dermatoses
Adrenocorticoid–Antifungal Combination			
Betamethasone, clotrimazole cream	Lotrisone Cream (Schering)	0.05% betamethasone, 1% clotrimazole	Relief, treatment of inflammatory pruritic manifestations that may be complicated by fungal overgrowth
Analgesic			
Capsaicin cream	Zostrix Cream (Healthcare Products)	0.025%	Relief of arthritic pain
Antiacne			
Tretinoin cream	Retin-A (Ortho)	0.025%, 0.05%, 0.1%	Derivative of vitamin A for topical treatment of acne vulgaris
Antianginal			
Nitroglycerin ointment	Nitro-Bid Ointment (Savage)	2%	Reduces workload of heart by smooth muscle relaxation of peripheral arteries and veins
Antibacterial/Anti-infectives			
Gentamicin sulfate cream, ointment	Garamycin Cream and Ointment (Schering)	0.1%	Local treatment of skin infections by susceptible microorganisms
Mupirocin calcium cream	Bactroban Cream (GlaxoSmithKline)	2%	Treatment of secondarily infected skin lesions due to susceptible strains of *S. aureus* and *S. pyogenes* Oil-in-water-based emulsion
Mupirocin calcium ointment	Bactroban Nasal Ointment (GlaxoSmithKline)	2%	Indicated for eradication of nasal colonization of methicillin-resistant *S. aureus* Petrolatum-based vehicle
Mupirocin ointment	Bactroban Ointment (GlaxoSmithKline)	2%	Vehicle of water-miscible polyethylene glycols

(Continued)

Table 10.1	**DERMATOLOGIC OINTMENTS AND CREAMS BY THERAPEUTIC CATEGORY (Continued)**		

PREPARATION	CORRESPONDING COMMERCIAL PRODUCT	USUAL STRENGTH OF ACTIVE INGREDIENT	USE
Nystatin cream	Mycostatin Cream (Bristol-Myers Squibb)	100,000 U/g	Local treatment of skin infections by susceptible microorganisms
Polymyxin B sulfate, bacitracin zinc, neomycin ointment	Neosporin Ointment (Johnson and Johnson)	5,000 U/g polymyxin B; 400 U/g bacitracin zinc; 3.5 mg/g neomycin	Treatment of minor cuts, scrapes
Retapamulin ointment	Altabax Ointment (GlaxoSmithKline)	1%	Treatment of impetigo
Antifungals			
Butenafine HCl cream	Mentax Cream (Mylan)	1%	Treatment of dermatologic infection, tinea versicolor due to *Malassezia furfur*
Miconazole nitrate cream	Monistat-Derm Cream (Personal Products)	2%	Cutaneous candidiasis, tinea infections of *Trichophyton* spp.
Tolnaftate cream	Tinactin Cream (Schering-Plough)	1%	Topical treatment of tinea pedis, tinea cruris, tinea corporis, tinea manuum
Antineoplastic			
Fluorouracil cream	Efudex Cream (Valeant Pharmaceuticals)	5%	Treatment of multiple actinic, solar keratoses
Antipruritic, Analgesic			
Lidocaine ointment	Xylocaine Ointment (APP Pharmaceutical)	2.5%	Relief of pain, itching of minor skin irritation, insect bites
Astringent, Protectant			
Zinc oxide ointment	Desitin Ointment (Pfizer)	40%	Topical astringent, protective in skin conditions such as diaper rash
Depigmenting Agents			
Hydroquinone cream	Eldopaque Cream (ICN)	4%	Temporary bleaching of skin with freckles, old age spots, chloasma
Scabicide			
Crotamiton cream	Eurax Cream (Bristol-Myers Squibb)	10%	Eradication of scabies, symptomatic treatment of pruritus

drugs are more capable of penetration than hydrophilic compounds (12).

In general, ocular ophthalmic drug penetration is limited by the short residence time on the surface of the eye because of rapid removal by tearing and other natural mechanisms, the small surface area of the cornea for drug absorption, and the cornea's natural resistance to drug penetration (12). Compared with ophthalmic solutions, ophthalmic ointments and gels provide extended residence time on the surface of the eye, increasing the duration of their surface effects and bioavailability for absorption into the ocular tissues. Ophthalmic ointments are cleared from the eye as slowly as 0.5% per minute, compared

Table 10.2	EXAMPLES OF TOPICAL GELS		
ACTIVE INGREDIENT	**PROPRIETARY PRODUCT**	**GELLING AGENT**	**ROUTE AND USE**
Acetic acid	Aci-Jel (Ortho-McNeil)	Tragacanth, acacia	Vaginal: restoration and maintenance of acidity
Becaplermin	Regranex Gel (Johnson & Johnson)	Sodium CMC	Dermatologic: recombinant human platelet–derived growth factor; promotes healing of diabetic ulcers of lower extremity
Benzoyl peroxide	Desquam-X Gel (Westwood-Squibb)	Carbomer 940	Dermatologic: acne vulgaris
Bexarotene	Targretin 1% Gel (Eisai)	Hydroxypropyl cellulose	Dermatologic: cutaneous T-cell lymphoma
Clindamycin	Cleocin T Topical Gel (Pfizer)	Carbomer 934P	Dermatologic: acne vulgaris
Clobetasol propionate	Temovate Gel (Pharmaderm)	Carbomer 934P	Dermatologic: antipruritic
Cyanocobalamin	Nascobal (Strativa Pharmaceuticals)	Methylcellulose	Nasal: hematologic
Desoximetasone	Topicort Gel (Taro)	Carbomer 940	Dermatologic: anti-inflammatory, antipruritic
Metronidazole	MetroGel Vaginal (Galderma)	Carbomer 934P	Vaginal: bacterial vaginosis
Podofilox	Condylox Gel (Watson)	Hydroxypropyl cellulose	Rectal: anogenital warts
Progesterone	Crinone Gel (Watson)	Carbomer 934P	Vaginal: bioadhesive gel for progesterone supplementation and replacement
Timolol maleate	Timoptic-XE (Aton Pharma)	Gelrite gellan gum	Ophthalmic gel-forming solution used in treatment of elevated intraocular pressure
Tretinoin	Retin-A Gel (Ortho)	Hydroxypropyl cellulose	Dermatologic: acne vulgaris

with solutions, which can lose up to 16% of their volume per minute (13,14).

The ointment base selected for an ophthalmic ointment must not be irritating to the eye and must permit the diffusion of the medicinal substance throughout the secretions bathing the eye. Ointment bases used for ophthalmics should have a softening point close to body temperature, both for comfort and for drug release. Most often, mixtures of white petrolatum and liquid petrolatum (mineral oil) are used as the base in medicated and unmedicated (lubricating) ophthalmic ointments. Sometimes a water-absorbing agent such as lanolin is added. A gel base of PEG and mineral oil is also used; this form permits water and water-insoluble drugs to be retained within the base.

Medicinal agents are added to an ointment base either as a solution or as a finely micronized powder. The ointment is made uniform and smooth by fine milling.

In addition to the previously stated quality standards for ointments, ophthalmic ointments must meet the USP *sterility tests* and the test for *metal particles in ophthalmic*

ointments. Rendering an ophthalmic ointment sterile requires special technique and processing. For a number of reasons, the terminal sterilization of a finished ointment by standard methods may be problematic. Steam sterilization or ethylene oxide methods are ineffective because neither is capable of penetrating the ointment base. Although dry heat sterilization can penetrate the ointment base, the high heat required may pose a threat to the stability of the drug substance and introduces the possibility of separating the ointment base from the other components (15). Because of these difficulties, terminal sterilization generally is not undertaken. Rather, strict methods of aseptic processing are employed as each drug and nondrug component is rendered sterile and then aseptically weighed and incorporated in a final product that meets the sterility requirement (15). When an antimicrobial preservative is needed, among those used are methylparaben (0.05%) and propylparaben (0.01%) combinations, phenylmercuric acetate (0.0008%), chlorobutanol (0.5%), and benzalkonium chloride (0.008%).

The USP test for metal particles is microscopic examination of a heat-melted ophthalmic ointment. Detected metal particles are counted and measured by a calibrated eyepiece micrometer disk. The requirements are met if the total number of particles 50 mm or larger from ten product tubes does not exceed 50 and if not more than one tube contains more than eight such particles (2).

The USP directs that ophthalmic ointments must be packaged in collapsible ointment tubes. These tubes have an elongated narrow tip to facilitate application of a narrow band of ointment to the eye.

In preparation to apply an ointment to the eye, the patient's or caregiver's hands should be washed and dried thoroughly. Then the ointment tube is held between the thumb and forefinger and the tip placed near the eyelid without touching it. The patient's head should be tilted back, and with the index finger of the opposite hand, the lower eyelid of the affected eye should be gently pulled downward. The tip of the ointment tube should be held slightly above the inside portion of the sack between the lower eyelid and eyeball. Without touching the tip to any part of the eye, a thin ribbon of ointment, approximately 0.25 to 0.5 inch, should be placed along the inside of the lower lid. The patient should face down and slowly close the eye for a few seconds. Then any excess ointment should be wiped from the eyelids and lashes with a clean tissue. To facilitate the procedure, a patient may sit in front of a mirror with elbows stabilized or have another person administer the ointment. After use, the ointment must be capped quickly and tightly.

The patient should be advised that blurred vision will occur as the ointment spreads over the eye and not to be alarmed. If the ointment is to be administered only once daily, it is often preferable to do so at bedtime, when vision impairment will be inconsequential.

It is important to emphasize to the patient that ocular products if handled improperly can become contaminated by bacteria that cause ocular infections, which may lead to serious consequences. Thus, every effort must be made to avoid touching the tip of the tube to the eye, eyelid, fingertip, or any other surface, and the ointment should be used by only one person. Examples of ophthalmic ointments and gels are presented in Table 10.3.

FEATURES AND USE OF NASAL OINTMENTS AND GELS

Among the dosage forms used in the topical treatment of the nasal mucosa are ointments and gels. Other dosage forms include inhalants, solutions, and suspensions, discussed elsewhere in this text.

The nose is a respiratory organ, a passageway for air to the lungs. Its surface is coated with a continuous thin layer of mucus produced by subepithelial mucous glands. The ciliated epithelium of the nasal passage facilitates the movement of the mucous layer. The mucus contains lysozyme, glycoproteins, and immunoglobulins that act against bacteria and protect against their entry into the

Table 10.3	EXAMPLES OF OPHTHALMIC OINTMENTS		
OINTMENT	**COMMERCIAL PRODUCT**	**ACTIVE INGREDIENT**	**CATEGORY**
Chloramphenicol ophthalmic	Chloromycetin Ophthalmic Ointment (Parke-Davis)	1%	Antibacterial antibiotic
Dexamethasone sodium phosphate ophthalmic	Decadron Phosphate Ophthalmic Ointment (Merck)	0.05%	Anti-inflammatory adrenocortical steroid
Gentamicin sulfate ophthalmic	Garamycin Ophthalmic Ointment (Schering)	0.3%	Antibacterial antibiotic
Isoflurophate ophthalmic	Floropryl Sterile Ophthalmic Ointment (Merck)	0.025%	Cholinesterase inhibitor
Polymyxin B–bacitracin ophthalmic	Polysporin Ophthalmic Ointment (Pfizer)	Per gram: polymyxin B sulfate, 10,000 U; bacitracin zinc, 500 U	Antimicrobial
Polymyxin B–bacitracin–neomycin ophthalmic	Neosporin Ophthalmic Ointment (Johnson & Johnson)	Per gram: polymyxin B sulfate, 10,000 U; bacitracin, zinc, 400 U; neomycin sulfate, 3.5 mg	Antimicrobial
Sulfacetamide sodium ophthalmic	Sodium Sulamyd Ophthalmic Ointment (Schering-Plough)	10%, 30%	Antibacterial
Tobramycin ophthalmic	Tobrex Ophthalmic Ointment (Alcon)	0.3%	Antibacterial antibiotic
Vidarabine ophthalmic	Vira-A Ophthalmic Ointment (Monarch)	3%	Antiviral

lungs. The ciliary action and the sneeze reflex add further defense against entry (16).

Drugs introduced into the nasal passage are primarily for local effects on the mucous membranes and underlying tissues (e.g., nasal decongestants). However, drug absorption to the general circulation does occur through the rich blood supply feeding the nasal lining. The nasal route of administration is also used for the systemic absorption of a number of drugs, including butorphanol tartrate (Stadol NS, Bristol-Myers Squibb), an analgesic; cyanocobalamin (Nascobal Gel, Schwartz), a hematopoietic; nafarelin acetate (Synarel, Searle) for the treatment of endometriosis; and nicotine (Nicotrol NS, McNeil) as an adjunct in smoking cessation. In addition, the nasal route holds great promise for the administration of insulin, vaccines, and a number of other polypeptides and proteins.

Cyanocobalamin (Nascobal Gel) for intranasal administration is used in the treatment of vitamin B_{12} deficiency, including pernicious anemia. It is self-administered as a nasal gel. Generally, 0.1 mL of the gel, containing 500 mg of cyanocobalamin, is administered intranasally once weekly. The cyanocobalamin is effectively absorbed through the nasal mucosa to produce therapeutic blood levels (17).

FEATURES AND USE OF RECTAL PREPARATIONS

Among the dosage forms used in the topical treatment of anorectal conditions are ointments, gels, creams, and creamlike aerosol foams. Other dosage forms are solutions (for enema or irrigation) and suppositories, discussed elsewhere in this text.

Ointments, creams, and gels are used for topical application to the perianal area and for insertion within the anal canal. They largely are used to treat local conditions of anorectal pruritus, inflammation, and the pain and discomfort associated with hemorrhoids. The drugs include astringents (e.g., zinc oxide), protectants and lubricants (e.g., cocoa butter, lanolin), local anesthetics (e.g., pramoxine HCl), and antipruritics, anti-inflammatory agents (e.g., hydrocortisone), and antiepileptics (diazepam).

The perianal area is the skin immediately surrounding the anus. The anal canal is approximately 3 cm long and connects to the rectum. Both the anal canal and rectum have mucosal linings. Healthy perianal skin and the mucosa act as barriers to infection.

Substances applied rectally may be absorbed by diffusion into the general circulation via the network of three hemorrhoidal arteries and accompanying veins in the anal canal (18). The rectal route *is* used for systemic absorption of therapeutic levels of certain drugs (e.g., prochlorperazine as suppositories) when the oral route is unsatisfactory, as during vomiting. However, systemic effects from ointments and creams intended for local action are usually limited by the insolubility of certain agents (e.g., zinc oxide) and absorption of only subtherapeutic amounts of soluble drugs in the formulation.

The bases used in anorectal ointments and creams include combinations of PEG 300 and 3350, emulsion cream bases using cetyl alcohol and cetyl esters wax, and white petrolatum and mineral oil. When antimicrobial preservatives are required, methylparaben, propylparaben, benzyl alcohol, and butylated hydroxyanisole are frequently used.

Before applying rectal ointments and creams to the perianal skin, the affected area should be cleansed and dried by gentle patting with toilet tissue. Then a portion of the ointment or cream is placed on a tissue, and a thin film is gently spread over the affected area. Products having a water-washable base are easier to spread and remove after

FIGURE 10.10 Rectal ointment with perforated inserter/ applicator tip.

application and tend to stain clothing less than the products having an oleaginous base.

Rectal ointments and creams are packaged with special perforated plastic tips for products to be administered into the anus, primarily in the treatment of the pain and inflammation associated with hemorrhoids (Fig. 10.10). Before use, the rectal tip should be thoroughly cleaned, screwed onto the ointment tube in place of the cap, and lubricated with mineral oil or a lubricating jelly. With the patient lying down on the back or side or in an otherwise comfortable position, the rectal tip is slowly and carefully inserted part way into the anus. Squeezing the tube forces medication through the perforations in the rectal tip and releases it to the inner lining of the anus. The tip is then slowly removed from the anus and any excess ointment or cream removed from the perianal area. The rectal tip should be cleaned thoroughly, the closure cap replaced on the tube, and the hands washed.

Rectal aerosol foam products (e.g., Proctofoam-HC, Schwarz) also are accompanied by applicators to facilitate administration. The applicator is attached to the aerosol container and filled with a measured dose of product. The applicator is then inserted into the anus and the product delivered by pushing the plunger of the applicator. After removal, the applicator and the patient's hands should be thoroughly washed.

Patients should be instructed on the proper use of the product dispensed and in case of rectal bleeding, advised to seek additional medical advice. Examples of rectal ointments and creams are presented in Table 10.4.

Table 10.4	EXAMPLES OF RECTAL AND VAGINAL CREAMS AND OINTMENTS		
COMMERCIAL PREPARATION	**ACTIVE INGREDIENTS**	**PRODUCT TYPE**	**PRIMARY USE**
Rectal			
Anusol (Salix)	Starch	Ointment	Hemorrhoid treatment
Tronolane (Monticello)	Pramoxine HCl	Cream	Hemorrhoidal analgesic, antipruritic
Vaginal			
Mycelex-7 (Ortho-McNeil)	Clotrimazole	Cream	Antifungal
AVC (Novavax)	Sulfanilamide	Cream	Vulvovaginitis (*C. albicans*)
Cleocin (Pfizer)	Clindamycin PO$_4$	Cream	Bacterial vaginosis
Terazol 7 (Ortho–McNeil)	Terconazole	Cream	Antifungal (*C. albicans*)
Ogen (Pharmacia)	Estropipate	Cream	Estrogenic for vulvar, vaginal atrophy
Premarin (Wyeth-Ayerst)	Conjugated estrogens	Cream	Atrophic vaginitis, kraurosis vulvae

FEATURES AND USE OF VAGINAL PREPARATIONS

Among the dosage forms used in the topical treatment of conditions and diseases of the vulvovaginal area are ointments, creams, creamlike foams, and gels. Other dosage forms include vaginal inserts, transdermal drug delivery systems, and oral forms, discussed elsewhere in this text.

The vaginal surface is lined with squamous epithelium cells and mucus produced by various underlying glands. Topical products are used to treat vulvovaginal infections, vaginitis, conditions of endometrial atrophy, and for contraception with spermatocidal agents.

The usual pathogenic organisms of vulvovaginal infections and vaginitis are *Trichomonas vaginalis*, *Candida* (*Monilia*) *albicans*, and *Haemophilus vaginalis*. Among the antiinfective agents are nystatin, clotrimazole, miconazole, clindamycin, and sulfonamides. Endometrial atrophy may be treated locally with the hormones dienestrol and progesterone, which are used to restore the vaginal mucosa to its normal state. Contraceptive preparations containing spermicidal agents such as nonoxynol-9 and octoxynol are used alone or in combination with a cervical diaphragm.

As noted previously, because products intended for use in the vulvovaginal area come into direct contact with tissues prone to infection, it is important these products be manufactured and tested to be free of offending microorganisms, yeasts, and molds. Because gels are especially subject to bacterial growth, most vaginal gels are preserved with antimicrobial agents.

Ointments, creams, and gels for vaginal use are packaged in tubes and vaginal foams in aerosol canisters. Although some preparations are applied externally to the vulva (e.g., Mycelex-7 Vaginal Cream, Ortho-McNeil), most are intended to be delivered to the vagina by means of applicator tips that accompany the products (Fig. 10.11).

In treating external vulvar conditions, the patient squeezes a small amount of product onto the fingers or tissue and gently spreads

FIGURE 10.11 Vaginal cream with inserter.

it over the affected area. For intravaginal treatment, the patient uses a plastic applicator, some of which are prefilled and disposable and others reusable and filled by the patient immediately prior to use.

To fill the applicator, the closure cap is removed from the tube, the applicator screwed on in its place, and the tube gently squeezed until the applicator is filled and the plunger rises to its marked stopping point. The filled applicator is unscrewed from the tube and replaced by the cap. Inserting intravaginal products is best accomplished with the patient lying on her back or in an otherwise comfortable position. The applicator barrel is firmly grasped and inserted into the vagina as far as possible without causing discomfort. The plunger is depressed until it stops, releasing the medication in the vagina. The applicator is carefully withdrawn for washing and ultimately discarding. The patient should be instructed to wash her hands thoroughly after use.

Aerosol foams are used intravaginally in the same general manner. The aerosol package contains an inserter device, which, when attached to the canister, may be filled with foam. The filled inserter is placed in the vagina and the product delivered by pushing the plunger. Vaginal foams are oil-in-water emulsions resembling light creams. They are water miscible and nongreasy. The patient should be instructed to wash her hands thoroughly after use.

When once-a-day administration is prescribed, it is best done at bedtime for reasons of medication retention, avoidance of daytime leakage, and lessened soiling of clothing. Creams with water-washable bases are preferred to oleaginous ointments. Patients who are pregnant must not use intravaginal products except with their doctor's approval and supervision. Tampons are not to be used during intravaginal treatment.

Unmedicated lubricant jellies are used by physicians in rectal, urethral, and vaginal examinations. All products should be tightly closed when not in use to prevent contamination. If left unsealed, gels and jellies are particularly prone to dry out. Examples of vaginal ointments, creams, and gels are presented in Tables 10.2 and 10.4.

DRUG RELEASE FROM SEMISOLID DOSAGE FORMS

Semisolid dosage forms are used for either topical/local or systemic effects. If the purpose is to deliver a drug to the surface of the skin or to be absorbed into the systemic circulation, it must be capable of being released from the vehicle in a reproducible way. For uniformity of the same product from batch to batch as well as for release of the drug for absorption, it is critical that the rate of release of the drug be reproducibly determined. In vitro release testing is recommended by the FDA as a measure of "product sameness" during scale-up and postapproval changes for semisolids (SUPAC-SS).

Semisolid dosage forms can produce distinct difficulties in the development of in vitro models due to the physicochemical properties of formulations and the specific physiological environment in which they must release their API. It is important to validate a release test before using it; it must be reproducible and reliable. Even though it is not a measure of bioavailability, the test must be capable of detecting changes in drug-release characteristics from the finished product. Changes in these release characteristics may alter the biological performance of the drug in the dosage form.

Drug-release measurements for ointments, creams, and gels have been in the literature for years. Formerly, the semisolid dosage form was placed in direct contact with a receptor fluid. Today, generally a Franz diffusion cell is used where the semisolid dosage form is placed on a membrane that is situated on top of a receptor chamber containing a receptor solution. The drug is released from the dosage form and passes through the membrane into the receptor solution where it is sampled and analyzed for content. The results are plotted as the concentration of the drug in the receptor fluid versus time. The rates of drug release can be calculated and compared.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

You have received the following prescription:

Rx:

Sulfur:	2 g
Salicylic acid:	2 g
Calamine:	5 g
Urea:	2 g
Hydrophilic petrolatum qs:	100 g

After you prepared the prescription, you observed it to be a granular ointment that is not appropriate for dispensing because it feels very coarse.

OBJECTIVE INFORMATION

In preparing the ointment, you weighed sublimed sulfur 2 g, salicylic acid 2 g, calamine 5 g, and urea 2 g and mixed the powders together on a pill tile using a spatula. However, you had difficulty with the sulfur, which seemed to be difficult to comminute and blend. Finally, you added the hydrophilic petrolatum and obtained a light pink, quite granular ointment.

Sulfur produces electrostatic charges when mixed on a pill tile using a spatula. It is official as the precipitated sulfur, a very fine powder, and sublimed sulfur, a fine powder. It is practically insoluble in water. Salicylic acid occurs as white crystals, usually in fine needles or a fluffy, white, crystalline powder, and is slightly soluble in water and freely soluble in alcohol. Calamine is a fine pink powder that is insoluble in water. Urea occurs as a white, crystalline powder and freely soluble in water. It is made up of zinc oxide with a small proportion of ferric oxide.

ASSESSMENT

Particle size reduction of sulfur is best accomplished using a levigating agent compatible with the base, in this case, hydrophilic petrolatum. Salicylic acid and calamine should pose no real problem in incorporation. Urea can be dissolved, if desired, in a small quantity of water (since it has a solubility of 1 g in 1.5 mL of water, it would take approximately 3 mL of water to dissolve it) and incorporated into the ointment, or it can be levigated with a small amount of mineral oil prior to incorporation if an anhydrous preparation is desired.

PLAN

In this case, an anhydrous preparation is desired, so the precipitated sulfur is levigated with about 2 to 3 mL of mineral oil. The urea is levigated with about 2 to 3 mL of mineral oil. The salicylic acid is comminuted to a fine powder, as is the calamine; the two powders are mixed together. The sulfur and urea mixtures are combined and the hydrophilic petrolatum incorporated geometrically. Following this, the salicylic acid and calamine powders are incorporated geometrically and the final preparation thoroughly mixed. This procedure produces a slightly thinner vehicle after the sulfur with urea in mineral oil is incorporated, which makes it easier to incorporate the additional powders. The preparation is then packaged and labeled.

CLINICAL CASE STUDY

A.R. is a 22-year-old WF who comes into the pharmacy complaining of a painful sunburn. She states she spent most of yesterday "on the beach with friends" and says she did not use any sunscreen, even though she does occasionally when exposed to the sun. A.R. admits she did not realize the extent of her sunburn until about 4 hours after her fun on the beach, at which time she began to have pain, chills, and fatigue. Now, she is also itching. When asked, she says she does not have any blisters on her burned skin. When asked if this has happened to her before, A.R. confides she has had sunburns similar to this about once a summer for approximately the past 5 years. When asked about her pain based on a scale of 1 to 10, she rates her pain as an 8.

PMH: Sunburns many times throughout her life

Moderate acne
Freckles easily, fair complexioned
Red hair
None significant otherwise

SH: None contributory

FH: Mother (−)
Father (−)
Grandfather (+) for melanoma

ALL: NKDA

MEDS: Ortho Tri-Cyclen, 1 tablet po qd
Differin Gel, apply thin layer hs

PHARMACEUTICAL CARE PLAN

S: Burning, painful, reddened skin, first-degree burn
General fatigue
Chills
Pain 8/10
Itching

O: Bright red skin on face, neck, shoulders, arms, and legs without any evidence of blistering

A: The patient is a 22-year-old WF with a PMH of sunburns and moderate acne. The patient is at increased risk for sunburns d/t her history of freckling, fair skin, red hair, current medications, and the frequency of past burns. In addition to these characteristics, her FH of melanoma increases her risk of future sunburns and skin cancer.

P: 1. Recommend an oral OTC analgesic to relieve the pain of sunburn. There are many choices, and product selection often depends on personal preferences. Any NSAID (e.g., ibuprofen 200 to 400 mg q4h to q6h prn pain not to exceed 1,200 mg per day, naproxen 200 mg q12h prn pain, aspirin 325 to 650 mg q3h to q4h prn not to exceed 4 g per day, or acetaminophen 325 to 650 mg q4h to q6h prn not to exceed 4 g per day) would be a good choice. The patient should understand to take these as recommended with a full glass of water and to continue taking them until the pain abates.

2. Applying a clean cloth soaked in cool tap water or taking a cool bath for 10 to 30 minutes will also help to alleviate pain. One can also recommend a topical anesthetic to aid in relieving pain, such as Solarcaine Aloe Extra Burn Relief Cream, Gel, or Spray. A.R. should be instructed that topical anesthetics should not be used more often than 3 or 4 times daily and continuous pain relief cannot be obtained with these agents. Before and after applying the product, the patient should wash her hands.

CLINICAL CASE STUDY CONT.

3. A W/O topical lotion can provide protection and moisture. These factors are important for sunburned skin because the goal is to replenish skin moisture lost to the sun and protect it from drying out further, which can lead to more irritation and itching. A lotion that could be recommended is Keri. A.R. should apply liberally as needed; however, she should avoid her face, because this lotion contains mineral oil, which may exacerbate her acne. Since this lotion has a W/O base, the patient should be told it will be necessary to use soap and water to remove it.

4. Counsel A.R. on her current medications, especially because the medications she is using for acne may have played a role in developing the sunburn (i.e., photosensitivity). A.R. should also be told that exposure to the sun can exacerbate her acne. A.R. should avoid excessive sun exposure, especially for the next few weeks, because the skin should have time to heal and will be more susceptible to sunburn during this time.

The patient should also be counseled on her many risk factors for skin cancer, including fair skin, red hair, a history of freckling, family history of melanoma, and the frequency of past burns. In the future, A.R. should completely avoid sun exposure. Because this may be unrealistic, she should be told to use a hat and clothing while in the sun to decrease the amount of skin exposed to the sun. If she believes she cannot comply with these suggestions, she should, at least, use a W/O-based sunscreen with an SPF of 30. This will also provide water resistance.

5. Monitoring: The patient should reassess her sunburn in another 24 hours, because the full extent of skin damage may not be initially apparent until 24 to 48 hours after exposure. If she notices any breaks in the skin and/or pain persists or increases, she should seek medical attention from a primary care provider.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Obtain three topical extemporaneous prescriptions for each of the four various types of ointment bases and outline a procedure to prepare each.
2. Create a listing of conceivable ways a consumer/patient might misuse a topical semisolid dosage form.
3. List five counseling points for proper administration of a topical semisolid dosage form and provide a rationale for each counseling point.
4. Determine how the preparation of an ophthalmic ointment differs from that of a rectal ointment.

Individual Activities

1. Identify three topical diseases where each of the four various types of ointment bases might be employed to deliver (an) active ingredient(s).
2. Identify three drugs whose topical concentration differs for the treatment of a specific topical affliction.
3. Develop a procedure to incorporate a water-soluble drug, for example, gentamicin sulfate, into an oleaginous ophthalmic ointment base, for example, white petrolatum.
4. List five drugs used topically that are available in ointment, cream, and gel dosage forms and identify conceivable disease states for which each is used.

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