16 **Colloidal Dispersions**

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Differentiate between different types of colloidal systems and their main characteristics.
2. Understand the main optical properties of colloids and applications of these properties for the analysis of colloids.
3. Know the main types of microscopic systems used for analysis of colloids.
4. Appreciate the major kinetic properties of colloids.
5. Understand the main electrical properties of colloids and their application for the stability, sensitization, and protective action of colloids.
6. Recognize the benefits of solubilization by colloids.
7. Understand the benefits and know the main types of modern colloidal drug delivery systems.

Introduction

It is important that the pharmacist understand the theory and technology of dispersed systems. Knowledge of interfacial phenomena and a familiarity with the characteristics of colloids and small particles are fundamental to an understanding of the behavior of pharmaceutical dispersions. There are three types of dispersed systems encountered in the pharmaceutical sciences: molecular, colloidal, and coarse dispersions. Molecular dispersions are homogeneous in character and form true solutions. The properties of these systems were discussed in earlier chapters. Colloidal dispersions will be considered in the present chapter. Powders and granules and coarse dispersions are discussed in other chapters; all are examples of heterogeneous systems. It is important to know that the only difference between molecular, colloidal, and coarse dispersions is the size of the dispersed phase and not its composition. Dispersions consist of at least one internal phase that is dispersed in a dispersion medium. Sometimes putting these systems into one of the three categories is a bit tricky. So, we will start by looking at an example of a complex dispersed system that we are all very familiar with—blood. Blood is a specialized fluid that delivers vital substances such as oxygen and nutrients to various cells and tissues in the body. The dispersion medium in blood is plasma, which is mostly water (~90% or so). Blood is composed of more than one dispersed phase. Nutrients such as peptides, proteins, and glucose are dissolved in plasma forming a molecular dispersion or true solution. Oxygen, however, is carried to cells and tissues by red blood cells. Given the size of red blood cells (~6 μm in diameter and 2 μm in width) they would be considered to form a coarse dispersion in blood. White blood cells such as leukocytes and platelets are the other major cells types carried in blood. The last major component of blood is serum albumin. Serum albumin forms a true solution in water. However, the size of the individual serum albumin particles in solution is >1 nm, which puts them into the colloidal dispersion group. As you can now see, blood is a complex bodily fluid that is an example of the three types of dispersed systems that you will encounter in the pharmaceutical sciences.

Size and Shape of Colloidal Particles

Particles in the colloidal size range possess a surface area that is enormous compared with the surface area of an equal volume of larger particles. Thus, a cube having a 1-cm edge and a volume of 1 cm^3 has a total surface area of 6 cm^2. If the same cube is subdivided into smaller cubes each having an edge of 100 μm, the total volume remains the same, but the total surface area increases to 600,000 cm^2. This represents a 10^5-fold increase in surface area. To compare the surface areas of different materials quantitatively, the term *specific surface* is used. This is defined as the surface area per unit weight or volume of material. In the example just given, the first sample had a specific surface of 6 cm^2/cm^3, whereas the second sample had a specific surface of 600,000 cm^2/cm^3. The possession of a large specific surface results in many of the unique properties of colloidal dispersions. For example,

platinum is effective as a catalyst only when in the colloidal form as platinum black. This is because catalysts act by adsorbing the reactants onto their surface. Hence, their catalytic activity is related to their specific surface. The color of colloidal dispersions is related to the size of the particles present. Thus, as the particles in a red gold sol increase in size, the dispersion takes on a blue color. Antimony and arsenic trisulfides change from red to yellow as the particle size is reduced from that of a coarse powder to that within the colloidal size range.

Because of their size, colloidal particles can be separated from molecular particles with relative ease. The technique of separation, known as *dialysis*, uses a semipermeable membrane of collodion or cellophane, the pore size of which will prevent the passage of colloidal particles, yet permit small molecules and ions, such as urea, glucose, and sodium chloride, to pass through. The principle is illustrated in Figure 16-1, which shows that, at equilibrium, the colloidal

material is retained in compartment A, whereas the subcolloidal material is distributed equally on both sides of the membrane. By continually removing the liquid in compartment B, it is possible to obtain colloidal material in A that is free from subcolloidal contaminants. Dialysis can also be used to obtain subcolloidal material that is free from colloidal contamination—in this case, one simply collects the effluent. *Ultrafiltration* has also been used to separate and purify colloidal material. According to one variation of the method, filtration is conducted under negative pressure (suction) through a dialysis membrane supported in a Büchner funnel. When dialysis and ultrafiltration are used to remove charged impurities such as ionic contaminants, the process can be hastened by the use of an electric potential across the membrane. This process is called *electrodialysis*.

Key Concept

Dispersed Systems

Dispersed systems consist of particulate matter, known as the *dispersed phase*, distributed throughout a *continuous* or*dispersion medium*. The dispersed material may range in size from particles of atomic and molecular dimensions to particles whose size is measured in millimeters. Accordingly, a convenient means of classifying dispersed systems is on the basis of the mean particle diameter of the dispersed material. Based on the size of the dispersed phase, three types of dispersed systems are generally considered: (*a*) *molecular* dispersions, (*b*) *colloidal*dispersions, and (*c*) *coarse* dispersions. The size ranges assigned to these classes, together with some of the associated characteristics, are shown in the accompanying table. The size limits are somewhat arbitrary, there being no distinct transition between either molecular and colloidal dispersions or colloidal and coarse dispersions. For example, certain *macro* (i.e., large) molecules, such as the polysaccharides, proteins, and polymers in general, are of sufficient size that they may be classified as forming both molecular and colloidal dispersions. Some suspensions and emulsions may contain a range of particle sizes such that the smaller particles lie within the colloidal range, whereas the larger ones are classified as coarse particles.

Classification of Dispersed Systems Based on Particle Size

Class	Particle Size*	Characteristics of System	Examples
Molecular dispersion	Less than 1 nm	Invisible in electron microscope Pass through ultrafilter and semipermeable membrane Undergo rapid diffusion	Oxygen molecules, ordinary ions, glucose
Colloidal dispersion	From 1 nm to 0.5 μm	Not resolved by ordinary microscope (although may be detected under ultramicroscope) Visible in electron microscope Pass through filter paper Do not pass semipermeable membrane Diffuse very slowly	Colloidal silver sols, natural and synthetic polymers, cheese, butter, jelly, paint, milk, shaving cream, etc.
Coarse dispersion	Greater than 0.5 μm	Visible under microscope Do not pass through normal filter paper Do not dialyze through semipermeable membrane Do not diffuse	Grains of sand, most pharmaceutical emulsions and suspensions, red blood cells

* 1 nm (nanometer) = 10^{-9} m; 1 μm (micrometer) = 10^{-6} m.

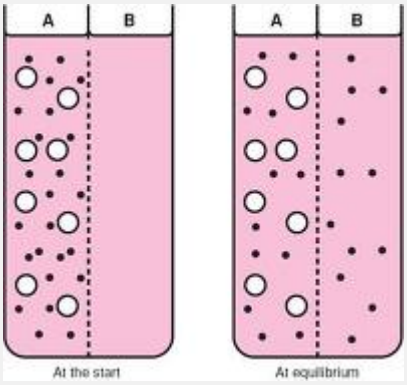


Fig. 16-1. Sketch showing the removal of electrolytes from colloidal material by diffusion through a semipermeable membrane. Conditions on the two sides, A and B, of the membrane are shown at the start and at equilibrium. The open circles are the colloidal particles that are too large to pass through the membrane. The solid dots are the electrolyte particles that pass through the pores of the membrane.

Dialysis has been used increasingly in recent years to study the binding of materials of pharmaceutical significance to colloidal particles. Dialysis occurs in vivo. Thus, ions and small molecules pass readily from the blood, through a natural semipermeable membrane, to the tissue fluids; the colloidal components of the blood remain within the capillary system. The principle of dialysis is utilized in the artificial kidney, which removes low–molecular-weight impurities from the body by passage through a semipermeable membrane.

The shape adopted by colloidal particles in dispersion is important because the more extended the particle, the greater

is its specific surface and the greater is the opportunity for attractive forces to develop between the particles of the dispersed phase and the dispersion medium. A colloidal particle is something like a hedgehog—in a friendly environment, it unrolls and exposes maximum surface area. Under adverse conditions, it rolls up and reduces its exposed area. Some representative shapes of spherocolloids and fibrous colloids are shown in Figure 16-2. As will be seen in later discussions, such properties as flow, sedimentation, and osmotic pressure are affected by changes in the shape of colloidal particles. Particle shape may also influence pharmacological action.

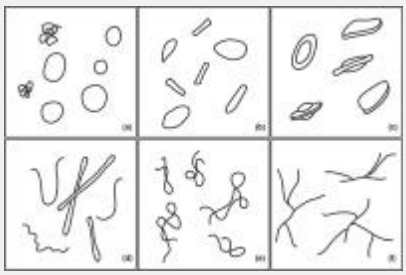


Fig. 16-2. Some shapes that can be assumed by colloidal particles: (*a*) spheres and globules, (*b*) short rods and prolate ellipsoids, (*c*) oblate ellipsoids and flakes, (*d*) long rods and threads, (*e*) loosely coiled threads, and (*f*) branched threads.

Types of Colloidal Systems

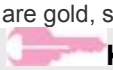
Lyophilic Colloids

Systems containing colloidal particles that interact to an appreciable extent with the dispersion medium are referred to as *lyophilic*(solvent-loving) colloids. Owing to their affinity for the dispersion medium, such materials form colloidal dispersions, or *sols*, with relative ease. Thus, lyophilic colloidal sols are usually obtained simply by dissolving the material in the solvent being used. For example, the dissolution of acacia or gelatin in water or celluloid in amyl acetate leads to the formation of a sol. The various properties of this class of colloids are due to the attraction between the dispersed phase and the dispersion medium, which leads to *solvation*, the attachment of solvent molecules to the molecules of the dispersed phase. In the case of hydrophilic colloids, in which water is the dispersion medium, this is termed *hydration*. Most lyophilic colloids are organic molecules, for example, gelatin, acacia, insulin, albumin, rubber, and polystyrene. Of these, the first four produce lyophilic colloids in aqueous dispersion media (hydrophilic sols). Rubber and polystyrene form lyophilic colloids in nonaqueous, organic solvents. These materials accordingly are referred to as *lipophilic* colloids. These examples illustrate the important point that the term *lyophilic* has meaning only when applied to the material dispersed in a specific dispersion medium. A material that forms a lyophilic colloidal system in one liquid (e.g., water) may not do so in another liquid (e.g., benzene).

Lyophobic Colloids

The second class of colloids is composed of materials that have little attraction, if any, for the dispersion medium. These

are the *lyophobic* (solvent-hating) colloids and, predictably, their properties differ from those of the lyophilic colloids. This is primarily due to the absence of a solvent sheath around the particle. Lyophobic colloids are generally composed of inorganic particles dispersed in water. Examples of such materials are gold, silver, sulfur, arsenous sulfide, and silver iodide.



Key Concept

Colloidal Systems

All kinds of dispersed phases might form colloids in all possible kinds of media, except for a gas–gas combination. Because all gases mix uniformly at the molecular level, gases only form solutions with each other. Possible types of colloidal dispersions are shown in the accompanying table. Colloidal systems are best classified into three groups—lyophilic, lyophobic, and association—on the basis of the interaction of the particles, molecules, or ions of the dispersed phase with the molecules of the dispersion medium.

Types of Colloidal Dispersions*

Dispersion Medium	Dispersed Phase	Colloid Type	Examples
Solid	Solid	Solid sol	Pearls, opals
Solid	Liquid	Solid emulsion	Cheese, butter
Solid	Gas	Solid foam	Pumice, marshmallow
Liquid	Solid	Sol, gel	Jelly, paint

Liquid	Liquid	Emulsion	Milk, mayonnaise
Liquid	Gas	Foam	Whipped cream, shaving cream
Gas	Solid	Solid aerosols	Smoke, dust
Gas	Liquid	Liquid aerosols	Clouds, mist, fog

* A gas in a gas always produces a solution.

In contrast to lyophilic colloids, it is necessary to use special methods to prepare lyophobic colloids. These are (*a*) dispersion methods, in which coarse particles are reduced in size, and (*b*) condensation methods, in which materials of subcolloidal dimensions are caused to aggregate into particles within the colloidal size range. Dispersion can be achieved by the use of high-intensity ultrasonic generators operating at frequencies in excess of 20,000 cycles per second. A second dispersion method involves the production of an electric arc within a liquid. Owing to the intense heat generated by the arc, some of the metal of the electrodes is dispersed as vapor, which condenses to form colloidal particles. Milling and grinding processes can be used, although their efficiency is low. So-called colloid mills, in which the material is sheared between two rapidly rotating plates set close together, reduce only a small amount of the total particles to the colloidal size range.

The required conditions for the formation of lyophobic colloids by condensation or aggregation involve a high degree of initial supersaturation followed by the formation and growth of nuclei. Supersaturation can be brought about by change in solvent or reduction in temperature. For example, if sulfur is dissolved in alcohol and the concentrated solution is then poured into an excess of water, many small nuclei form in the supersaturated solution. These grow rapidly to form a colloidal sol. Other condensation methods depend on a chemical reaction, such as reduction, oxidation, hydrolysis, and double decomposition. Thus, neutral or slightly alkaline solutions of the noble metal salts, when treated with a reducing agent such as formaldehyde or pyrogallol, form atoms that combine to form charged aggregates. The oxidation of hydrogen sulfide leads to the formation of sulfur atoms and the production of a sulfur sol. If a solution of ferric chloride is added to a large volume of water, hydrolysis occurs with the formation of a red sol of hydrated ferric oxide. Chromium and aluminum salts also hydrolyze in this manner. Finally, the double decomposition between hydrogen sulfide and arsenous acid results in an arsenous sulfide sol. If an excess of hydrogen sulfide is used, HS^- ions are adsorbed onto the particles. This creates a large negative charge on the particles, leading to the formation of a stable sol.

Association Colloids: Micelles and the Critical Micelle Concentration

Association or *amphiphilic* colloids form the third group in this classification. As shown in the Interfacial Phenomena chapter, certain molecules or ions, termed *amphiphiles* or *surface-active agents*, are characterized by having two distinct regions of opposing solution affinities within the same molecule or ion. When present in a liquid medium at low concentrations, the amphiphiles exist separately and are of such a size as to be subcolloidal. As the concentration is increased, aggregation occurs over a narrow concentration range. These aggregates, which may contain 50 or more monomers, are called *micelles*.

Because the diameter of each micelle is of the order of 50 Å, micelles lie within the size range we have designated as colloidal. The concentration of monomer at which micelles form is termed the *critical micelle concentration*(*CMC*). The number of monomers that aggregate to form a micelle is known as the *aggregation number* of the micelle.

The phenomenon of micelle formation can be explained as follows. Below the CMC, the concentration of amphiphile undergoing adsorption at the air–water interface increases as the total concentration of amphiphile is raised. Eventually,

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a point is reached at which both the interface and the bulk phase become saturated with monomers. This is the CMC. Any further amphiphile added in excess of this concentration aggregates to form micelles in the bulk phase, and, in this manner, the free energy of the system is reduced. The effect of micellization on some of the physical properties of solutions containing surface-active agents is shown in Figure 16-3. Note particularly that surface tension decreases up to the CMC. From the Gibbs' adsorption equation, this means increasing interfacial adsorption. Above the CMC, the surface tension remains essentially constant, showing that the interface is saturated and micelle formation has taken place in the bulk phase.

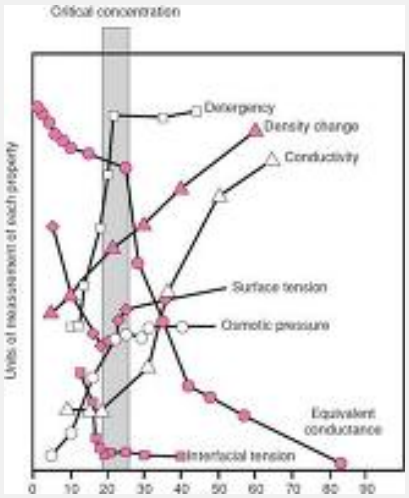

Fig. 16-3. Properties of surface-active agents showing changes that occur sharply at the critical micelle concentration. (Modified from W. J. Preston, Phys. Coll. Chem. **52,** 85, 1948.)

In the case of amphiphiles in water, the hydrocarbon chains face inward into the micelle to form, in effect, their own hydrocarbon environment. Surrounding this hydrocarbon core are the polar portions of the amphiphiles associated with the water molecules of the continuous phase. Aggregation also occurs in nonpolar liquids. The orientation of the molecules is now reversed, however, with the polar heads facing inward while the hydrocarbon chains are associated with the continuous nonpolar phase. These situations are shown in Figure 16-4, which also shows some of the shapes postulated for micelles. It seems likely that spherical micelles exist at concentrations relatively close to the CMC. At higher concentrations, laminar micelles have an increasing tendency to form and exist in equilibrium with spherical micelles. The student is cautioned against regarding micelles as solid particles. The individual molecules forming the micelle are in dynamic equilibrium with those monomers in the bulk and at the interface.

As with lyophilic sols, formation of association colloids is spontaneous, provided that the concentration of the amphiphile in solution exceeds the CMC.

Amphiphiles may be anionic, cationic, nonionic, or ampholytic (zwitterionic), and this provides a convenient means of classifying association colloids. A typical example of each type is given in Table 16-1. Thus, Figure 16-4a represents the micelle of an anionic association colloid. A certain number of the sodium ions are attracted to the surface of the micelle, reducing the overall negative charge somewhat. These bound ions are termed counter ions or*gegenions*.

Mixtures of two or more amphiphiles are usual in pharmaceutical formulations. Assuming an ideal mixture, one can predict the CMC of the mixture from the CMC values of the pure amphiphiles and their mole fractions, x, in the mixture, according to the expression1

$$\frac{1}{\text{CMC}} = \frac{x_1}{\text{CMC}_1} + \frac{x_2}{\text{CMC}_2} \qquad (16\text{–}1)$$

Example 16-1
Critical Micelle Concentration
Compute the CMC of a mixture of *n*-dodecyl octaoxyethylene glycol monoether ($C_{12}E_8$) and *n*-dodecyl *β*-D-maltoside (DM). The CMC of $C_{12}E_8$ is $CMC_1 = 8.1 \times 10^{-5}$M (mole/liter) and its mole fraction is $x_1 = 0.75$; the CMC of DM is $CMC_2 = 15 \times 10^{-5}$ M.
We have

$$x_2 = (1 - x_2) = (1 - 0.75) = 0.25$$

From equation (16-1),

$$\frac{1}{\text{CMC}} = \frac{0.75}{8.1 \times 10^{-5}} + \frac{0.25}{15 \times 10^{-5}} = 10{,}926$$

$$\text{CMC} = \frac{1}{10{,}926} = 9.15 \times 10^{-5}\text{M}$$

The experimental value is 9.3×10^{-5} M.
The properties of lyophilic, lyophobic, and association colloids are outlined in Table 16-2. These properties, together with the relevant methods, will be discussed in the following sections.

Optical Properties of Colloids

The Faraday–Tyndall Effect

When a strong beam of light is passed through a colloidal sol, a visible cone, resulting from the scattering of light by the colloidal particles, is formed. This is the *Faraday–Tyndall effect*.
The *ultramicroscope*, developed by Zsigmondy, allows one to examine the light points responsible for the *Tyndall cone*. An intense light beam is passed through the sol against a dark background at right angles to the plane of observation, and, although the particles cannot be seen directly, the

bright spots corresponding to particles can be observed and counted.

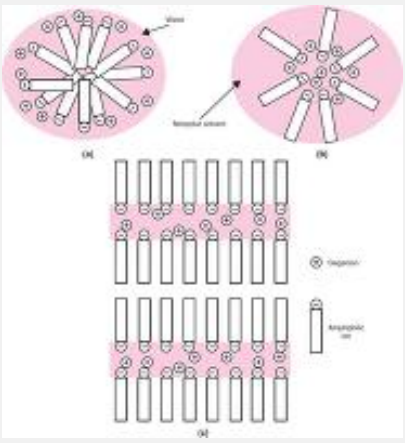

Fig. 16-4. Some probable shapes of micelles: (*a*) spherical micelle in aqueous media, (*b*) reversed micelle in nonaqueous media, and (*c*) laminar micelle, formed at higher amphiphile concentration, in aqueous media.

Electron Microscope

The *electron microscope*, capable of yielding pictures of the actual particles, even those approaching molecular dimensions, is now widely used to observe the size, shape, and structure of colloidal particles.

The success of the electron microscope is due to its high resolving power, which can be defined in terms of *d*, the smallest distance by which two objects are separated and yet remain distinguishable. The smaller the wavelength of the radiation used, the smaller is *d*and the greater is the resolving power. The optical microscope uses visible light as its radiation source and is able to resolve only two particles separated by about 20 nm (200 Å). The radiation source of the electron microscope is a beam of high-energy electrons having wavelengths in the region of 0.01 nm (0.1 Å). With current instrumentation, this results in *d* being approximately 0.5 nm (5 Å), a much-increased power of resolution over the optical microscope.

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Table 16-1 Classification and Typical Examples of Association Colloids

	Example		
Type	**Compound**	**Amphiphile**	**Gegenions**
Anionic	Sodium lauryl sulfate	$CH_3(CH_2)_{11}OSO_3^-$	Na^+
Cationic	Cetyl trimethyl-ammonium bromide	$CH_3(CH_2)_{15}N^+(CH_3)_3$	Br^-
Nonionic	Polyoxyethylene lauryl ether	$CH_3(CH_2)_{10}CH_2O(CH_2OCH_2)_{23}H$	–
Ampholytic	Dimethyldodecylammoniopropane sulfonate	$CH_3(CH_2)_{11}N^+(CH_3)_2(CH_2)_3OSO_2^-$	–

Light Scattering

This property depends on the Faraday–Tyndall effect and is widely used for determining the molecular weight of colloids. It can also be used to obtain information on the shape and size of these particles. Scattering can be described in terms of the turbidity, τ, the fractional decrease in intensity due to scattering as the incident light passes through 1 cm of solution. It can be expressed as the intensity of light scattered in all directions, I_s, divided by the intensity of the incident light, I. At a given concentration of dispersed phase, the turbidity is proportional to the molecular weight of the lyophilic colloid. Because of the low turbidities of most lyophilic colloids, it is more convenient to measure the scattered light (at a particular angle relative to the incident beam) rather than the transmitted light.

The turbidity can then be calculated from the intensity of the scattered light, provided that the dimensions of the particle are small compared with the wavelength of the light used. The molecular weight of the colloid can be obtained from the following equation:

$$\frac{Hc}{\tau} = \frac{1}{M} + 2Bc \qquad (16\text{–}2)$$

Table 16-2 Comparison of Properties of Colloidal Sols*

Lyophilic	Association (Amphiphilic)	Lyophobic
Dispersed phase consists generally of large organic*molecules* lying within colloidal size range	Dispersed phase consists of aggregates (*micelles*) of small organic molecules or ions whose size*individually* is below the colloidal range	Dispersed phase ordinarily consists of inorganic particles, such as gold or silver
Molecules of dispersed phase are solvated, i.e., they are associated with the molecules comprising the dispersion medium	Hydrophilic or lipophilic portion of the molecule is solvated, depending on whether the dispersion medium is aqueous or nonaqueous	Little if any interaction (solvation) occurs between particles and dispersion medium
Molecules disperse spontaneously to form colloidal solution	Colloidal aggregates are formed spontaneously when the concentration of amphiphile exceeds the critical micelle concentration	Material does not disperse spontaneously, and special procedures therefore must be adopted to produce colloidal dispersion
Viscosity of the dispersion medium ordinarily is increased greatly by the presence of the dispersed phase; at sufficiently high concentrations, the sol may become a gel; viscosity and gel formation are related to solvation effects and to the shape of the molecules, which are usually highly asymmetric	Viscosity of the system increases as the concentration of the amphiphile increases, as micelles increase in number and become asymmetric	Viscosity of the dispersion medium is not greatly increased by the presence of lyophobic colloidal particles, which tend to be unsolvated and symmetric

Dispersions are stable generally in the presence of electrolytes; they may be salted out by high concentrations of very soluble electrolytes; effect is due primarily to desolvation of lyophilic molecules	In aqueous solutions, the critical micelle concentration is reduced by the addition of electrolytes; salting out may occur at higher salt concentrations	Lyophobic dispersions are unstable in the presence of even small concentrations of electrolytes; effect is due to neutralization of the charge on the particles; lyophilic colloids exert a protective effect

*From J. Swarbick and A. Martin, *American Pharmacy*, 6th Ed., Lippincott, Philadelphia, 1966, p. 161.

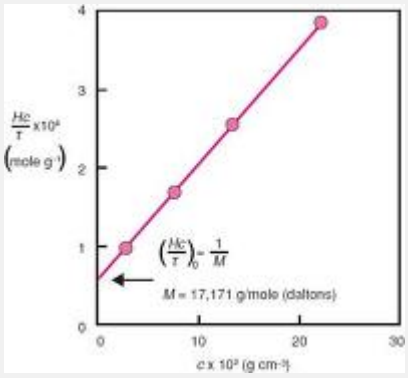

Fig. 16-5. A plot of Hc/τ against the concentration of a polymer (colloid).

where τ is the turbidity in cm^{-1}, c is the concentration of solute in g/cm^3 of solution, M is the weight-average molecular weight in g/mole or daltons, and B is an interaction constant (see osmotic pressure). H is constant for a particular system and is written as

$$H = \frac{32\pi^3 n^2 (dn/dc)^2}{3\lambda^4 N}$$

where n (dimensionless) is the refractive index of the solution of concentration c(g/cm^3) at a wavelength λ in cm^{-1}, dn/dc is the change in refractive index with concentration at c, and N is Avogadro's number. A plot of Hc/τ against concentration (Fig. 16-5) results in a straight line with a slope of $2B$. The intercept on the Hc/τ axis is $1/M$, the reciprocal of which yields the molecular weight of the colloid.

When the molecule is asymmetric, the intensity of the scattered light varies with the angle of observation. Data of this kind permit an estimation of the shape and size of the particles. Light scattering has been used to study proteins, synthetic polymers, association colloids, and lyophobic sols.

Chang and Cardinal2 used light scattering to study the pattern of self-association in aqueous solution of the bile salts sodium deoxycholate and sodium taurodeoxycholate. Analysis of the data showed that the bile salts associate to form dimers, trimers, and tetramers and a larger aggregate of variable size.

Racey et al.3 used quasielastic light scattering, a new light-scattering technique that uses laser light and can determine diffusion coefficients and particle sizes (Stokes's diameter) of macromolecules in solution. Quasielastic light scattering allowed the examination of heparin aggregates in commercial preparations stored for various times and at various temperatures. Both storage time and refrigeration caused an increase in the aggregation state of heparin solutions. It has not yet been determined whether the change in aggregation has any effect on the biologic activity of commercial preparations.

Light Scattering and Micelle Molecular Weight

Equation (16-2) can be applied after suitable modification to compute the molecular weight of colloidal aggregates and micelles. When amphiphilic molecules associate to form micelles, the turbidity of the micellar dispersion differs from the turbidity of the solution of the amphiphilic molecules because micelles are now also present in equilibrium with the monomeric species. Below the CMC, the concentration of monomers increases linearly with the total concentration, c; above the CMC, the monomer concentration remains nearly constant; that is, $c_{monomer}$ [congruent] CMC. The concentration of micelles can therefore be written as

$$c_{micelle} = c - c_{monomer} \cong c - c_{CMC} \qquad (16\text{–}3)$$

The corresponding turbidity of the solution due to the presence of micelles is obtained by subtracting the turbidity due to monomers, $\tau_{monomer} = \tau_{CMC}$, from the total turbidity of the solution:

$$\tau_{micelle} = \tau - \tau_{CMC} \qquad (16\text{–}4)$$

Accordingly, equation (16-2) is modified to

$$\frac{H(c - c_{CMC})}{(\tau - \tau_{CMC})} = \frac{1}{M} + 2B(c - c_{CMC}) \qquad (16\text{–}5)$$

where the subscript CMC indicates the turbidity or concentration at the critical micelle concentration, and B and H have the same meaning as in equation (16-2). Thus, the molecular weight, M, of the micelle and the second virial coefficient, B, are obtained from the intercept and the slope, respectively, of a plot of $H(c - c_{CMC})/(\tau - \tau_{CMC})$ versus $(c - c_{CMC})$. Equation (16-5) is valid for two-component systems, that is, for a micelle and a molecular surfactant in this instance.

When the micelles interact neither among themselves nor with the molecules of the medium, the slope of a plot of equation (16-5) is zero; that is, the second virial coefficient, B, is zero and the line is parallel to the horizontal axis, as seen in Figure 16-6. This behavior is typical of nonionic and zwitterionic micellar systems in which the size distribution is narrow. However, as the concentration of micelles increases, intermicellar interactions lead to positive values of B, the slope of the line having a positive value. For ionic micelles the plots are linear with positive slopes, owing to repulsive intermicellar interactions that result in positive values of the interaction coefficient, B. A negative second virial coefficient is usually an indication that the micellar system is polydisperse.4,5

Example 16-2

Computation of the Molecular Weight of Micelles

Using the following data, compute the molecular weight of micelles of dimethylalkylammoniopropane sulfonate, a zwitterionic surfactant investigated by Herrmann5:

$(c - c_{CMC}) \times 10^3$ g/mL)	0.98	1.98	2.98	3.98	4.98
$\left\lvert \frac{H(c - c_{CMC})}{(\tau - \tau_{CMC})} \right\rvert \times 10^5$ (mole/g)	1.66	1.65	1.66	1.69	1.65

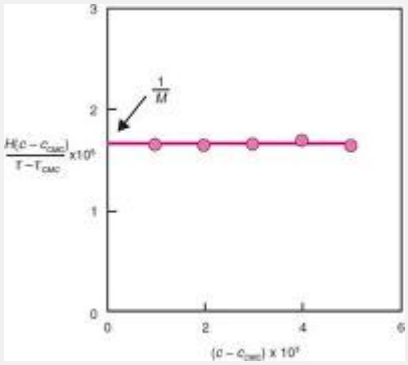

Fig. 16-6.A plot of$H(c - c_{CMC})/(\tau - \tau_{CMC})$ versus $(c - c_{CMC}) \times 10^3$ for a zwitterionic surfactant in which *B*is zero. (From K. W. Hermann, J. Colloid Interface Sci. **22,**352, 1966.)

Using equation (16-5), we obtain the micellar molecular weight from a plot of $H(c - c_{CMC})/\tau - \tau_{CMC}$ versus $(c - c_{CMC})$ (see Fig. 16-6); the intercept is $1/M = 1.66 \times 10^{-5}$ mole/g; therefore, $M =$ 60, 241 g/mole. The slope is zero, that is, $2B$in equation (16-5) is zero.

Example 16-3
Why is the Sky Blue?

When a beam of light passes through a colloid, colloidal particles scatter the light. The intensity of scattered, I_s, light is inversely proportional to the fourth power of the wavelength, λ (Rayleigh law):

$$I_s \sim \frac{1}{\lambda^4}$$

Thus, shorter-wavelength light (blue) is scattered more intensely than longer-wavelength light (yellow and red), and so the scattered light is mostly blue, whereas transmitted light has a yellow or reddish color (Fig. 16-7). Because of the constant motion of molecules, the atmosphere is inhomogeneous and constantly forms clusters with higher density of air. These inhomogeneities may be considered as colloidal particles. The scattering of short-wavelength light gives the sky its blue color. In contrast, transmitted light has a yellow color. At sunrise

and sunset, sunlight has to travel a longer distance through the atmosphere than at noon. This is especially important in the lower atmosphere because it has a higher density (i.e., more gas molecules). Because of this longer distance, the yellow light also scatters. Sunsets can be more spectacular than sunrises because of an increase in the number of particles in the atmosphere due to pollution or natural causes (wind, dust), throughout the day.

Kinetic Properties of Colloids

Grouped under this heading are several properties of colloidal systems that relate to the motion of particles with respect to the dispersion medium. The motion may be thermally induced (Brownian movement, diffusion, osmosis), gravitationally induced (sedimentation), or applied externally (viscosity). Electrically induced motion is considered in the section on electrical properties of colloids.

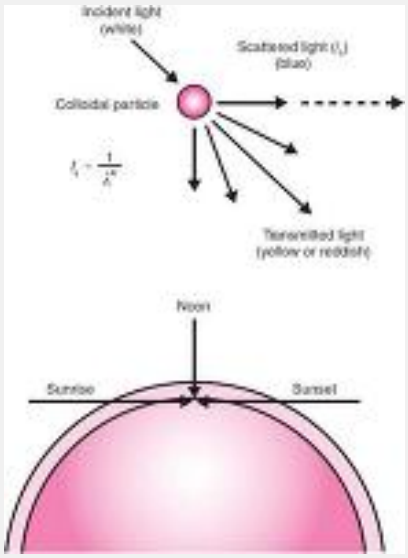

Fig. 16-7. Because of the constant motion of molecules, the atmosphere is inhomogeneous and constantly forms clusters with higher density of air. These inhomogeneities can be considered as colloidal particles, which scatter the light. The intensity of scattered light is inversely proportional to the fourth power of the wavelength, (λ) (Rayleigh law). The scattering of short-wavelength light gives the sky its blue color. In contrast, transmitted light has a yellow or reddish color.

Brownian Motion

Brownian motion describes the random movement of colloidal particles. The erratic motion, which may be observed with particles as large as about 5 μm, was explained as resulting from the bombardment of the particles by the molecules of the dispersion medium. The motion of the molecules cannot be observed, of course, because the molecules are too small to see. The velocity of the particles increases with decreasing particle size. Increasing the viscosity of the medium, which may be accomplished by the addition of glycerin or a similar agent, decreases and finally stops the Brownian movement.

Diffusion

Particles diffuse spontaneously from a region of higher concentration to one of lower concentration until the concentration of the system is uniform throughout. Diffusion is a direct result of Brownian movement. According to *Fick's first law*, the amount, *dq*, of substance diffusing in time, *dt*, across a plane of area, *S*, is directly proportional to the change of concentration, *dc*, with distance traveled, *dx*.

Fick's law is written as

$$dq = -DS\frac{dc}{dx}dt \qquad (16\text{–}6)$$

D is the *diffusion coefficient*, the amount of material diffusing per unit time across a unit area when *dc*/*dx*, called the *concentration gradient*, is unity. *D* thus has the dimensions of area per unit time. The coefficient can be obtained in colloidal chemistry by diffusion experiments in which the material is allowed to pass through a porous disk, and samples are removed and analyzed periodically. Another method involves measuring the change in the concentration or refractive index gradient of the free

boundary that is formed when the solvent and colloidal solution are brought together and allowed to diffuse.

If the colloidal particles can be assumed to be approximately spherical, the following equation, suggested by Sutherland and Einstein6, can be used to obtain the radius of the particle and the particle weight or molecular weight:

$$D = \frac{kT}{6\pi\eta r}$$

or

$$D = \frac{RT}{6\pi\eta r N} \qquad (16\text{–}7)$$

where D is the diffusion coefficient obtained from Fick's law as already explained, k is the Boltzmann constant, R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent, r is the radius of the spherical particle, and N is Avogadro's number. Equation (16-7) is called the *Sutherland–Einstein* or the *Stokes–Einstein* equation. The measured diffusion coefficient can be used to obtain the molecular weight of approximately spherical molecules, such as egg albumin and hemoglobin, by use of the equation

$$D = \frac{RT}{6\pi\eta N}\sqrt[3]{\frac{4\pi N}{3M\bar{v}}} \qquad (16\text{–}8)$$

where M is molecular weight and [v with bar above] is the partial specific volume (approximately equal to the volume in cm^3 of 1 g of the solute, as obtained from density measurements).

Analysis of equations (16-6) and (16-7) allows us to formulate the following three main rules of diffusion: (*a*) the velocity of the molecules increases with decreasing particle size; (*b*) the velocity of the molecules increases with increasing temperature; and (*c*) the velocity of the molecules decreases with increasing viscosity of the medium.

Example 16-4

The Computation of Protein Properties from its Diffusion Coefficient

The diffusion coefficient for a spherical protein at 20°C is 7.0×10^{-7} cm^2/sec and the partial specific volume is 0.75 cm^3/g. The viscosity of the solvent is 0.01 poise (0.01 g/cm sec). Compute (*a*) the molecular weight and (*b*) the radius of the protein particle.

(*a*) By rearranging equation (16-8), we obtain

$$M = \frac{1}{162\bar{v}}\left(\frac{1}{\pi N}\right)^2\left(\frac{RT}{D\eta}\right)^3$$

$$M = \frac{1}{162 \times 0.75}\left(\frac{1}{3.14 \times (6.02 \times 10^{23})}\right)^2\left(\frac{(8.31 \times 10^7) \times 293}{(7.0 \times 10^{-7}) \times 0.01}\right)^3$$

$$\cong 100{,}000 \text{ g/mole}$$

(*b*) From equation (16-7),

$$r = \frac{RT}{6\pi\eta ND} = \frac{(8.31 \times 10^7) \times 293}{6 \times 3.14 \times 0.01 \times (6.02 \times 10^{23}) \times (7.0 \times 10^{-7})}$$

$$= 31 \times 10^{-8} \text{ cm} = 31 \text{ Å} = 3.1 \text{ nm}$$

Osmotic Pressure

The osmotic pressure, π, of a dilute colloidal solution is described by the van't Hoff equation:

$$\pi = cRT \qquad (16\text{–}9)$$

where c is molar concentration of solute. This equation can be used to calculate the molecular weight of a colloid in a dilute solution. Replacing c with c_g/M in equation (16-9), in which c_g is the grams of solute per liter of solution and M is the molecular weight, we obtain

$$\pi = \frac{c_g}{M}RT \qquad (16\text{–}10)$$

Then,

$$\frac{\pi}{c_g} = \frac{RT}{M} \qquad (16\text{–}11)$$

which applies in a very dilute solution. The quantity π/c_g for a polymer having a molecular weight of, say, 50,000 is often a linear function of the concentration, c_g, and the following equation can be written:

$$\frac{\pi}{c_g} = RT\left(\frac{1}{M} + Bc_g\right) \qquad (16\text{–}12)$$

where *B* is a constant for any particular solvent/solute system and depends on the degree of interaction between the solvent and the solute molecules. The term Bc_g in equation (16-12) is needed because equation (16-11) holds only for ideal solutions, namely, those containing low concentrations of spherocolloids. With linear lyophilic molecules, deviations occur because the solute molecules become solvated, leading to a reduction in the concentration of "free" solvent and an apparent increase in solute concentration. The role of*B* in estimating the asymmetry of particles and their interactions with solute was discussed by Hiemenz.7

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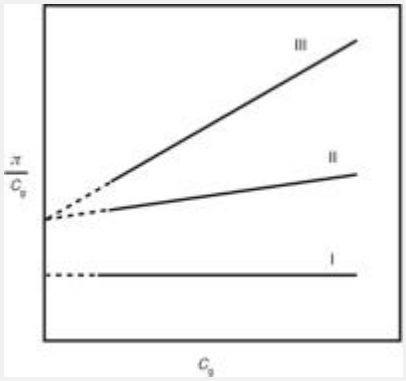

Fig. 16-8. Determination of molecular weight by means of the osmotic pressure method. Extrapolation of the line to the vertical axis where $c_g = 0$ gives RT/M, from which $M$is obtained. Refer to text for significance of lines I, II, and III. Lines II and III are taken to represent two samples of a species of hemoglobin.

A plot of π/c_g against c_g generally results in one of three lines (Fig. 16-8), depending on whether the system is ideal (line I) or real (lines II and III). Equation (16-11) applies to line I and equation (16-12)describes lines II and III. The intercept is RT/M, and if the temperature at which the determination was carried out is known, the molecular weight of the solute can be calculated. In lines II and III, the slope of the line is *B*, the interaction constant. In line I, *B*equals zero and is typical of a dilute spherocolloidal system. Line III is typical of a linear colloid in a solvent having a high affinity for the dispersed particles. Such a solvent is referred to as a "good" solvent for that particular colloid. There is a marked deviation from ideality as the concentration is increased and *B* is large. At higher concentrations, or where interaction is marked, type III lines can become nonlinear, requiring that equation (16-12) be expanded and written as a power series:

$$\frac{\pi}{c_g} = RT\left(\frac{1}{M} + Bc_g + Cc_g^2 + \cdots\right) \qquad (16\text{–}13)$$

where *C* is another interaction constant. Line II depicts the situation in which the same colloid is present in a relatively poor solvent having a reduced affinity for the dispersed material. Note, however, that the extrapolated intercept on the π/c_g axis is identical for both lines II and III, showing that the calculated molecular weight is independent of the solvent used.

Example 16-5
Calculation of Molecular Weight of Hemoglobin

Let us assume that the intercept $(\pi/c_g)_0$ for line III in Figure 16-8 has the value 3.623×10^{-4} liter atm/g, and the slope of the line is 1.80×10^{-6} liter^2 atm/g^2. What is the molecular weight and the second virial coefficient, *B*, for a sample of hemoglobin using the data given here?
In Figure 16-8, line III crosses the vertical intercept at the same point as line II. These two samples of hemoglobin have the same *limiting reduced osmotic pressure*, as $(\pi/c_g)_0$ is called, and therefore have the same molecular weight. The *B* values, and therefore the shape of the two samples and their interaction with the medium, differ as evidenced by the different slopes of lines II and III.
At the intercept, $(\pi/c_g)_0 = RT/M$. Therefore,

$$M = \frac{RT}{\pi/c_g} = \frac{(0.08206 \text{ liter atm/deg mole})(298 \text{ K})}{3.623 \times 10^{-4} \text{ liter atm/g}}$$

$$M = 67{,}498 \text{ g/mole (daltons) for both hemoglobins}$$

The slope of line III, representing one of the hemoglobin samples, is divided by *RT* to obtain *B*, as observed in equation (16-12):

$$B = \frac{1.80 \times 10^{-6} \text{ liter}^2 \text{ atm/g}^2}{(0.08206 \text{ liter atm/mole deg})(298 \text{ K})}$$

$$= 7.36 \times 10^{-8} \text{ liter mole/g}^2$$

The other hemoglobin sample, represented by line II, has a slope of 4.75×10^{-9} liter^2 atm/g^2, and its *B* value is therefore calculated as follows:

$$B = \frac{4.75 \times 10^{-9} \text{ liter}^2 \text{ atm/g}^2}{(0.08206 \text{ liter atm/mole deg})(298 \text{ K})}$$

$$= 1.94 \times 10^{-10} \text{ liter mole/g}^2$$

Estimate the *B* value for the protein represented by line I. Is its molecular weight larger or smaller than that of samples II and III? Refer to equations (16-11) and (16-12) in arriving at your answers.

Sedimentation

The velocity, *v*, of sedimentation of spherical particles having a density ρ in a medium of density ρ_0 and a viscosity η_0 is given by*Stokes's law*:

$$v = \frac{2r^2(\rho - \rho_0)g}{9\eta_0} \qquad (16\text{–}14)$$

where *g* is the acceleration due to gravity. If the particles are subjected only to the force of gravity, then the lower size limit of particles obeying Stokes's equation is about 0.5 μm. This is because Brownian movement becomes significant and tends to offset sedimentation due to gravity and promotes mixing instead. Consequently, a stronger force must be applied to bring about the sedimentation of colloidal particles in a quantitative and measurable manner. This is accomplished by use of the *ultracentrifuge*, developed by Svedberg in 1925,8 which can produce a force one million times that of gravity.
In a centrifuge, the acceleration of gravity is replaced by $\omega^2 x$, where $\omega$is the angular velocity and *x* is the distance of the particle from the center of rotation. Equation (16-14) is accordingly modified to

$$v = \frac{dx}{dt} = \frac{2r^2(\rho - \rho_0)\omega^2 x}{9\eta_0}$$

The speed at which a centrifuge is operated is commonly expressed in terms of the number of revolutions per minute (rpm) of the rotor. It is frequently more desirable to express the rpm as angular acceleration ($\omega^2 x$) or the number of times that the force of gravity is exceeded.

Example 16-6
Calculation of Centrifuge Force

A centrifuge is rotating at 1500 rpm. The midpoint of the cell containing the sample is located 7.5 cm from the center of the rotor (i.e., x = 7.5 cm). What is the average angular acceleration and the number of *g*'s on the suspended particles?
We have

$$\text{Angular acceleration} = \omega^2 x$$
$$= \left(\frac{1500 \text{ revolutions}}{\text{minute}} \times \frac{2\pi}{60}\right)^2 \times 7.5 \text{ cm}$$
$$= 1.851 \times 10^5 \text{ cm/sec}^2$$
$$\text{Number of } g\text{'s} = \frac{1.851 \times 10^5 \text{ cm/sec}^2}{981 \text{ cm/sec}^2} = 188.7 \, g\text{'s}$$

that is, the force produced is 188.7 times that due to gravity.

The instantaneous velocity, $v = dx/dt$, of a particle in a unit centrifugal field is expressed in terms of the *Svedberg sedimentation coefficient* s,

$$s = \frac{dx/dt}{\omega^2 x} \qquad (16\text{–}15)$$

Owing to the centrifugal force, particles having a high molecular weight pass from position x_1 at time t_1 to position x_2 at time t_2, and the sedimentation coefficient is obtained by integrating equation (16-15) to give

$$s = \frac{\ln(x_2/x_1)}{\omega^2(t_2 - t_1)} \qquad (16\text{–}16)$$

The distances x_1 and x_2 refer to positions of the boundary between the solvent and the high–molecular-weight component in the centrifuge cell. The boundary is located by the change of refractive index, which can be attained at any time during the run and translated into a peak on a photographic plate. Photographs are taken at definite intervals, and the peaks of the *schlieren patterns*, as they are called, give the position x of the boundary at each time t. If the sample consists of a component of a definite molecular weight, the schlieren pattern will have a single sharp peak at any moment during the run. If components with different molecular weights are present in the sample, the particles of greater weight will settle faster, and several peaks will appear on the schlieren patterns. Therefore, ultracentrifugation not only is useful for determining the molecular weight of polymers, particularly proteins, but also can be used to ascertain the degree of homogeneity of the sample. Gelatin, for example, is found to be a polydisperse protein with fractions of molecular weight 10,000 to 100,000. (This accounts in part for the fact that gelatin from various sources is observed to have variable properties when used in pharmaceutical preparations.) Insulin, on the other hand, is a monodisperse protein composed of two polypeptide chains, each made up of a number of amino acid molecules. The two chains are attached together by disulfide (S—S) bridges to form a definite unit having a molecular weight of about 6000.
The sedimentation coefficient, s, can be computed from equation (16-16) after the two distances x_1 and x_2 are measured on the schlieren photographs obtained at times t_1 and t_2; the angular velocity ω is equal to 2π times the speed of the rotor in revolutions per second. Knowing s and obtaining D from diffusion data, it is possible to determine the molecular weight of a polymer, such as a protein, by use of the expression

$$M = \frac{RT_s}{D(1 - \bar{v}\rho_0)} \qquad (16\text{–}17)$$

where R is the molar gas constant, T is the absolute temperature, [v with bar above] is the partial specific volume of the protein, and ρ_0 is the density of the solvent. Both s and D must be obtained at, or corrected to, 20°C for use in equation (16-17).

Example 16-7

Molecular Weight of Methylcellulose Based on the Sedimentation Coefficient

The sedimentation coefficient, s, for a particular fraction of methylcellulose at 20°C (293 K) is 1.7×10^{-13} sec, the diffusion coefficient, D, is 15×10^{-7} cm^2/sec, the partial specific volume, [v with bar above], of the gum is 0.72 cm^3/g, and the density of water at 20°C is 0.998 g/cm^3.

Compute the molecular weight of methylcellulose. The gas constant R is 8.31×10^7 erg/(deg mole).
We have

$$M = \frac{(8.31 \times 10^7) \times 293 \times (1.7 \times 10^{-13})}{15 \times 10^{-7}[1 - (0.72 \times 0.998)]} = 9800 \text{ g/mole}$$

Kirschbaum9 reviewed the usefulness of the analytic ultracentrifuge and used it to study the micellar properties of drugs (Fig. 16-9). Richard10 determined the apparent micellar molecular weight of the antibiotic fusidate sodium by ultracentrifugation. He concluded that the primary micelles composed of five monomer units are formed, followed by aggregation of these pentamers into larger micelles at higher salt concentrations.
The sedimentation method already described is known as the*sedimentation velocity* technique. A second method, involving*sedimentation equilibrium*, can also be used. Equilibrium is established when the sedimentation force is just balanced by the counteracting diffusional force and the boundary is therefore stationary. In this method, the diffusion coefficient need not be determined; however, the centrifuge may have to be run for several weeks to attain equilibrium throughout the cell. Newer methods of calculation have been developed recently for obtaining molecular weights by the equilibrium method without requiring these long periods of centrifugation, enabling the protein chemist to obtain molecular weights rapidly and accurately.
Molecular weights determined by sedimentation velocity, sedimentation equilibrium, and osmotic pressure determinations are in good agreement, as can be seen from Table 16-3.
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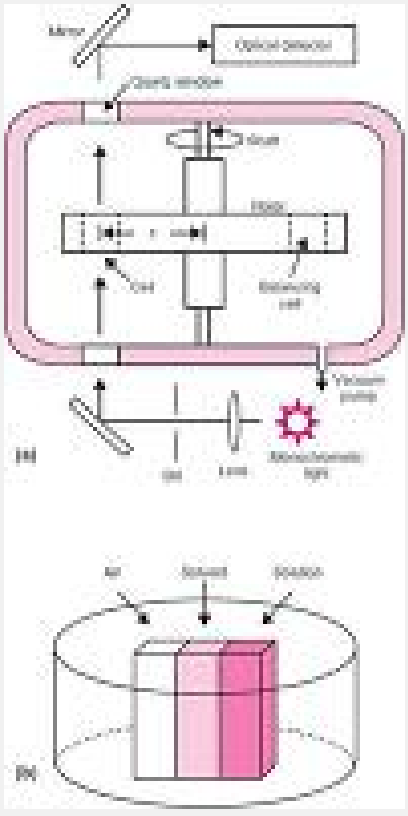

Fig. 16-9. (*a*) Schematic of an ultracentrifuge. (*b*) Centrifuge cell. (From H. R. Allok and F. W. Lampe,*Contemporary Polymer Chemistry*, Prentice-Hall, Englewood Cliffs, N. J., 1981, pp. 366, 367. With permission.)

Viscosity

Viscosity is an expression of the resistance to flow of a system under an applied stress. The more viscous a liquid is, the greater is the applied force required to make it flow at a particular rate. The

fundamental principles and applications of viscosity are discussed in detail in Chapter 19. This section is concerned with the flow properties of dilute colloidal systems and the manner in which viscosity data can be used to obtain the molecular weight of material comprising the disperse phase. Viscosity studies also provide information regarding the shape of the particles in solution.

Table 16-3 Molecular Weights of Proteins in Aqueous Solution Determined by Different Methods*

Material	Molecular Weight		
	Sedimentation Velocity	Sedimentation Equilibrium	Osmotic Pressure
Ribonuclease	12,700	13,000	–
Myoglobin	16,900	17,500	17,000
Ovalbumin	44,000	40,500	45,000
Hemoglobin (horse)	68,000	68,000	67,000
Serum albumin (horse)	70,000	68,000	73,000
Serum globulin (horse)	167,000	150,000	175,000
Tobacco mosaic virus	59,000,000	–	–

*From D. J. Shaw, *Introduction to Colloidal and Surface Chemistry*, Butterworths, London, 1970, p. 32. For and extensive listing of molecular weights of macromolecules, see C. Tanford, *Physical Chemistry of Macromolecules*, Wiley, New York, 1961.

Einstein developed an equation of flow applicable to dilute colloidal dispersions of spherical particles, namely,

$$\eta = \eta_0(1 + 2.5\phi) \qquad \textbf{(16–18)}$$

In equation **(**16-18**)**, which is based on hydrodynamic theory, η_0 is the viscosity of the dispersion medium and η is the viscosity of the dispersion when the volume fraction of colloidal particles present is φ. The volume fraction is defined as the volume of the particles divided by the total volume of the dispersion; it is therefore equivalent to a concentration term. Both η_0 and η can be determined using a capillary viscometer.

Several viscosity coefficients can be defined with respect to this equation. These include *relative viscosity* (η_{rel}), *specific viscosity*(η_{sp}), and *intrinsic viscosity* (η). From equation **(**16-18**),**

$$\eta_{rel} = \frac{\eta}{\eta} = 1 + 2.5\phi \qquad (16\text{–}19)$$

and

$$\eta_{sp} = \frac{\eta}{\eta_0} - 1 = \frac{\eta - \eta_0}{\eta_0} = 2.5\phi \qquad (16\text{–}20)$$

or

$$\frac{\eta_{sp}}{\phi} = 2.5 \qquad (16\text{–}21)$$

Because volume fraction is directly related to concentration, equation (16-21) can be written as

$$\frac{\eta_{sp}}{c} = k \qquad (16\text{–}22)$$

where c is expressed in grams of colloidal particles per 100 mL of total dispersion. For highly polymeric materials

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dispersed in the medium at moderate concentrations, the equation is best expressed as a power series:

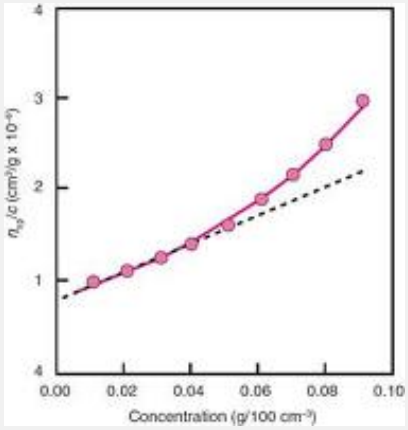

Fig. 16-10. Determination of molecular weight using viscosity data. (Replotted from D. R. Powell, J. Swarbrick, and G. S. Banker, J. Pharm. Sci. **55,** 601, 1966. With permission.)

$$\frac{\eta_{sp}}{c} = k_1 + k_2 c + k_2 c + k_3 c^2 \qquad (16\text{–}23)$$

By determining η at various concentrations and knowing η_0, one can calculate η_{sp} from equation (16-20). If η_{sp}/c is plotted against c (Fig. 16-10) and the line extrapolated to infinite dilution, the intercept is k_1 [equation (16-23)]. This constant, commonly known as the intrinsic viscosity, $[\eta]$, is used to calculate the approximate molecular weights of polymers. According to the so-called Mark–Houwink equation,

$$[\eta] = KM^a \qquad (16\text{–}24)$$

where K and a are constants characteristic of the particular polymer–solvent system. These constants, which are virtually independent of molecular weight, are obtained initially by determining $[\eta]$ experimentally for polymer fractions whose molecular weights have been determined by other methods such as light scattering, osmotic pressure, or sedimentation. Once K and a are known, measurement of $[\eta]$ provides a simple yet accurate means of obtaining molecular weights for fractions not yet subjected to other methods. Intrinsic viscosity $[\eta]$, together with an interaction constant, k', provides the equation, $\eta_{sp}/c = [\eta] + k'[\eta]^2 c$, which is used in choosing solvent mixtures for tablet film coating polymers such as ethyl cellulose.11

The shapes of particles of the disperse phase affect the viscosity of colloidal dispersions. Spherocolloids form dispersions of relatively low viscosity, whereas systems containing linear particles are more viscous. As we saw in previous sections, the relationship of shape and viscosity reflects the degree of solvation of the particles. If a linear colloid is placed in a solvent for which it has a low affinity, it tends to "ball up," that is, to assume a spherical shape, and the viscosity falls. This provides a means of detecting changes in the shape of flexible colloidal particles and macromolecules.

The characteristics of polymers used as substitutes for blood plasma (plasma extenders) depend in part on the molecular weight of the material. These characteristics include the size and shape of the macromolecules and the ability of the polymers to impart the proper viscosity and osmotic pressure to the blood. The methods described in this chapter are used to determine the average molecular weights of hydroxyethyl starch, dextran, and gelatin preparations used as plasma extenders. Ultracentrifugation, light scattering, x-ray analysis (small-angle x-ray scattering12), and other analytic tools13 were used by Paradies to determine the structural properties of tyrothricin, a mixture of the peptide antibiotics gramicidin and tyrocidine B. The antibiotic aggregate has a molecular weight of 28,600 daltons and was determined to be a rod 170 Å in length and 30 Å in diameter.

Electrical Properties of Colloids

The properties of colloids that depend on, or are affected by, the presence of a charge on the surface of a particle are discussed under this heading. The various ways in which the surfaces of particles dispersed in a liquid medium acquire a charge were outlined in the Interfacial Phenomena chapter. Mention was also made of the *zeta* (*electrokinetic*) potential and how it is related to the*Nernst* (*electrothermodynamic*) potential. The potential versus distance diagram for a spherical colloidal particle can be represented as shown in Figure 16-11. Such a system can be formed, for example, by adding a dilute solution of potassium iodide to an equimolar solution of silver nitrate. A colloidal precipitate of silver iodide

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particles is produced, and, because the silver ions are in excess and are adsorbed, a positively charged particle is produced. If the reverse procedure is adopted, that is, if silver nitrate is added to the potassium iodide solution, iodide ions are adsorbed on the particles as the potential-determining ion and result in the formation of a negatively charged sol.

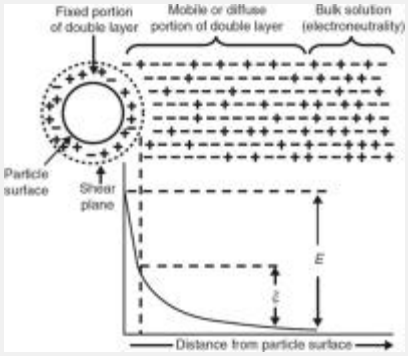

Fig. 16-11. Diffuse double layer and the zeta potential.

Electrokinetic Phenomena

The movement of a charged surface with respect to an adjacent liquid phase is the basic principle underlying four electrokinetic phenomena: *electrophoresis*, *electroosmosis*, *sedimentation potential*, and *streaming potential*.

Electrophoresis involves the movement of a charged particle through a liquid under the influence of an applied potential difference. An electrophoresis cell fitted with two electrodes contains the dispersion. When a potential is applied across the electrodes, the particles migrate to the oppositely charged electrode. Figure 16-12illustrates the design of a commercially available instrument. The rate of particle migration is observed by means of an ultramicroscope and is a function of the charge on the particle. Because the shear plane of the particle is located at the periphery of the tightly bound layer, the rate-

determining potential is the zeta potential. From knowledge of the direction and rate of migration, the sign and magnitude of the zeta potential in a colloidal system can be determined. The relevant equation,

$$\zeta = \frac{v}{E} \times \frac{4\pi\eta}{\varepsilon} \times (9 \times 10^4) \qquad \textbf{(16–25)}$$

which yields the zeta potential, ζ, in volts, requires a knowledge of the velocity of migration, v, of the sol in cm/sec in an electrophoresis tube of a definite length in cm, the viscosity of the medium, η, in poises (dynes sec/cm^2), the dielectric constant of the medium, ε, and the potential gradient, $\boldsymbol{E}$, in volts/cm. The term $v/\boldsymbol{E}$ is known as the *mobility*.

It is instructive to carry out the dimensional analysis of equation **(**16-25**)**. In one system of fundamental electric units, $\boldsymbol{E}$, the electric field strength, can be expressed in electrostatic units of statvolt/cm (1 coulomb = 3 × 10^9 statcoulombs, and 1 statvolt = 300 practical volts). The dielectric constant is not dimensionless here, but rather from Coulomb's law may be assigned the units of statcoulomb2/(dyne cm^2). The

$$\zeta = \frac{v}{E}\frac{4\pi\eta}{\varepsilon} \qquad \textbf{(16–26)}$$

equation can then be written dimensionally, recognizing that statvolts × statcoulombs = dyne cm, as

$$\zeta = \frac{\text{cm/sec}}{\text{statvolts/cm}} \times \frac{\text{dyne sec/cm}^2}{\text{statcoulomb}^2/(\text{dyne cm}^2)} = \text{statvolts} \qquad \textbf{(16–27)}$$

It is more convenient to express the zeta potential in practical volts than in statvolts. Because 1 statvolt = 300 practical volts, equation**(**16-27**)** is multiplied by 300 to make this conversion, that is, statvolts × 300 practical volts/statvolt = 300 practical volts. Furthermore, $\boldsymbol{E}$ is ordinarily measured in practical volts/cm and not in statvolt/cm, and this conversion is made by again multiplying the right-hand side of equation **(**16-27**)** by 300. The final expression is equation **(**16-25**)**, in which the factor 300 × 300 = 9 × 10^4 converts electrostatic units to volts.

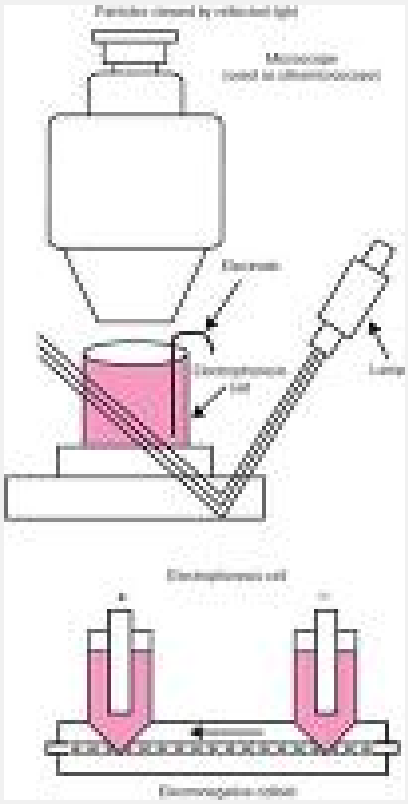

Fig. 16-12. Principle of zeta potential measurement (based on the zeta meter) showing the ultramicroscope and the flow cell.

For a colloidal system at 20°C in which the dispersion medium is water, equation **(**16-25**)** reduces approximately to

$$\zeta \cong 141\frac{v}{E} \qquad (16\text{–}28)$$

The coefficient of 141 at 20°C becomes 128 at 25°C.

P.401

Example 16-8

Determination of the Zeta Potential from Electrophoretic Data

The velocity of migration of an aqueous ferric hydroxide sol was determined at 20°C using the apparatus shown inFigure 16-12 and was found to be 16.5×10^{-4} cm/sec. The distance between the electrodes in the cell was 20 cm, and the applied emf was 110 volts. What is (*a*) the zeta potential of the sol and (*b*) the sign of the charge on the particles?

a. $$\frac{v}{E} = \frac{16.5 \times 10^{-4}\ \text{cm/sec}}{110/20\ \text{volts/cm}} = 3 \times 10^{-4}\ \text{cm}^2/\text{volt sec}$$

$$\zeta = 141 \times (3 \times 10^{-4}) = 0.042\ \text{volt}$$

b. The particles were seen to migrate toward the negative electrode of the electrophoresis cell; therefore, the colloid is positively charged. The zeta potential is often used to estimate the stability of colloids, as discussed in a later section.

Electroosmosis is essentially opposite in principle to electrophoresis. In the latter, the application of a potential causes a charged particle to move relative to the liquid, which is stationary. If the solid is rendered immobile (e.g., by forming a capillary or making the particles into a porous plug), however, the liquid now moves relative to the charged surface. This is electroosmosis, so called because liquid moves through a plug or a membrane across which a potential is applied. Electroosmosis provides another method for obtaining the zeta potential by determining the rate of flow of liquid through the plug under standard conditions.

Sedimentation potential, the reverse of electrophoresis, is the creation of a potential when particles undergo sedimentation. The*streaming potential* differs from electroosmosis in that forcing a liquid to flow through a plug or bed of particles creates the potential.

Schott14 studied the electrokinetic properties of magnesium hydroxide suspensions that are used as antacids and laxatives. The zero point of charge occurred at pH [congruent] 10.8, the zeta potential, ζ, of magnesium hydroxide being positive below this pH value. Increasing the pH or hydroxide ion concentration produced a change in the sign of ζ from positive to negative, with the largest negative ζ value occurring at pH 11.5.

Takenaka and associates15 studied the electrophoretic properties of *microcapsules* of sulfamethoxazole in droplets of a gelatin–acacia coacervate as part of a study to stabilize such drugs in microcapsules.

Donnan Membrane Equilibrium

If sodium chloride is placed in solution on one side of a semipermeable membrane and a negatively charged colloid together with its counterions R^-Na^+ is placed on the other side, the sodium and chloride ions can pass freely across the barrier but not the colloidal anionic particles. The system at equilibrium is represented in the following diagram, in which R^- is the nondiffusible colloidal anion and the vertical line separating the various species represents the semipermeable membrane. The volumes of solution on the two sides of the membrane are considered to be equal.

Outside (o)	Inside (i)
	R^-
Na^+	Na^+
Cl^-	Cl^-

After equilibrium has been established, the concentration in dilute solutions (more correctly the activity) of sodium chloride must be the same on both sides of the membrane, according to the principle of escaping tendencies. Therefore,

$$[Na^+]_o[Cl^-]_o = [Na^+]_i[Cl^-]_i \qquad (16\text{–}29)$$

The condition of electroneutrality must also apply. That is, the concentration of positively charged ions in the solutions on either side of the membrane must balance the concentration of negatively charged ions. Therefore, on the outside,

$$[Na^+]_o = [Cl^-]_o \qquad (16\text{–}30)$$

and inside,

$$[Na^+]_i = [R^-]_i + [Cl^-]_i \qquad (16\text{–}31)$$

Equations (16-30) and (16-31) can be substituted into equation (16-29) to give

$$[Cl^-]_o^2 = ([Cl^-]_i + [R^-]_i)[Cl^-]_i = [Cl^-]_i^2\left(1 + \frac{[R^-]}{[Cl^-]_i}\right) \qquad (16\text{–}32)$$

$$\frac{[Cl^-]_o}{[Cl^-]_i} = \sqrt{1 + \frac{[R^-]_i}{[Cl^-]_i}} \qquad (16\text{–}33)$$

Equation **(16-33)**, the *Donnan membrane equilibrium*, gives the ratio of concentrations of the diffusible anion outside and inside the membrane at equilibrium. The equation shows that a negatively charged polyelectrolyte inside a semipermeable sac would influence the equilibrium concentration ratio of a diffusible anion. It tends to drive the ion of like charge out through the membrane. When $[R^-]_i$ is large compared with $[Cl^-]_i$, the ratio roughly equals

$(c - c_{CMC}) \times 10^3$ g/mL)	0.98	1.98	2.98	3.98	4.98
$\left\|\frac{H(c - c_{CMC})}{(\tau - \tau_{CMC})}\right\| \times 10^5$ (mole/g)	1.66	1.65	1.66	1.69	1.65

If, on the other hand, $[Cl^-]_i$ is quite large with respect to $[R^-]_i$, the ratio in equation **(16-33)** becomes equal to unity, and the concentration of the salt is thus equal on both sides of the membrane.

The unequal distribution of diffusible electrolyte ions on the two sides of the membrane will obviously result in erroneous values for osmotic pressures of polyelectrolyte solutions. If, however, the concentration of salt in the solution is made large, the Donnan equilibrium effect can be practically eliminated in the determination of molecular weights of proteins involving the osmotic pressure method. Higuchi et al.16 modified the Donnan membrane equilibrium, equation (16-33), to demonstrate the use of the polyelectrolyte sodium carboxymethylcellulose for enhancing the absorption of drugs such as sodium salicylate and potassium benzylpenicillin. If $[Cl^-]$ in equation (16-33) is replaced by

the concentration of the diffusible drug, anion $[D^-]$ at equilibrium, and $[R^-]$ is used to represent the concentration of sodium carboxymethylcellulose at equilibrium, we have a modification of the *Donnan membrane equilibrium* for a diffusible drug anion, $[D^-]$:

$$\frac{[D^-]_o}{[D^-]_i} = \sqrt{1 + \frac{[R^-]_i}{[D^-]_i}} \qquad (16\text{–}34)$$

It will be observed that when $[R^-]_i/[D^-]_i = 8$, the ratio $[D^-]_o/[D^-]_i = 3$, and when $[R^-]_i/[D^-]_i = 99$, the ratio $[D^-]_o/[D^-]_i = 10$. Therefore, the addition of an anionic polyelectrolyte to a diffusible drug anion should enhance the diffusion of the drug out of the chamber. By kinetic studies, Higuchi et al.16 showed that the presence of sodium carboxymethylcellulose more than doubled the rate of transfer of the negatively charged dye scarlet red sulfonate.

Other investigators have found by in vivo experiments that ion-exchange resins and even sulfate and phosphate ions that do not diffuse readily through the intestinal wall tend to drive anions from the intestinal tract into the bloodstream. The opposite effect, that of retardation of drug absorption, may occur if the drug complexes with the macromolecule.

Example 16-9

Donnan Membrane Expression

A solution of dissociated nondiffusible carboxymethylcellulose is equilibrated across a semipermeable membrane with a solution of sodium salicylate. The membrane allows free passage of the salicylate ion. Compute the ratio of salicylate on the two sides of the membrane at equilibrium, assuming that the equilibrium concentration of carboxymethylcellulose is 1.2×10^{-2} g equivalent/liter and the equilibrium concentration of sodium salicylate is 6.0×10^{-3} g equivalent/liter. Use the modified Donnan membrane expression, equation (16-34):

$$\frac{[D^-]_o}{[D^-]_i} = \sqrt{1 + \frac{[R^-]_i}{[D^-]_i}} = \sqrt{1 + \frac{12 \times 10^{-3}}{6 \times 10^{-3}}} = 1.73$$

Stability of Colloid Systems

The presence and magnitude, or absence, of a charge on a colloidal particle is an important factor in the stability of colloidal systems. Stabilization is accomplished essentially by two means: providing the dispersed particles with an electric charge, and surrounding each particle with a protective solvent sheath that prevents mutual adherence when the particles collide as a result of Brownian movement. This second effect is significant only in the case of lyophilic sols.

A lyophobic sol is thermodynamically unstable. The particles in such sols are stabilized only by the presence of electric charges on their surfaces. The like charges produce a repulsion that prevents coagulation of the particles. If the last traces of ions are removed from the system by dialysis, the particles can agglomerate and reduce the total surface area, and, owing to their increased size, they may settle rapidly from suspension. Hence, addition of a small amount of electrolyte to a lyophobic sol tends to stabilize the system by imparting a charge to the particles. Addition of electrolyte beyond that necessary for maximum adsorption on the particles, however, sometimes results in the accumulation of opposite ions and reduces the zeta potential below its *critical value*. The critical potential for finely dispersed oil droplets in water (oil hydrosol) is about 40 millivolts, this high value signifying relatively great instability. The critical zeta potential of a gold sol, on the other hand, is nearly zero, which suggests that the particles require only a minute charge for stabilization; hence, they exhibit marked stability against added electrolytes. The valence of the ions having a charge opposite to that of the particles appears to determine the effectiveness of the electrolyte in coagulating the colloid. The precipitating power increases rapidly with the valence or charge of the ions, and a statement of this fact is known as the *Schulze–Hardy rule*.

These observations permitted Verwey and Overbeek17 and Derjaguin and Landau18 to independently develop a theory that describes the stability of lyophobic colloids. According to this approach, known as the DLVO theory, the forces on colloidal particles in a dispersion are due to electrostatic repulsion and London-type van der Waals attraction. These forces result in potential energies of repulsion, V_R, and attraction, V_A, between particles. These are shown in Figure 16-13 together with the curve for the composite potential energy, V_T. There is a deep potential "well" of attraction near the origin and a high potential barrier of repulsion at moderate distances. A shallow secondary trough of attraction (or minimum) is sometimes observed at longer distances of separation. The presence of a secondary minimum is significant in

the controlled flocculation of coarse dispersions. Following this principle, one can determine somewhat quantitatively the amount of electrolyte of a particular valence type required to precipitate a colloid.

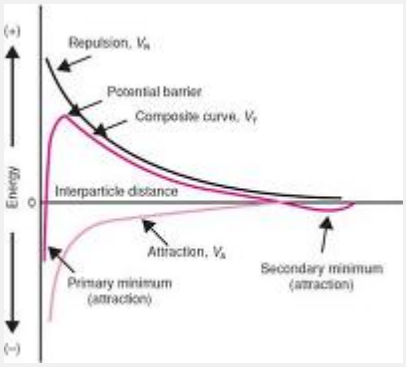

Fig. 16-13. Potential energy versus interparticle distance for particles in suspension.

Not only do electrolytes bring about coagulation of colloidal particles, but the mixing of oppositely charged colloids can also result in mutual agglomeration.

Lyophilic and association colloids are thermodynamically stable and exist in true solution so that the system constitutes a single phase. The addition of an electrolyte to a lyophilic colloid in moderate amounts does not result in coagulation, as was evident with lyophobic colloids. If sufficient salt is added, however, agglomeration and sedimentation of the particles may result. This phenomenon, referred to as "salting out," was discussed in the chapter on solubility.

Just as the Schulze–Hardy rule arranges ions in the order of their capacity to coagulate hydrophobic colloids, the *Hofmeister* or*lyotropic series* ranks cations and anions in order of coagulation of hydrophilic sols. Several anions of the Hofmeister series in decreasing order of precipitating power are citrate, tartrate, sulfate, acetate, chloride, nitrate, bromide, and iodide. The precipitating power is directly related to the hydration of the ion and hence to its ability to separate water molecules from the colloidal particles.

Alcohol and acetone can also decrease the solubility of hydrophilic colloids so that the addition of a small amount of electrolytes may then bring about coagulation. The addition of the less polar solvent renders the solvent mixture unfavorable for the colloid, and electrolytes can then salt out the colloid with relative ease. We can thus regard flocculation on the addition of alcohol, followed by salts, as a gradual transformation from a sol of a lyophilic nature to one of a more lyophobic character.

When negatively and positively charged hydrophilic colloids are mixed, the particles may separate from the dispersion to form a layer rich in the colloidal aggregates. The colloid-rich layer is known as a*coacervate*, and the phenomenon in which macromolecular solutions separate into two liquid layers is referred to as*coacervation*. As an example, consider the mixing of gelatin and acacia. Gelatin at a pH below 4.7 (its isoelectric point) is positively charged; acacia carries a negative charge that is relatively unaffected by pH in the acid range. When solutions of these colloids are mixed in a certain proportion, coacervation results. The viscosity of the upper layer, now poor in colloid, is markedly decreased below that of the coacervate, and in pharmacy this is considered to represent a physical incompatibility. Coacervation need not involve the interaction of charged particles; the coacervation of gelatin may also be brought about by the addition of alcohol, sodium sulfate, or a macromolecular substance such as starch.

Sensitization and Protective Colloidal Action

The addition of a small amount of hydrophilic or hydrophobic colloid to a hydrophobic colloid of opposite charge tends to sensitize or even coagulate the particles. This is considered by some workers to be due

to a reduction of the zeta potential below the critical value (usually about 20–50 millivolts). Others attribute the instability of the hydrophobic particles to a reduction in the thickness of the ionic layer surrounding the particles and a decrease in the coulombic repulsion between the particles. The addition of large amounts of the*hydrophile* (hydrophilic colloid), however, stabilizes the system, the hydrophile being adsorbed on the hydrophobic particles. This phenomenon is known as *protection*, and the added hydrophilic sol is known as a *protective colloid*. The several ways in which stabilization of hydrophobic colloids can be achieved (i.e., protective action) have been reviewed by Schott.19

Table 16-4 The Gold Number of Protective Colloids

Protective Colloid	Gold Number
Gelatin	0.005–0.01
Albumin	0.1
Acacia	0.1–0.2
Sodium oleate	1–5
Tragacanth	2

The protective property is expressed most frequently in terms of the*gold number*. The gold number is the minimum weight in milligrams of the protective colloid (dry weight of dispersed phase) required to prevent a color change from red to violet in 10 mL of a gold sol on the addition of 1 mL of a 10% solution of sodium chloride. The gold numbers for some common protective colloids are given in Table 16-4.
A pharmaceutical example of sensitization and protective action is provided when bismuth subnitrate is suspended in a tragacanth dispersion; the mixture forms a gel that sets to a hard mass in the bottom of the container. Bismuth subcarbonate, a compound that does not dissociate sufficiently to liberate the bismuth ions, is compatible with tragacanth.
These phenomena probably involve a sensitization and coagulation of the gum by the Bi^{3+} ions. The flocculated gum then aggregates with the bismuth subnitrate particles to form a gel or a hard cake. If phosphate, citrate, or tartrate is added, it protects the gums from the coagulating influence of the Bi^{3+} ions, and, no doubt, by reducing the zeta potential on the bismuth particles, partially flocculates the insoluble material. Partially flocculated systems tend to cake considerably less than deflocculated systems, and this effect is significant in the formulation of suspensions.20

Solubilization

An important property of association colloids in solution is the ability of the micelles to increase the solubility of materials that are normally insoluble, or only slightly soluble, in the dispersion medium used. This phenomenon, known as

solubilization, has been reviewed by many authors, including Mulley,21 Nakagawa,22 Elworthy et al.,23 and Attwood and Florence.24 Solubilization has been used with advantage in pharmacy for many years; as early as 1892, Engler and Dieckhoff25solubilized a number of compounds in soap solutions. Knowing the location, distribution, and orientation of solubilized drugs in the micelle is important to understanding the kinetic aspect of the solubilization process and the interaction of drugs with the different elements that constitute the micelle. These factors may also affect the stability and

bioavailability of the drug. The location of the molecule undergoing solubilization in a micelle is related to the balance between the polar and nonpolar properties of the molecule. Lawrence26 was the first to distinguish between the various sites. He proposed that nonpolar molecules in aqueous systems of ionic surface-active agents would be located in the hydrocarbon core of the micelle, whereas polar solubilizates would tend to be adsorbed onto the micelle surface. Polar–nonpolar molecules would tend to align themselves in an intermediate position within the surfactant molecules forming the micelle. Nonionic surfactants are of most pharmaceutical interest as solubilizing agents because of their lower toxicity. Their micelles show a gradient of increased polarity from the core to the polyoxyethylene–water surface. The extended interfacial region between the core and the aqueous solution, that is, the polar mantle, is greatly hydrated. The anisotropic distribution of water molecules within the polar mantle favors the inclusion (solubilization) of a wide variety of molecules.27 Solubilization may therefore occur in both the core and the mantle, also called the*palisade layer*. Thus, certain compounds (e.g., phenols and related compounds with a hydroxy group capable of bonding with the ether oxygen of the polyoxyethylene group) are held between the polyoxyethylene chains. Under these conditions, such compounds can be considered as undergoing inclusion within the polyoxyethylene exterior of the micelle rather than adsorption onto the micelle surface.

Figure 16-14 depicts a spherical micelle of a nonionic, polyoxyethylene monostearate, surfactant in water. The figure is drawn in conformity with Reich's suggestion28 that such a micelle may be regarded as a hydrocarbon core, made up of the hydrocarbon chains of the surfactant molecules, surrounded by the polyoxyethylene chains protruding into the continuous aqueous phase. Benzene and toluene, nonpolar molecules, are shown solubilized in the hydrocarbon interior of the micelle. Salicylic acid, a more polar molecule, is oriented with the nonpolar part of the molecule directed toward the central region of the micelle and the polar group toward the hydrophilic chains that spiral outward into the aqueous medium. Parahydroxybenzoic acid, a predominantly polar molecule, is found completely between the hydrophilic chains.

The pharmacist must give due attention to several factors when attempting to formulate solubilized systems successfully. It is essential that, at the concentration employed, the surface-active agent, if taken internally, be nontoxic, miscible with the solvent (usually water), compatible with the material to be solubilized, free from disagreeable odor and taste, and relatively nonvolatile. Toxicity is of paramount importance, and, for this reason, most solubilized systems are based on nonionic surfactants. The amount of surfactant used is important: A large excess is undesirable, from the point of view of both possible toxicity and reduced absorption and activity; an insufficient amount can lead to precipitation of the solubilized material. The amount of material that can be solubilized by a given amount of surfactant is a function of the polar–nonpolar characteristics of the surfactant (commonly termed the *hydrophile–lipophile balance* %HLB) and of the molecule being solubilized.

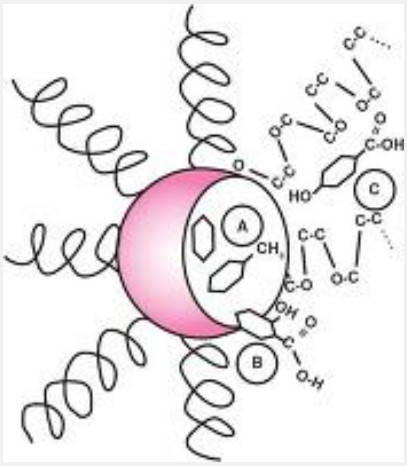

Fig. 16-14. A spherical micelle of nonionic surfactant molecules. (A) A nonpolar molecule solubilized in the nonpolar region of the micelle. (B) A more polar molecule found partly embedded in the central region and partially extending into the palisade region. (C) A polar molecule found lying well out in the palisade layer attracted by dipolar forces to the polyoxyethylene chains.

It should be appreciated that changes in absorption and biologic availability and activity may occur when the material is formulated in a solubilized system. Drastic changes in the bactericidal activity of certain compounds take place when they are solubilized, and the pharmacist must ensure that the concentration of surface-active agent present is optimum for that particular system. The stability of materials against oxidation and hydrolysis may be modified by solubilization.

Solubilization has been used in pharmacy to bring into solution a wide range of materials, including volatile oils, coal tar and resinous materials, phenobarbital, sulfonamides, vitamins, hormones, and dyes.[23,29]

P.405

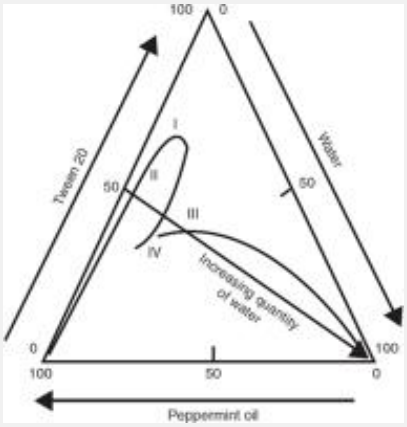

Fig. 16-15. Phase diagram for the ternary system water, Tween 20, and peppermint oil.

O'Malley et al.[30] investigated the solubilizing action of Tween 20 on peppermint oil in water and presented their results in the form of a ternary diagram as shown in Figure 16-15. They found that on the gradual addition of water to a 50:50 mixture of peppermint oil and Tween 20, polysorbate 20, the system changed from a homogeneous mixture (region I) to a viscous gel (region II). On the further addition of water, a clear solution (region III) again formed, which then separated into two layers (region IV). This sequence of changes corresponds to the results one would obtain by diluting a peppermint oil concentrate in compounding and manufacturing processes. Analyses such as this therefore can provide important clues for the research pharmacist in the formulation of solubilized drug systems.

Determination of a phase diagram was also carried out by Boon et al.[31] to formulate a clear, single-phase liquid vitamin A preparation containing the minimum quantity of surfactant needed to solubilize the vitamin. Phase equilibrium diagrams are particularly useful when the formulator wishes to predict the effect on the phase equilibria of the system of dilution with one or all of the components in any desired combination or concentration.

Factors Affecting Solubilization

The solubilization capacity of surfactants for drugs varies greatly with the chemistry of the surfactants and with the location of the drug in the micelle. If a hydrophobic drug is solubilized in the micelle core, an increase of the lipophilic alkyl chain length of the surfactant should enhance solubilization. At the same time, an increase in the micellar radius by increasing the alkyl chain length reduces the Laplace pressure, thus favoring the entry of drug molecules into the micelle (see *Example 16-10*).

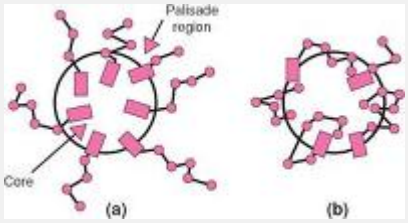

Fig. 16-16. Schematic of nonionic micelle of *n*-polyoxyethylene glycol monoether showing the intrusion of polyoxyethylene chains into the micelle core. (*a*) Micelle with palisade environment intact. (*b*) Palisade layer partially destroyed by loss of polyoxyethylene groups into the hydrophobic core.

For micelles consisting of ionic surfactants, an increase in the radius of the hydrocarbon core is the principal method of enhancing solubilization,32 whereas for micelles built up from nonionic surfactants, evidence of this effect is not well grounded. Attwood et al.33 showed that an increase of carbon atoms above 16 in an *n*-polyoxyethylene glycol monoether—a nonionic surfactant—increases the size of the micelle, but, for a number of drugs, does not enhance solubilization. Results from NMR imaging, viscosity, and density testing34 suggested that some of the polar groups of the micelle, that is, some polyoxyethylene groups outside the hydrocarbon core of the micelle, double back and intrude on the core, depressing its melting point and producing a fluid micellar core (Fig. 16-16). However, this movement of polyethylene groups into the hydrocarbon core disrupts the palisade layer and tends to destroy the region of solubilization for polar–nonpolar compounds (semipolar drugs). Patel et al.35 suggested that the solubilizing nature of the core be increased with a more polar surfactant that would not disrupt the palisade region. Attwood et al.33 investigated the manner in which an ether or a keto group introduced into the hydrophobic region of a surfactant, octadecylpolyoxyethylene glycol monoether, affects the solubilization and micellar character of the surfactant. It was observed that the ether group lowered the melting point of the hydrocarbon and thus was able to create a liquid core without the intrusion phenomenon, which reduced the solubilizing nature of the surfactant for semipolar drugs.

The principal effect of pH on the solubilizing power of nonionic surfactants is to alter the equilibrium between the ionized and un-ionized drug (solubilizate). This affects the solubility in water and modifies the partitioning of the drug between the micellar and the aqueous phases. As an example, the more lipophilic un-ionized form of benzoic acid is solubilized to a greater extent in polysorbate 80 than the more hydrophilic ionized form.36 However, solubilization of drugs having hydrophobic parts in the molecule and more than one

dissociation constant may not correlate with the lipophilicity of the drug.37

Key Concept

Pharmaceutical Applications of Colloids

Colloids are extensively used for modifying the properties of pharmaceutical agents. The most common property that is affected is the solubility of a drug. However, colloidal forms of many drugs exhibit substantially different properties when compared with traditional forms of these drugs. Another important pharmaceutical application of colloids is their use as drug delivery systems. The most often-used colloid-type drug delivery systems include hydrogels, microspheres, microemulsions, liposomes, micelles, nanoparticles, and nanocrystals.

Pharmaceutical Applications of Colloids

Certain medicinals have been found to possess unusual or increased therapeutic properties when formulated in the colloidal state. Colloidal silver chloride, silver iodide, and silver protein are effective germicides and do not cause the irritation that is characteristic of ionic silver salts. Coarsely powdered sulfur is poorly absorbed when administered orally, yet the same dose of colloidal sulfur may be absorbed so completely as to cause a toxic reaction and even death. Colloidal copper has been used in the treatment of cancer, colloidal gold as a diagnostic agent for paresis, and colloidal mercury for syphilis.

Many natural and synthetic polymers are important in contemporary pharmaceutical practice. Polymers are macromolecules formed by the polymerization or condensation of smaller, noncolloidal molecules. Proteins are important natural colloids and are found in the body as components of muscle, bone, and skin. The plasma proteins are responsible for binding certain drug molecules to such an extent that the pharmacologic activity of the drug is affected. Naturally occurring plant macromolecules such as starch and cellulose that are used as pharmaceutical adjuncts are capable of existing in the colloidal state. Hydroxyethyl starch is a macromolecule used as a plasma substitute. Other synthetic polymers are applied as coatings to solid dosage forms to protect drugs that are susceptible to atmospheric moisture or degradation under the acid conditions of the stomach. Colloidal electrolytes (surface-active agents) are sometimes used to increase the solubility, stability, and taste of certain compounds in aqueous and oily pharmaceutical preparations.

Table 16-5 Colloid-Based Delivery Systems for Therapeutics*

Typical Mean Particle Diameter	Delivery System Type	Representative Systems of Each Type	Characteristic Applications
0.5–20 μm	Microspheres, hydrogels	Alginate, gelatin, chitosan, polymeric microspheres, synthetic, biodegradable, polymeric hydrogels	Sustained release of therapeutics, scaffolds for cell delivery in tissue engineering
0.2–5 μm	Microparticles	Polystyrene, poly(lactide) microspheres	Targeted delivery of therapeutics
0.15–2 μm	Emulsions, microemulsions	Oil-in-water, water-in-oil, lipid emulsions, oil-in-water microemulsions	Controlled and targeted delivery of therapeutics
30–1000 nm	Liposomes	Phospholipid and polymer-based bilayer vesicles	Targeted delivery of therapeutics

3–80 nm	Micelles	Natural and synthetic surfactant micelles	Targeted delivery of therapeutics
2–100 nm	Nanoparticles	Lipid, polymer, inorganic nanoparticles	Targeted delivery of therapeutics, in vivo navigational devices
2–100 nm	Nanocrystals	Quantum dots	Imaging agents

*Based on K. Kostarelos, Adv. Colloid Interface Sci. **106,** 147, 2003.

In addition to mentioned pharmaceutical application, colloids are used as delivery systems for therapeutics. Seven main types of colloidal drug delivery systems in use are: hydrogels, microparticles, microemulsions, liposomes, micelles, nanoparticles, and nanocrystals (Table 16-538). A more detailed description of different drug delivery systems is given in Chapter 23. Here, we mention the main characteristics of each colloidal delivery system.

Hydrogels

Whereas a gel is a colloid with a liquid as dispersion medium and a solid as a dispersed phase (see Key Concept, Colloidal Systems), a hydrogel is a colloidal gel in which water is the dispersion medium. Natural and synthetic hydrogels are now used for wound healing, as scaffolds in tissue engineering, and as sustained-release delivery systems. Wound gels

are excellent for helping create or maintain a moist environment. Some hydrogels provide absorption, desloughing, and debriding capacities to necrotic and fibrotic tissue. When used as scaffolds for tissue engineering, hydrogels may contain human cells to stimulate tissue repair.39 Because they are loaded with pharmaceutical ingredients, hydrogels provide a sustained release of drugs. Special attention has been given to environmentally sensitive hydrogels.40These hydrogels have the ability to sense changes in pH, temperature, or the concentration of a specific metabolite and release their load as a result of such a change. These hydrogels can be used as site-specific controlled drug delivery systems. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. Light-sensitive, pressure-responsive, and electrosensitive hydrogels also have the potential to be used in drug delivery. Although the concepts of these environment-sensitive hydrogels are sound, the practical applications require significant improvements in the hydrogel properties. The most important challenges that should be addressed in designing useful environmentally sensitive hydrogels include slow response time, limited biocompatibility, and biodegradability. However, if the achievements of the past can be extrapolated into the future, it is highly likely that responsive hydrogels with a wide array of desirable properties will be forthcoming.40

Microparticles

Microparticles are small (0.2–5 μm), loaded microspheres of natural or synthetic polymers. Microparticles were initially developed as carriers for vaccines and anticancer drugs. More recently, novel properties of microparticles have been developed to increase the efficiency of drug delivery and improve release profiles and drug targeting. Several investigations have focused on the development of methods of reducing the uptake of the nanoparticles by the cells of the reticuloendothelial system and enhance their uptake by the targeted cells. For instance, functional surface coatings of nonbiodegradable carboxylated polystyrene or biodegradable poly(D,L-lactide-co-glycolide) microspheres with poly(L-lysine)-g-poly(ethylene glycol) (PLL-g-PEG) were investigated in attempts to shield them from nonspecific phagocytosis and to allow ligand-specific interactions via molecular recognition.41 It was found that coatings of PLL-g-PEG-ligand conjugates provided for the specific targeting of microspheres to human blood–derived macrophages and dendritic cells while reducing nonspecific phagocytosis. Microparticles can also be used to facilitate nontraditional routes of drug administration. For example, it was found that microparticles can be used to improve immunization using the mucosal route of administration of therapeutics.42 It was found in this study that after mucosal delivery, microparticles can translocate to tissues in the systemic compartment of the immune system and provoke immunologic reactions.

Emulsions and Microemulsions

Microemulsions are excellent candidates as potential drug delivery systems because of their improved drug solubilization, long shelf life, and ease of preparation and administration. Three distinct microemulsions—oil external, water external, and middle phase—can be used for drug delivery, depending upon the type of drug and the site of action.43,44 In contrast to microparticles, which demonstrate distinct differences between the outer shell and core, microemulsions are usually formed with more or less homogeneous particles. Microemulsions are used for controlled release and targeted delivery of different pharmaceutic agents. For instance, microemulsions were used to deliver oligonucleotides (small fragments of DNA) specifically to ovarian cancer cells.45 In contrast to microemulsions, nanoemulsions consist in very fine oil-in-water dispersions, having droplet diameter smaller than 100 nm. Compared to microemulsions, they are in a metastable state, and their structure depends on the history of the system. Nanoemulsions are very fragile systems. The nanoemulsions can find an application in skin care due to their good sensorial properties (rapid penetration, merging textures) and their biophysical properties (especially their hydrating power).46

Liposomes

Liposomes consist of an outer uni- or multilaminar membrane and an inner liquid core. In most cases, liposomes are formed with natural or synthetic phospholipids similar to those in cellular plasma membrane. Because of this similarity, liposomes are easily utilized by cells. Liposomes can be loaded by pharmaceutical or other ingredients by two principal ways: lipophilic compounds can be associated with liposomal membrane, and hydrophilic substances can be dissolved in the inner liquid core of liposomes. To decrease uptake by the cells of the reticuloendothelial system and/or enhance their uptake by the targeted cells, the membrane of liposomes can be modified by polymeric chains and/or targeting moieties or antibodies specific to the targeted cells. Because they are relatively easy to prepare, biodegradable, and nontoxic, liposomes have found numerous applications as drug delivery systems.47,48

Micelles

Micelles are structures similar to liposomes but do not have an inner liquid compartment. Therefore, they can be used as water-soluble biocompatible microcontainers for the delivery of poorly soluble hydrophobic pharmaceuticals.49 Similar to liposomes, their surface can be modified with antibodies (immunomicelles) or other targeting moieties providing the ability of micelles to specifically interact with their antigens.50 One type of micelles, Pluronic block copolymers, are recognized pharmaceutical excipients listed in the US and British Pharmacopoeia. They have been used extensively in a

variety of pharmaceutical formulations including delivery of low–molecular-mass drugs, polypeptides,

and DNA.51 Furthermore, Pluronic block copolymers are versatile molecules that can be used as structural elements of polycation-based gene delivery systems (polyplexes).

Nanoparticles

Nanocapsules are submicroscopic colloidal drug carrier systems composed of an oily or an aqueous core surrounded by a thin polymer membrane. Two technologies can be used to obtain such nanocapsules: the interfacial polymerization of a monomer or the interfacial nanodeposition of a preformed polymer.52 Solid lipid nanoparticles were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes, and polymeric nanoparticles. They were used, in particular, in topical cosmetic and pharmaceutical formulations.53 A novel nanoparticle-based drug carrier for photodynamic therapy has been developed by Roy et al.54This carrier can provide stable aqueous dispersion of hydrophobic photosensitizers, yet preserve the key step of photogeneration of singlet oxygen, necessary for photodynamic action. Nanoparticles have also found applications as nonviral gene delivery systems.55

Nanocrystals

Inorganic nanostructures that interface with biologic systems have recently attracted widespread interest in biology and medicine.56Larson et al.57 set out to explore the feasibility of in vivo targeting by using semiconductor quantum dots (qdots), which are small (<10 nm) inorganic nanocrystals that possess unique luminescent properties; their fluorescence emission is stable and tuned by varying the particle size or composition. By adding a targeting moiety, one can direct these qdots specifically to the targeted organs and tissues. In particular, it was found that ZnS-capped CdSe qdots coated with a lung-targeting peptide accumulate in the lungs of mice after intravenous injection, whereas two other peptides specifically direct qdots to blood vessels or lymphatic vessels in tumors.57 As in case of liposomes, adding polyethylene glycol to the qdot coating prevents nonselective accumulation of qdots in reticuloendothelial tissues. All these make qdots promising imaging agents. The use of semiconductor quantum dots as fluorescent labels for multiphoton microscopy enables multicolor imaging in demanding biologic environments such as living tissue.57

Chapter Summary

Although colloidal dispersion have been important in the pharmaceutical sciences for decades, with the advent of nanotechnology, they are now becoming a driving force behind drug delivery systems and technology. This chapter provided basic information on colloidal dispersions such as basic definitions, the types of colloidal systems, electric, kinetic, and optical properties, their role in solubilization, and applications of colloids in the pharmaceutical sciences. The drug delivery aspects of colloids are discussed inChapter 23 as well.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

References

1. C. J. Drummond, G. G. Warr, F. Grieser, B. W. Nihaen and D. F. Evans, J. Phys. Chem. **89,** 2103, 1985.
2. Y. Chang and J. R. Cardinal, J. Pharm Sci. **67,** 994, 1978.
3. T. J. Racey, P. Rochon, D. V. C. Awang and G. A. Neville, J. Pharm. Sci. **76,** 314, 1987; T. J. Racey, P. Rochon, F. Mori and G. A. Neville, J. Pharm. Sci. **78,** 214, 1989.
4. P. Mukerjee, J. Phys. Chem. **76,** 565, 1972.
5. K. W. Herrmann, J. Colloid Interface Sci. **22,** 352, 1966.
6. P. Atkins, J. D. Paula, Physical Chemistry, W. H. Freeman, NY and Company, 7 Ed., 2006.
7. P. C. Hiemenz, *Principles of Colloid and Surface Chemistry*, 2nd Ed., Marcel Dekker, New York, 1986, pp. 127, 133, 148.
8. T. Svedberg and J. B. Nicholas, J. Am. Chem. Soc. **49,** 2920, 1927.
9. J. Kirschbaum, J. Pharm. Sci. **63,** 981, 1974.
10. A. J. Richard, J. Pharm. Sci. **64,** 873, 1975.
11. H. Arwidsson and M. Nicklasson, Int. J. Pharm. **58,** 73, 1990.
12. H. H. Paradies, Eur. J. Biochem. **118,** 187, 1981.

13. H. H. Paradies, J. Pharm. Sci. **78,** 230, 1989.
14. H. Schott, J. Pharm. Sci. **70,** 486, 1981.
15. H. Takenaka, Y. Kawashima and S. Y. Lin, J. Pharm. Sci.**70,** 302, 1981.
16. T. Higuchi, R. Kuramoto, L. Kennon, T. L. Flanagan and A. Polk, J. Am. Pharm. Assoc. Sci. **43,** 646, 1954.
17. E. J. W. Verwey and J. Th. G. Overbeek, *Theory of the Stability of Lyophobic Colloids*, Elsevier, Amsterdam, 1948.
18. B. Derjaguin and L. Landau, Acta Phys. Chim. USSR **14,**663, 1941; J. Exp. Theor. Physics USSR **11,** 802, 1941.
19. H. Schott, in *Remington's Pharmaceutical Sciences*, 16th Ed., Mack, Easton, PA, 1980, Chapter 20.
20. B. Haines and A. N. Martin, J. Pharm. Sci. **50,** 228, 753, 756, 1961.
21. B. A. Mulley, in *Advances in Pharmaceutical Sciences*, Academic Press, New York, 1964, Vol. 1, pp. 87–194.
22. T. Nakagawa, in *Nonionic Surfactants*, M. J. Schick, Marcel Dekker, New York, 1967.
23. P. H. Elworthy, A. T. Florence and C. B. Macfarlane,*Solubilization by Surface-Active Agents*, Chapman & Hall, London, 1968.
24. D. Attwood and A. T. Florence, *Surfactant Systems*, Chapman & Hall, London, 1983.
25. C. Engler and E. Dieckhoff, Arch. Pharm. **230,** 561, 1892.
26. A. S. C. Lawrence, Trans. Faraday Soc. **33,** 815, 1937.
27. E. Keh, S. Partyka and S. Zaini, J. Colloid Interface Sci. **129,**363, 1989.
28. I. Reich, J. Phys. Chem. **60,** 260, 1956.
29. B. W. Barry and D. I. El Eini, J. Pharm. Pharmacol. **28,** 210, 1976.
30. W. J. O'Malley, L. Pennati and A. Martin, J. Am. Pharm. Assoc. Sci. **47,** 334, 1958.
31. P. F. G. Boon, C. L. J. Coles and M. Tait, J. Pharm. Pharmacol. **13,** 200T, 1961.
32. T. Anarson and P. H. Elworthy, J. Pharm. Pharmacol. **32,**381, 1980.
33. D. Attwood, P. H. Elworthy and M. J. Lawrence, J. Pharm. Pharmacol. **41,** 585, 1989.
34. P. H. Elworthy and M. S. Patel, J. Pharm. Pharmacol. **36,**565, 1984; J. Pharm. Pharmacol. **36,** 116, 1984.
35. M. S. Patel, P. H. Elworthy and A. K. Dewsnup, J. Pharm. Pharmacol. **33,** 64P, 1981.
36. J. H. Collett and L. Koo, J. Pharm. Sci. **64,** 1253, 1975.
37. K. Ikeda, H. Tomida and T. Yotsuyanagi, Chem. Pharm. Bull. **25,** 1067, 1977.

38. K. Kostarelos, Adv. Colloid Interface Sci. **106,** 147, 2003.
39. J. Kisiday, M. Jin, B. Kurz, H. Hung, C. Semino, S. Zhang and A. J. Grodzinsky, Proc. Natl. Acad. Sci. USA **99,** 9996, 2002.
40. Y. Qiu and K. Park, Adv. Drug Deliv. Rev. **53,** 321, 2001.
41. S. Faraasen, J. Voros, G. Csucs, M. Textor, H. P. Merkle and E. Walter, Pharm. Res. **20,** 237, 2003.
42. J. E. Eyles, V. W. Bramwell, E. D. Williamson and H. O. Alpar, Vaccine **19,** 4732, 2001.
43. R. P. Bagwe, J. R. Kanicky, B. J. Palla, P. K. Patanjali and D. O. Shah, Crit. Rev. Ther. Drug Carrier Syst. **18,** 77, 2001.
44. S. Benita (Ed.), *Submicron Emulsion in Drug Targeting and Delivery*, Harwood Academic Publishers, Amsterdam, 1998.
45. H. Teixeira, C. Dubernet, H. Chacun, L. Rabinovich, V. Boutet, J. R. Deverre, S. Benita and P. Couvreur, J. Controlled Release **89,** 473, 2003.
46. O. Sonneville-Aubrun, J. T. Simonnet and F. L'Alloret, Adv. Colloid Interface Sci. **108–109,** 145, 2004.
47. D. J. Crommelin and G. Storm, J. Liposome Res. **13,** 33, 2003.
48. D. D. Lasic and D. Papahadjopoulos (Eds.), *Medical Applications of Liposomes*, Elsevier Health Sciences, Amsterdam, 1998.

49. R. Savic, L. Luo, A. Eisenberg and D. Maysinger, Science**300,** 615, 2003.
50. V. P. Torchilin, A. N. Lukyanov, Z. Gao and B. Papahadjopoulos-Sternberg, Proc. Natl. Acad. Sci. USA **100,**6039, 2003.
51. A. V. Kabanov, P. Lemieux, S. Vinogradov and V. Alakhov, Adv. Drug Deliv. Rev. **54,** 223, 2002.
52. P. Couvreur, G. Barratt, E. Fattal, P. Legrand and C. Vauthier, Crit. Rev. Ther. Drug Carrier Syst. **19,** 99, 2002.
53. R. H. Muller, M. Radtke and S. A. Wissing, Adv. Drug Deliv. Rev. **54**(Suppl 1), S131, 2002.
54. I. Roy, T. Y. Ohulchanskyy, H. E. Pudavar, E. J. Bergey, A. R. Oseroff, J. Morgan, T. J. Dougherty and P. N. Prasad, J. Am. Chem. Soc. **125,** 7860, 2003.
55. F. Scherer, M. Anton, U. Schillinger, J. Henke, C. Bergemann, A. Kruger, B. Gansbacher and C. Plank, Gene Ther. **9,** 102, 2002.
56. M. E. Akerman, W. C. Chan, P. Laakkonen, S. N. Bhatia and E. Ruoslahti, Proc. Natl. Acad. Sci. USA **99,** 12617, 2002.
57. D. R. Larson, W. R. Zipfel, R. M. Williams, S. W. Clark, M. P. Bruchez, F. W. Wise and W. W. Webb, Science **300,** 1434, 2003.

Recommended Readings

T. Cosgrove, *Colloid Science: Principles, Methods and Applications*, Blackwell, Oxford, UK, 2005.
P. C. Hiemenz, R. Rajagopalan, *Principles of Colloid and Surface Chemistry*, 3rd Ed., Marcel Dekker, New York, 1997.

Chapter Legacy

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