# 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 $\mu$m in diameter and 2 $\mu$m 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 $\mu$m, 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

## KEY CONCEPTS 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<br>Pass through ultrafilter and semipermeable membrane<br>Undergo rapid diffusion | Oxygen molecules, ordinary ions, glucose |
| Colloidal dispersion | From 1 nm to 0.5 $\mu$m | Not resolved by ordinary microscope (although may be detected under ultramicroscope)<br>Visible in electron microscope<br>Pass through filter paper<br>Do not pass semipermeable membrane<br>Diffuse very slowly | Colloidal silver sols, natural and synthetic polymers, cheese, butter, jelly, paint, milk, shaving cream, etc. |
| Coarse dispersion | Greater than 0.5 $\mu$m | Visible under microscope<br>Do not pass through normal filter paper<br>Do not dialyze through semipermeable membrane<br>Do not diffuse | Grains of sand, most pharmaceutical emulsions and suspensions, red blood cells |

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

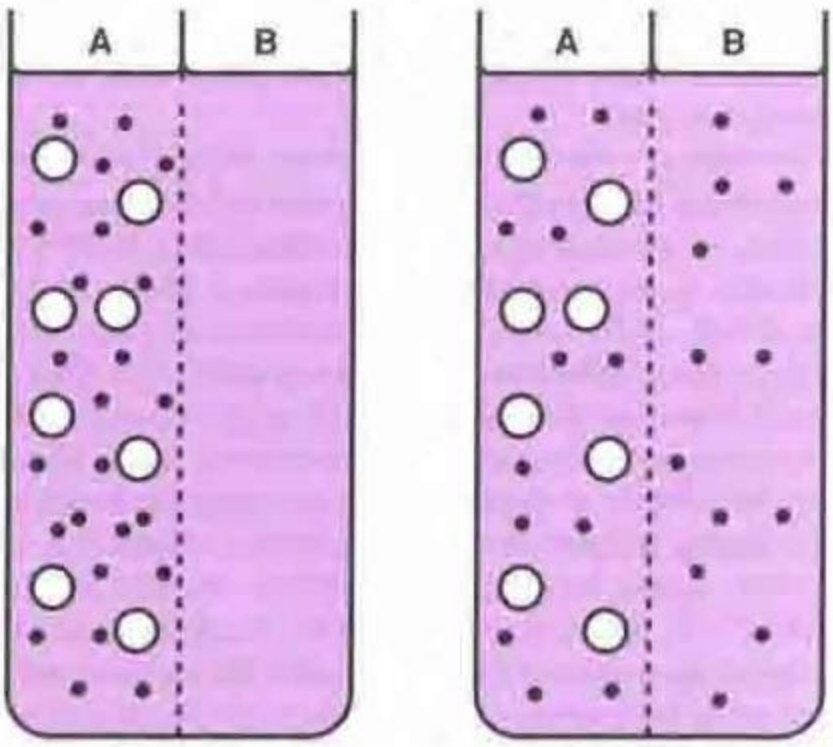


**Fig. 16–1.** Sketch showing the removal of electrolytes from colloidal material by diffusion through a semipermeable membrane. Conditions on the two sides, A and B, of the membrane are shown at the start and at equilibrium. The open circles are the colloidal particles that are too large to pass through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

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*.

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

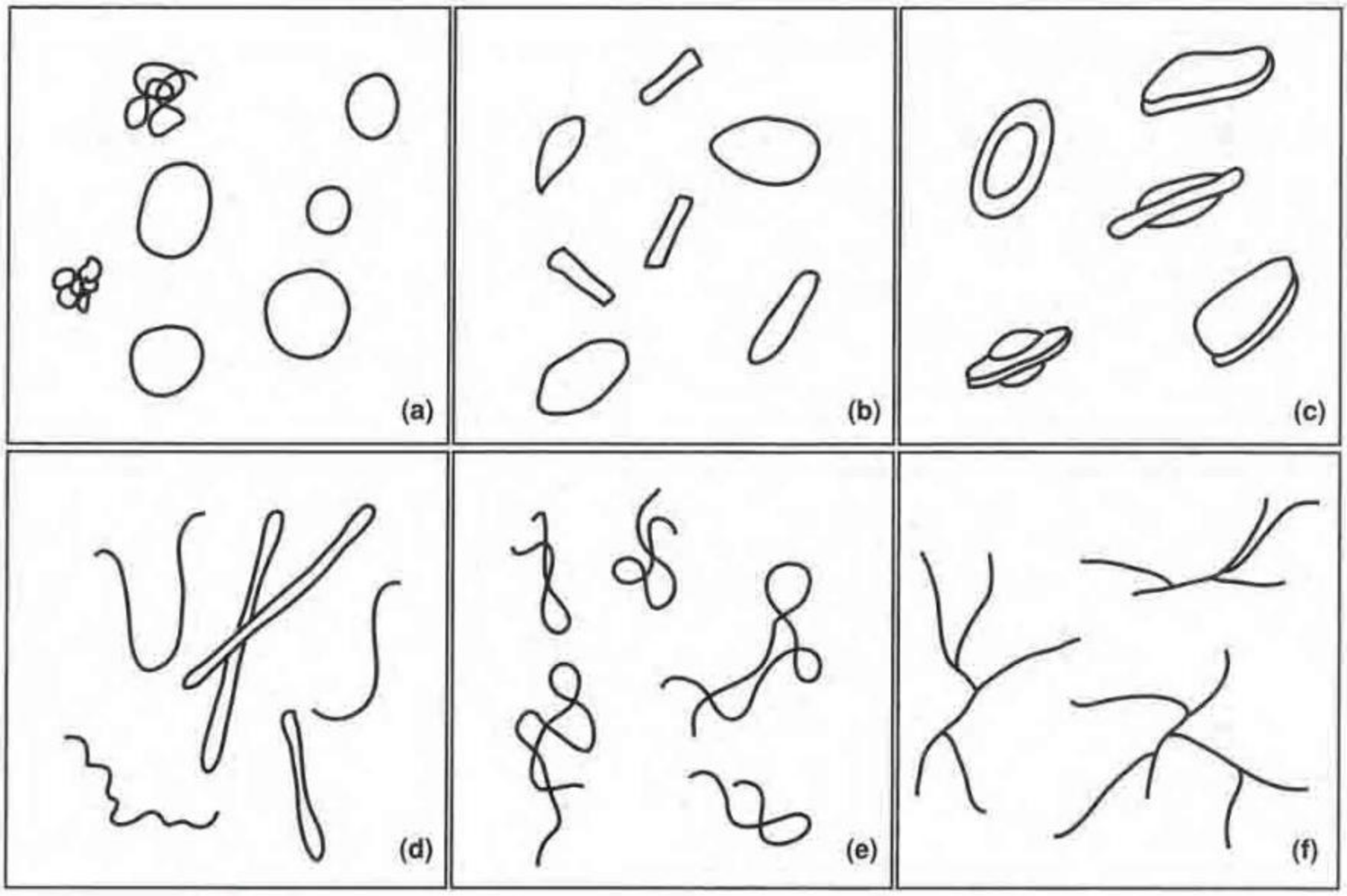


Fig. 16–2. Some shapes that can be assumed by colloidal particles: (*a*) spheres and globules, (*b*) short rods and prolate ellipsoids, (*c*) oblate ellipsoids and flakes, (*d*) long rods and threads, (*e*) loosely coiled threads, and (*f*) branched threads.

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.

## 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

## 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.

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.

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,

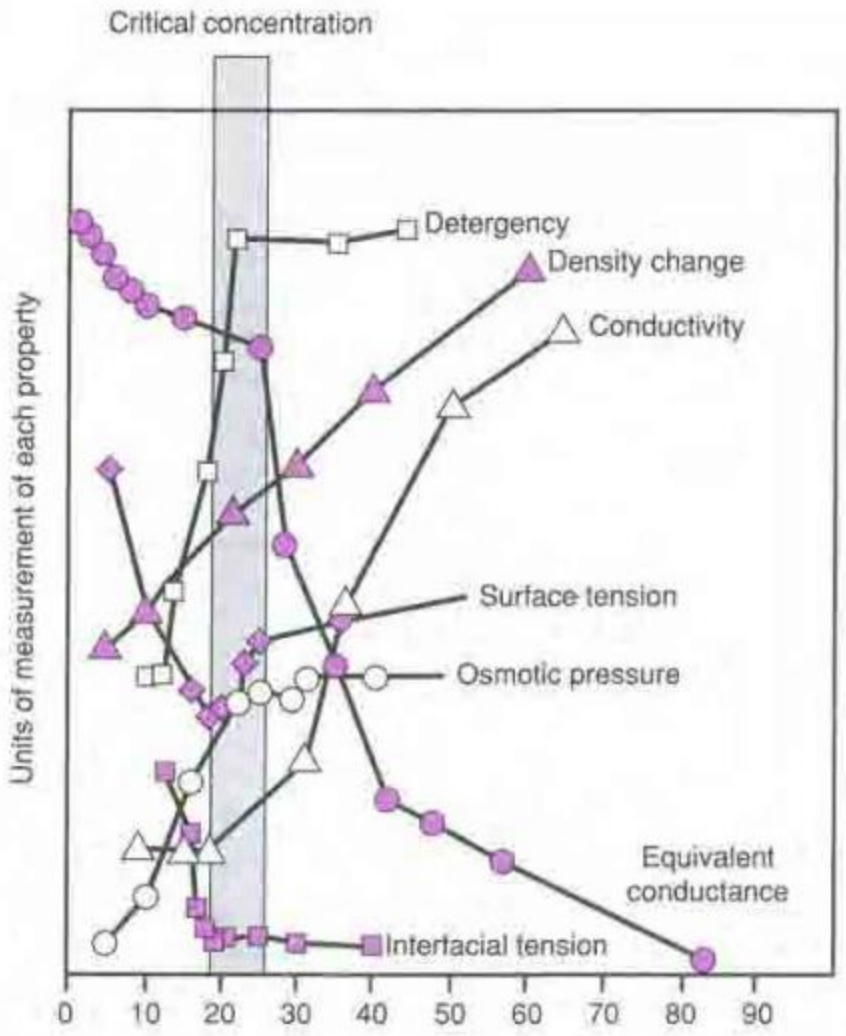


Fig. 16–3. Properties of surface-active agents showing changes that occur sharply at the critical micelle concentration. (Modified from W. J. Preston, Phys. Coll. Chem. **52**, 85, 1948.)

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.

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 16–4*a*** 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 expression[1]

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

**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 $\text{CMC}_1 = 8.1 \times 10^{-5}$ M (mole/liter) and its mole fraction is $x_1 = 0.75$; the CMC of DM is $\text{CMC}_2 = 15 \times 10^{-5}$ 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 $9.3 \times 10^{-5}$ 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

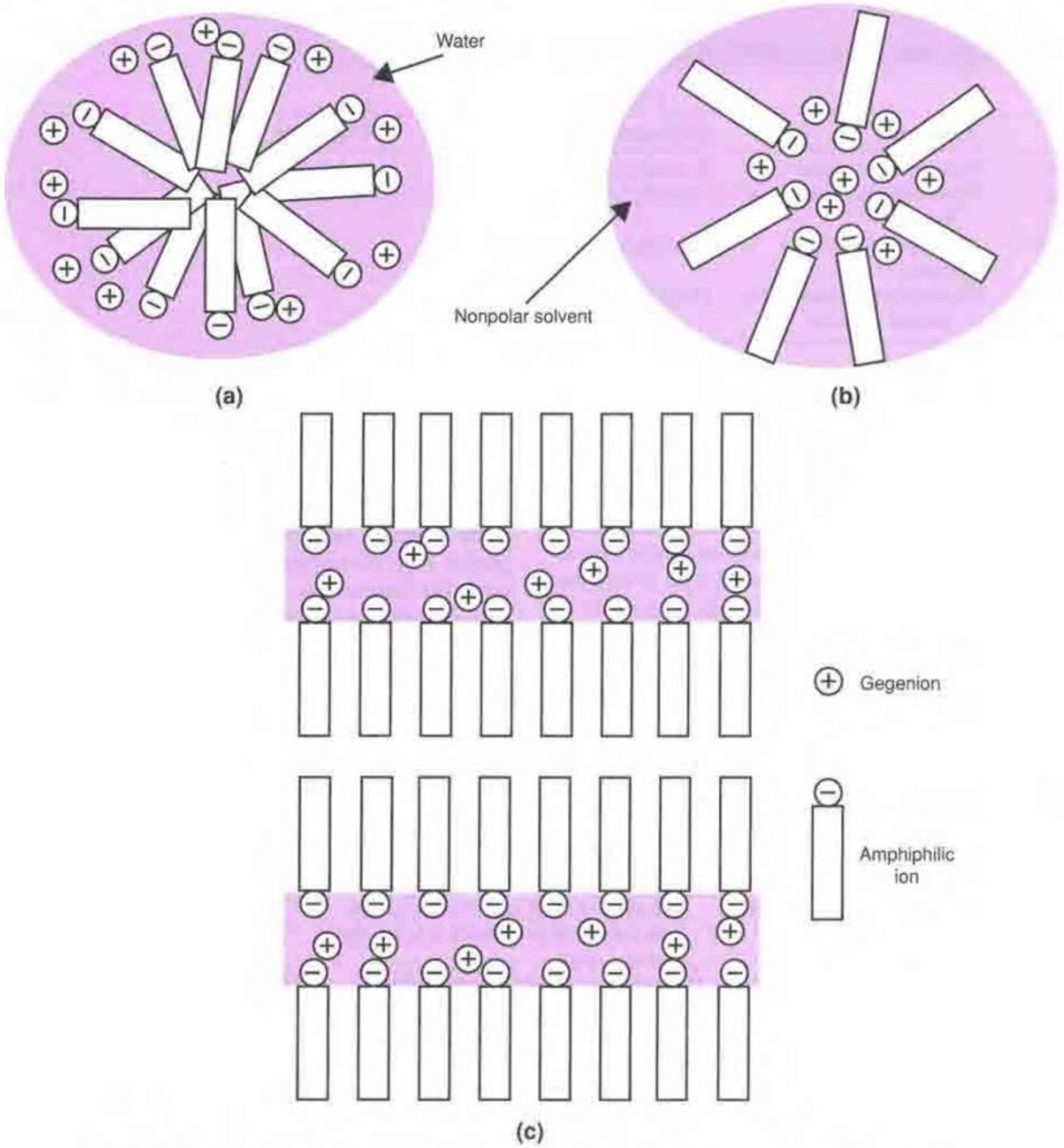


**Fig. 16–4.** Some probable shapes of micelles: (*a*) spherical micelle in aqueous media, (*b*) reversed micelle in nonaqueous media, and (*c*) laminar micelle, formed at higher amphiphile concentration, in aqueous media.

bright spots corresponding to particles can be observed and counted.

## 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.

**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 | Dimethyldodecylammonio-propane 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, $\tau$, 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.

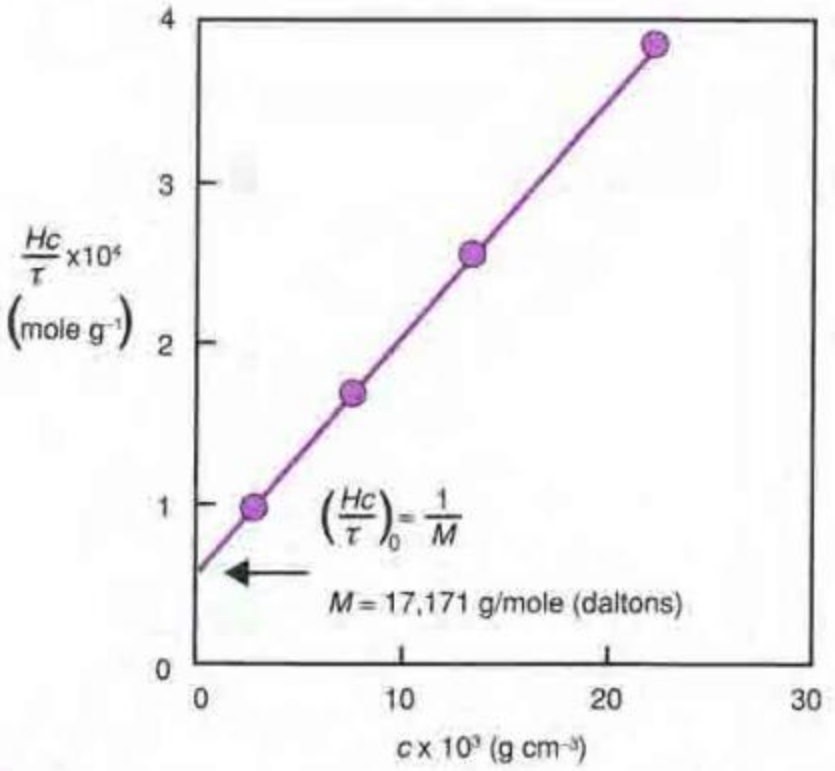


Fig. 16–5. A plot of $Hc/\tau$ against the concentration of a polymer (colloid).

where $\tau$ 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 $\lambda$ in $cm^{-1}$, $dn/dc$ is the change in refractive index with concentration at $c$, and $N$ is Avogadro's number. A plot of $Hc/\tau$ against concentration (**Fig. 16–5**) results in a straight line with a slope of $2B$. The intercept on the $Hc/\tau$ 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 Cardinal[2] 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, $c_{\text{monomer}} \cong \text{CMC}$. The concentration of micelles can therefore be written as

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

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

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

Accordingly, equation **(16–2)** is modified to

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

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 $H(c - c_{\text{CMC}})/(\tau - \tau_{\text{CMC}})$ versus $(c - c_{\text{CMC}})$. 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 Herrmann[5]:**

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

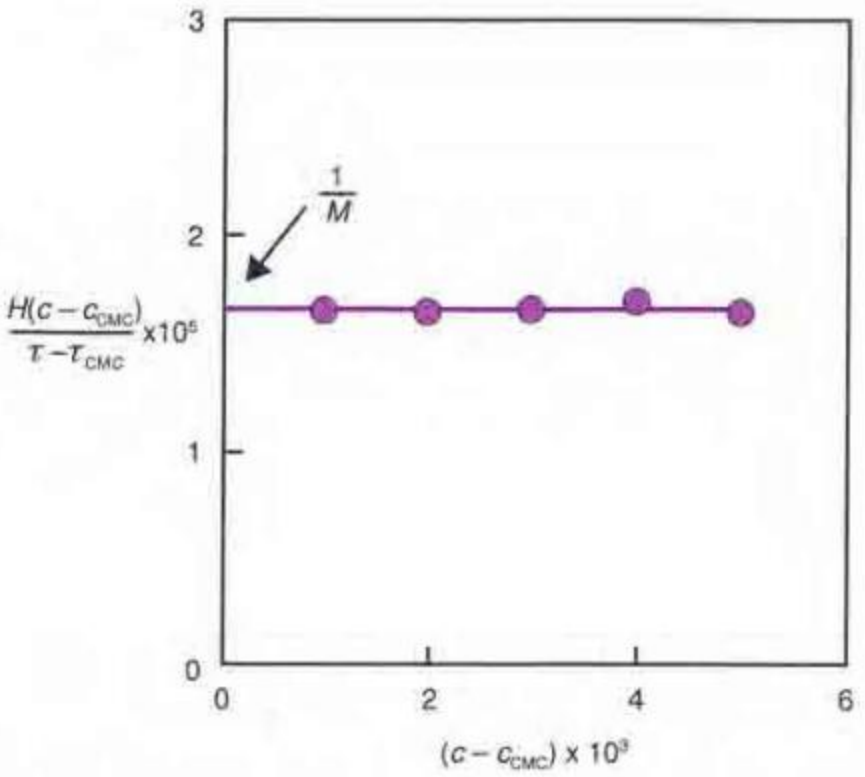


**Fig. 16–6.** A plot of $H(c - c_{CMC})/(\tau - \tau_{CMC})$ versus $(c - c_{CMC}) \times 10^3$ for a zwitterionic surfactant in which $B$ is zero. (From K. W. Hermann, J. Colloid Interface Sci. **22**, 352, 1966.)

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, $\lambda$ (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.

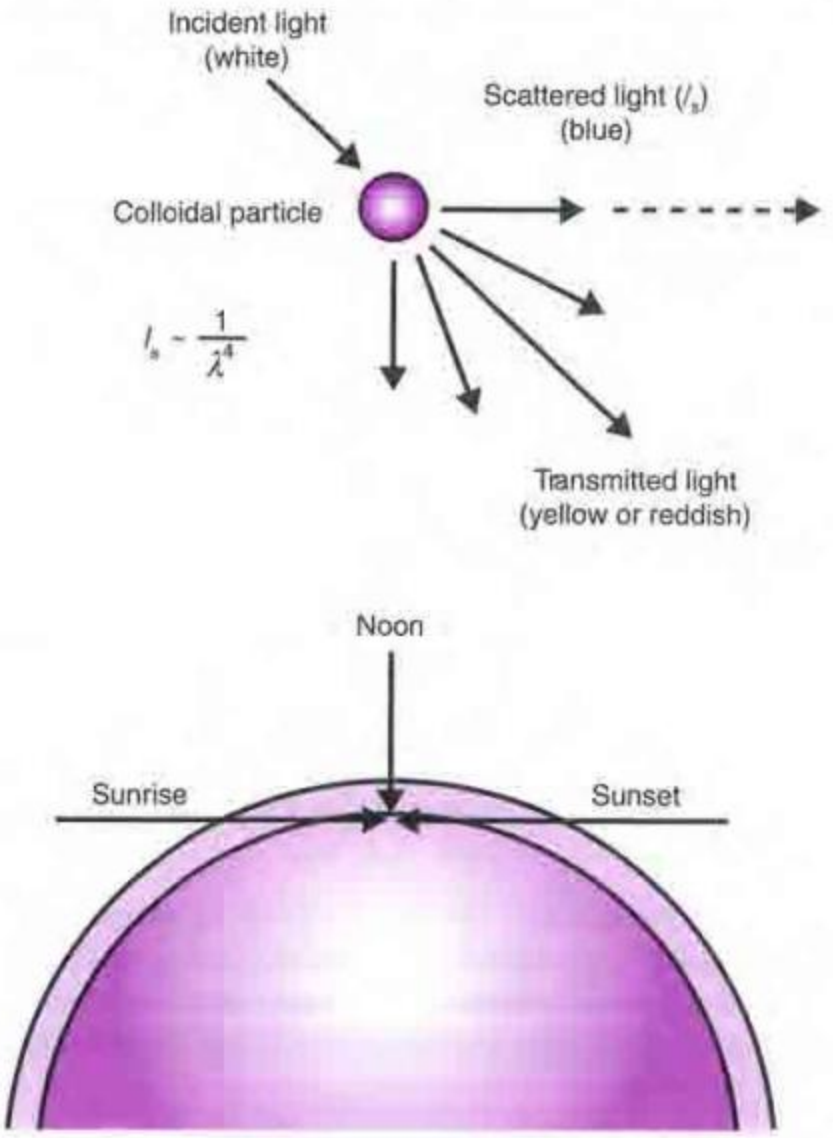


**Fig. 16–7.** Because of the constant motion of molecules, the atmosphere is inhomogeneous and constantly forms clusters with higher density of air. These inhomogeneities can be considered as colloidal particles, which scatter the light. The intensity of scattered light is inversely proportional to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

## 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.

### 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 $\mu$m, 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 Einstein[6], 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, $\eta$ 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 $\bar{v}$ 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 $7.0 \times 10^{-7}$ $cm^2$/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, $\pi$, 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 $\pi/c_g$ 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]

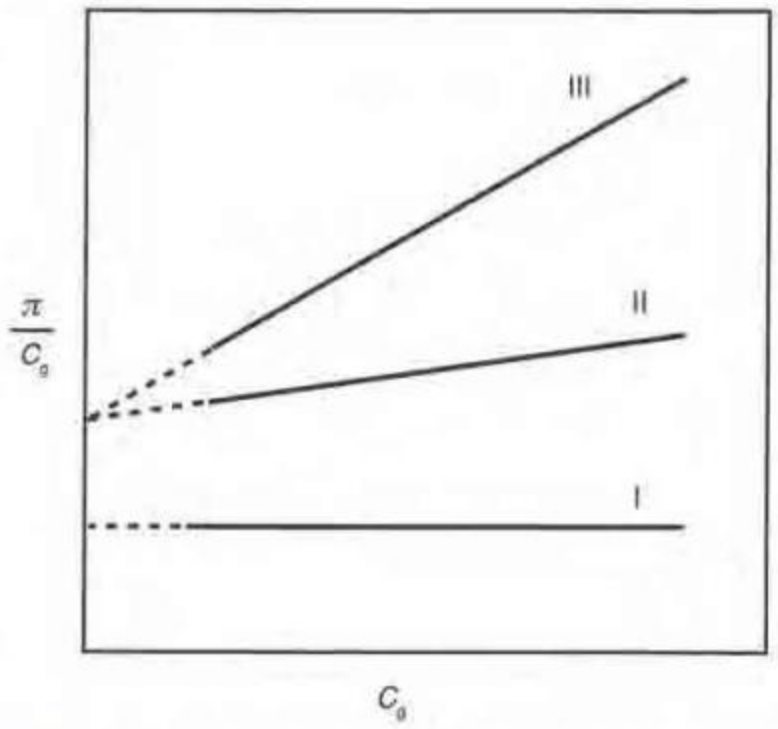


Fig. 16–8. Determination of molecular weight by means of the osmotic pressure method. Extrapolation of the line to the vertical axis where $c_g = 0$ gives $RT/M$, from which $M$ is obtained. Refer to text for significance of lines I, II, and III. Lines II and III are taken to represent two samples of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

A plot of $\pi/c_g$ 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:

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

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 $\pi/c_g$ 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 $3.623 \times 10^{-4}$ liter atm/g, and the slope of the line is $1.80 \times 10^{-6}$ 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 $4.75 \times 10^{-9}$ 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 $\rho$ in a medium of density $\rho_0$ and a viscosity $\eta_0$ is given by *Stokes's law*:

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

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 $\mu$m. 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

$$\text{Angular acceleration} = \omega^2 x$$

$$= \left(\frac{1500 \text{ revolutions}}{\text{minute}} \times \frac{2\pi}{60}\right)^2 \times 7.5 \text{ cm}$$

$$= 1.851 \times 10^5 \text{ cm/sec}^2$$

$$\text{Number of } g\text{'s} = \frac{1.851 \times 10^5 \text{ cm/sec}^2}{981 \text{ cm/sec}^2} = 188.7 \text{ } g\text{'s}$$

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* $s$,

$$s = \frac{dx/dt}{\omega^2 x} \tag{16–15}$$

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

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

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 $\omega$ is equal to $2\pi$ 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

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

where $R$ is the molar gas constant, $T$ is the absolute temperature, $\bar{v}$ is the partial specific volume of the protein, and $\rho_0$ 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 $1.7 \times 10^{-13}$ sec, the diffusion coefficient, $D$, is $15 \times 10^{-7}$ cm²/sec, the partial specific volume, $\bar{v}$, of the gum is 0.72 cm³/g, and the density of water at 20°C is 0.998 g/cm³. Compute the molecular weight of methylcellulose. The gas constant $R$ is $8.31 \times 10^7$ erg/(deg mole).

We have

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

Kirschbaum[9] reviewed the usefulness of the analytic ultracentrifuge and used it to study the micellar properties of drugs (**Fig. 16–9**). Richard[10] 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**.

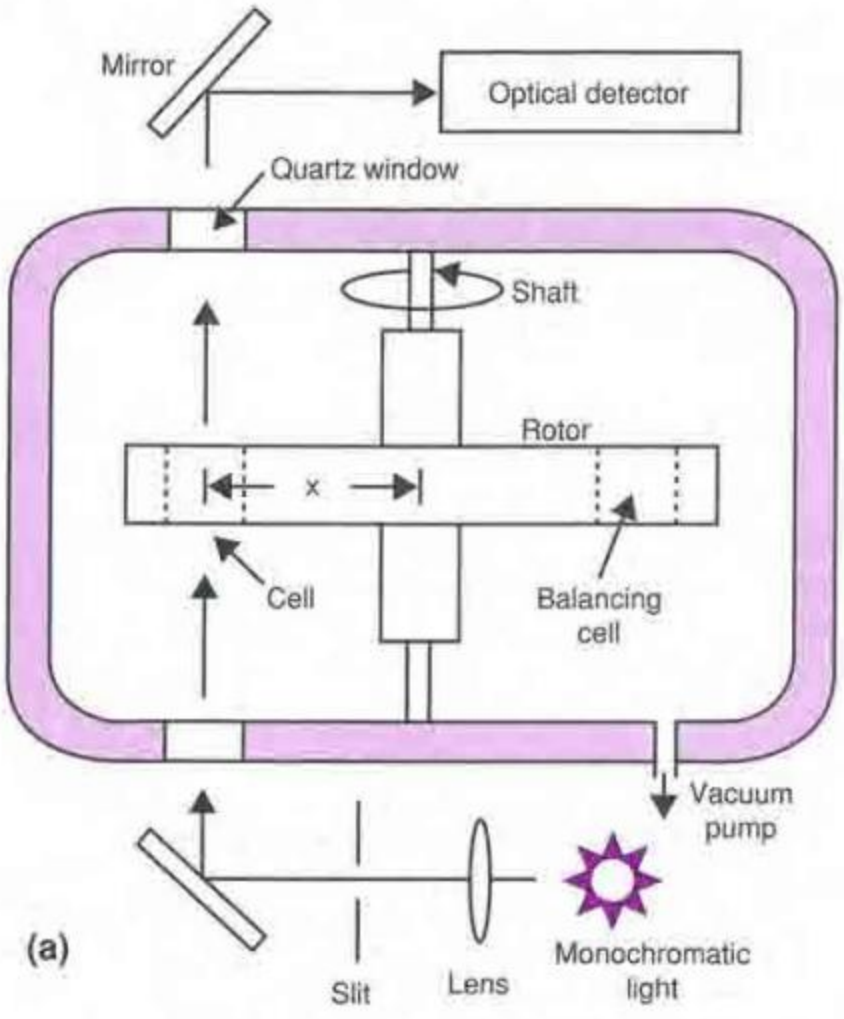


**Fig. 16–9.** (*a*) Schematic of an ultracentrifuge. (*b*) Centrifuge cell. (From H. R. Allok and F. W. Lampe, *Contemporary Polymer Chemistry*, Prentice-Hall, Englewood Cliffs, N. J., 1981, pp. 366, 367. With permission.)

## 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***

| | Molecular Weight | | |
|---|---|---|---|
| **Material** | **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, $\eta_0$ is the viscosity of the dispersion medium and $\eta$ is the viscosity of the dispersion when the volume fraction of colloidal particles present is $\phi$. 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 $\eta_0$ and $\eta$ can be determined using a capillary viscometer.

Several viscosity coefficients can be defined with respect to this equation. These include *relative viscosity* ($\eta_{rel}$), *specific viscosity* ($\eta_{sp}$), and *intrinsic viscosity* ($\eta$). From equation **(16–18)**,

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

and

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

or

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

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

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

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

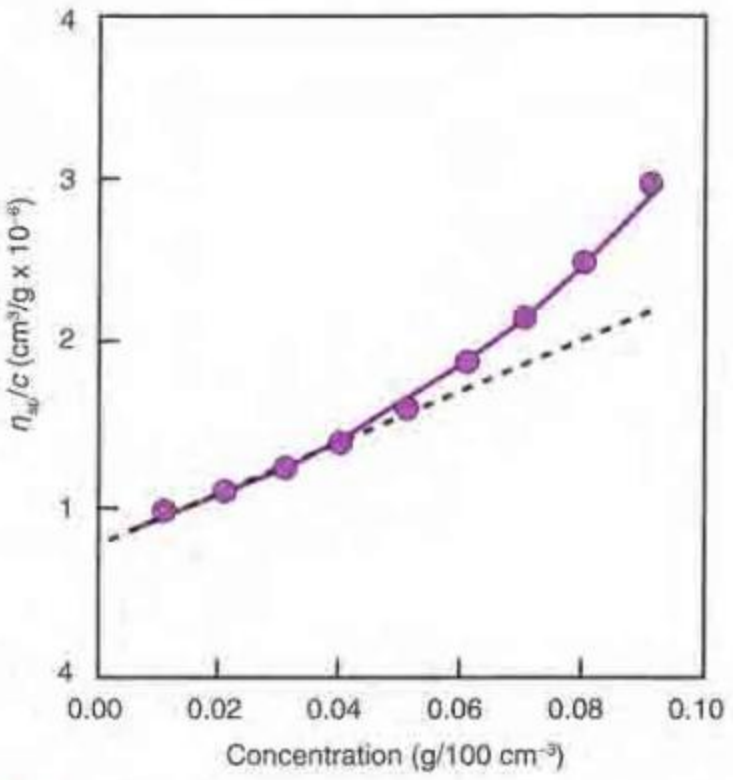


**Fig. 16–10.** Determination of molecular weight using viscosity data. (Replotted from D. R. Powell, J. Swarbrick, and G. S. Banker, J. Pharm. Sci. **55**, 601, 1966. With permission.)

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

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

By determining $\eta$ at various concentrations and knowing $\eta_0$, one can calculate $\eta_{sp}$ from equation **(16–20)**. If $\eta_{sp}/c$ 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,

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

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 scattering[12]), and other analytic tools[13] 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

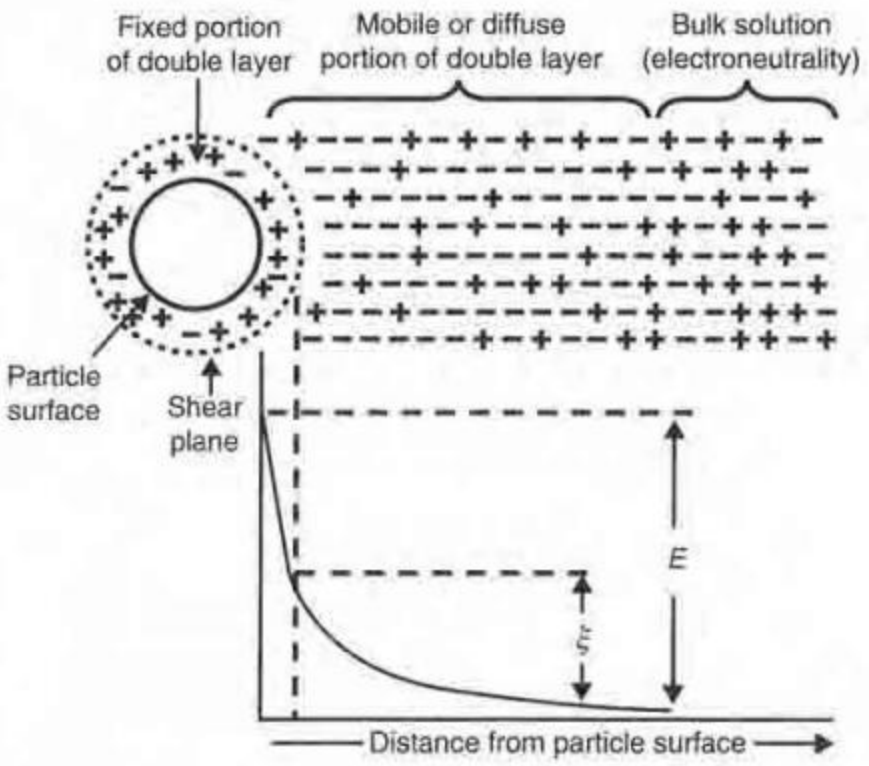


**Fig. 16–11.** Diffuse double layer and the zeta potential.

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.

## 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 16–12** illustrates 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, $\zeta$, 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, $\eta$, in poises (dynes sec/cm$^2$), the dielectric constant of the medium, $\varepsilon$, 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 $= 3 \times 10^9$ 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 statcoulomb$^2$/(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

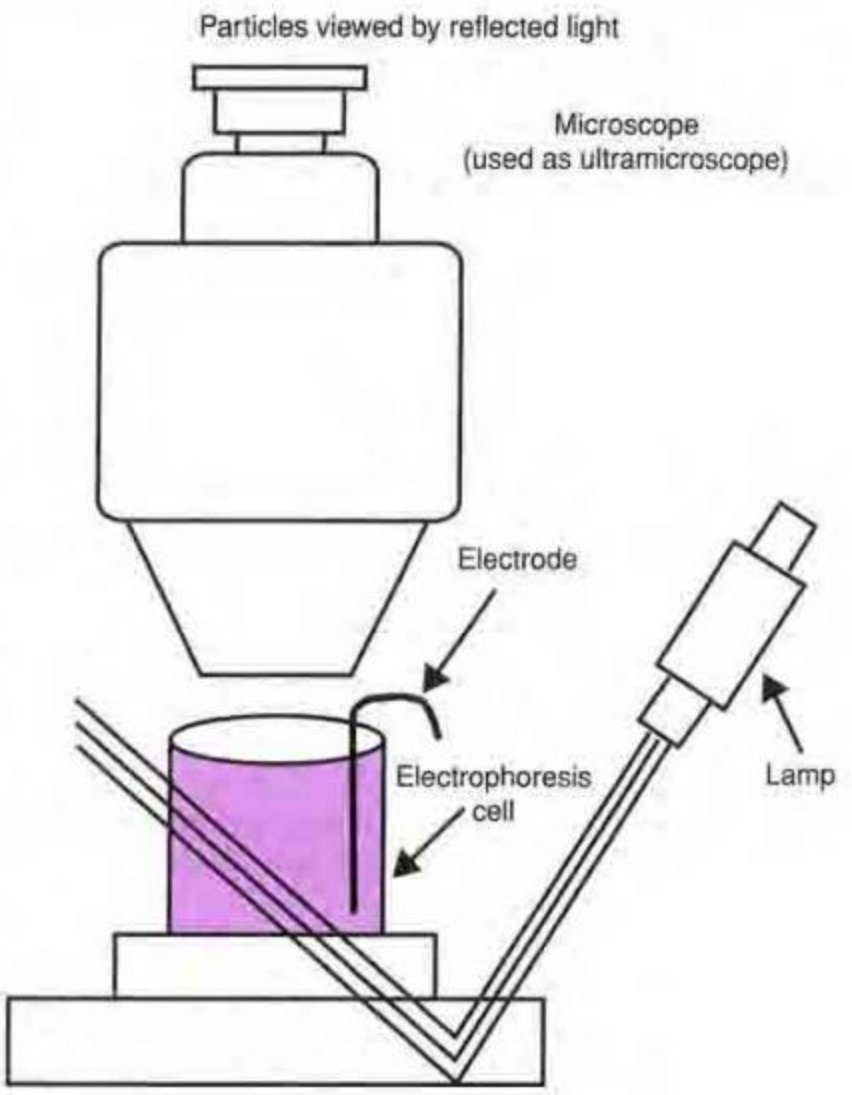


**Fig. 16–12.** Principle of zeta potential measurement (based on the zeta meter) showing the ultramicroscope and the flow cell.

= 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 $300 \times 300 = 9 \times 10^4$ converts electrostatic units to volts.

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

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

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

**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 in Figure 16–12 and was found to be $16.5 \times 10^{-4}$ 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.

Schott[14] studied the electrokinetic properties of magnesium hydroxide suspensions that are used as antacids and laxatives. The zero point of charge occurred at pH $\cong$ 10.8, the zeta potential, $\zeta$, of magnesium hydroxide being positive below this pH value. Increasing the pH or hydroxide ion concentration produced a change in the sign of $\zeta$ from positive to negative, with the largest negative $\zeta$ value occurring at pH 11.5.

Takenaka and associates[15] 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,

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

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,

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

and inside,

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

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

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

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

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 $\sqrt{[R^-]_i}$. 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,

$[D^-]$:

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

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 $1.2 \times 10^{-2}$ g equivalent/liter and the equilibrium concentration of sodium salicylate is $6.0 \times 10^{-3}$ 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 Overbeek[17] and Derjaguin and Landau[18] 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

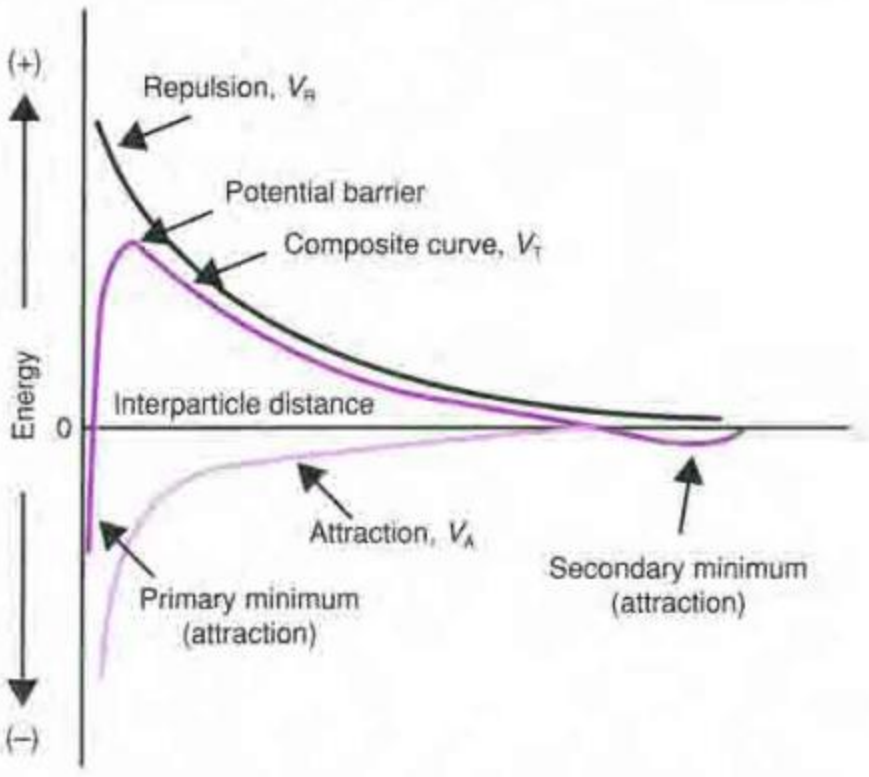


**Fig. 16–13.** Potential energy versus interparticle distance for particles in suspension.

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.

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 Dieckhoff[25] solubilized 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. Lawrence[26] 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 suggestion[28] 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.

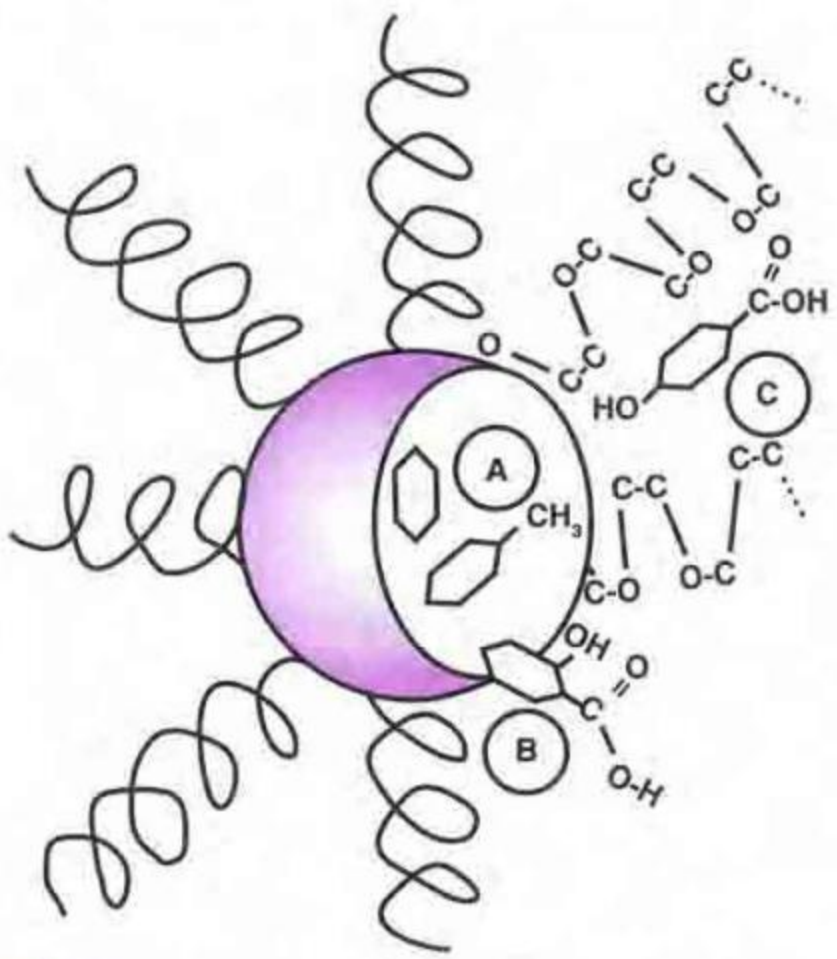


Fig. 16–14. A spherical micelle of nonionic surfactant molecules. (A) A nonpolar molecule solubilized in the nonpolar region of the micelle. (B) A more polar molecule found partly embedded in the central region and partially extending into the palisade region. (C) A polar molecule found lying well out 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]

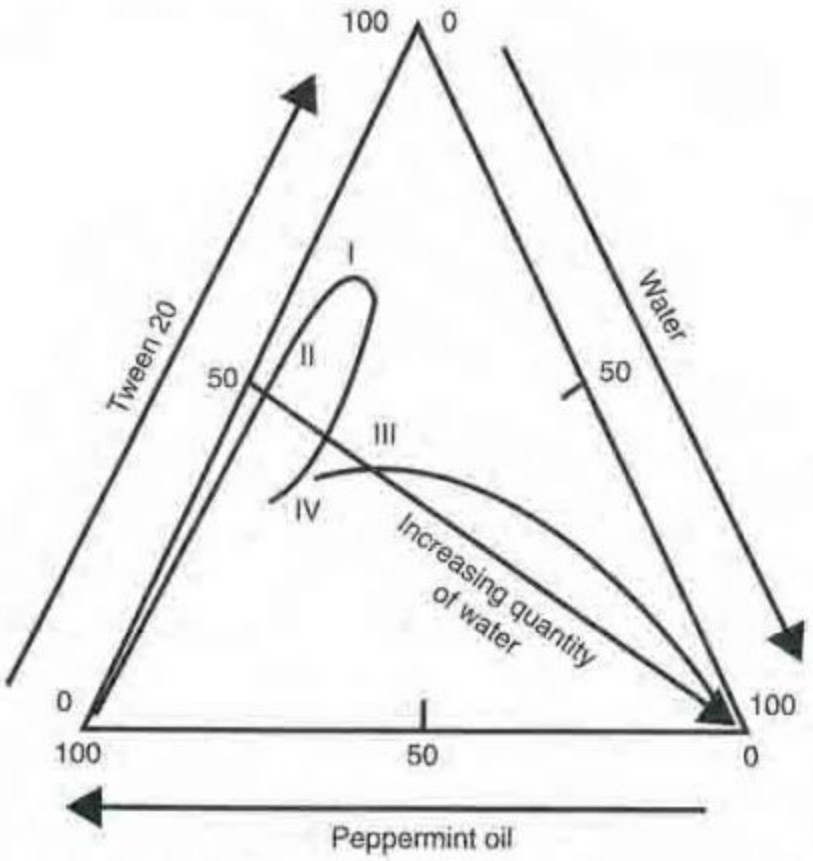


Fig. 16–15. Phase diagram for the ternary system water, Tween 20, and peppermint oil.

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*).

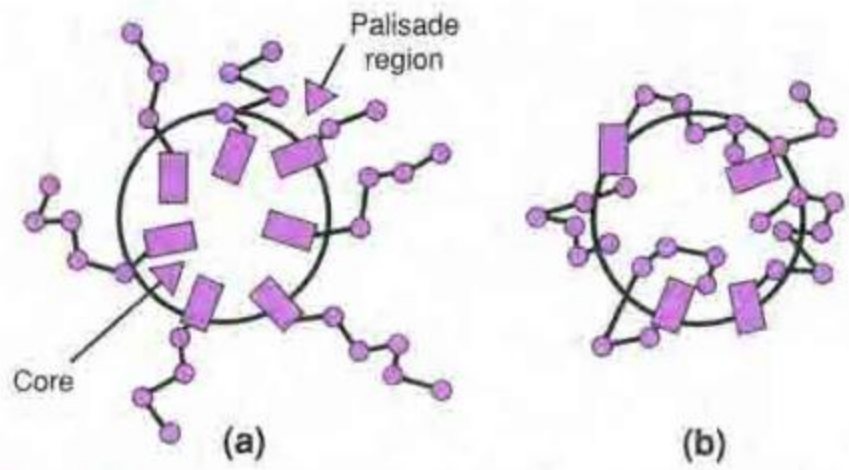


Fig. 16–16. Schematic of nonionic micelle of *n*-polyoxyethylene glycol monoether showing the intrusion of polyoxyethylene chains into the micelle core. (*a*) Micelle with palisade environment intact. (*b*) Palisade layer partially destroyed by loss of polyoxyethylene groups into the hydrophobic core.

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 testing[34] 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

## 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.

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

## 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.

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 16–5**[38]). 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

**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 $\mu$m | 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 $\mu$m | Microparticles | Polystyrene, poly(lactide) microspheres | Targeted delivery of therapeutics |
| 0.15–2 $\mu$m | 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.

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.[40] These 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 $\mu$m), 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.[54] This 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.[56] Larson 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 in Chapter 23 as well.

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

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## Recommended Readings

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P. C. Hiemenz, R. Rajagopalan, *Principles of Colloid and Surface Chemistry*, 3rd Ed., Marcel Dekker, New York, 1997.

### CHAPTER LEGACY

**Fifth Edition**: published as Chapter 17 (Colloids). Updated by Tamara Minko.

**Sixth Edition**: published as Chapter 16 (Colloidal Dispersions). Updated by Patrick Sinko.

CHAPTER

# 3 Pharmaceutical Rheology

*Rheology* (derived from Greek *rheos* meaning 'flow' and *logos* meaning 'science') is the study of the flow or deformation of matter under the influence of stress. Rheology can be applied to solids (completely resistant to deformation), liquids (moderately resistant to deformation) and gases (completely nonresistant to deformation).

In pharmaceutical technology, rheological measurements are involved in the following:

1. Pharmaceutical processing operations such as mixing of materials, filling and packaging into containers
2. Removal of product from package such as pouring from a bottle, extrusion from a tube, spraying liquids from atomizers and passage from syringe needle
3. Topical application of product onto skin
4. Physical stability of suspensions, emulsions and semisolids
5. Bioavailability, since viscosity has been shown to affect the absorption rate of drugs
6. Release of drug from dosage forms and delivery systems

## FUNDAMENTAL CONCEPTS

### Elastic Deformation and Viscous Flow

The deformation of matter under influence of force or stress can be described by two components namely (1) elasticity and (2) viscosity.

#### *Elasticity*

Pure *elasticity* is achieved if the shape of the body is restored once the force is withdrawn. Elasticity is the property of solid materials and Hooke's law is used to describe the elastic deformation of solids.

### *Hooke's law of elasticity*

If stress is directly proportional to strain, the body returns to its original shape and size, after the stress applied has been relieved. The proportionality between stress and strain is quantified by the constant known as the *modulus of elasticity* or *Young's modulus* ($E$) (unit: pascal).

$$dl = \frac{\sigma}{E} \tag{3.1}$$

where $\sigma$ is the applied stress and $dl$ the elastic deformation or strain caused by the application of stress.

## *Viscosity*

Pure *viscosity* or pure viscous flow occurs if there is continuous movement during the applied force, and no restorative motion occurs once the force is withdrawn. Viscosity is the property of liquid materials to undergo permanent or irreversible deformation and is explained by Newton's law of viscous flow.

### *Newton's law of viscous flow*

To understand the fundamental components of viscous flow, consider Figure 3.1. Two parallel planes are a distance $dx$ apart; the viscous body is confined between the planes. When force, $F$, is applied the top, plane A, moves horizontally with a velocity $dv$ but the lower plane B remains motionless. As a consequence, there exists a velocity gradient $dv/dx$ between the planes. This velocity gradient over a distance is known as the *rate of shear*, $D$ ($dv/dx$). The horizontal force per unit area ($F/A$) creating the deformation is known as the *shear stress*, $S$ ($F/A$). According to Newton's law of viscous flow:

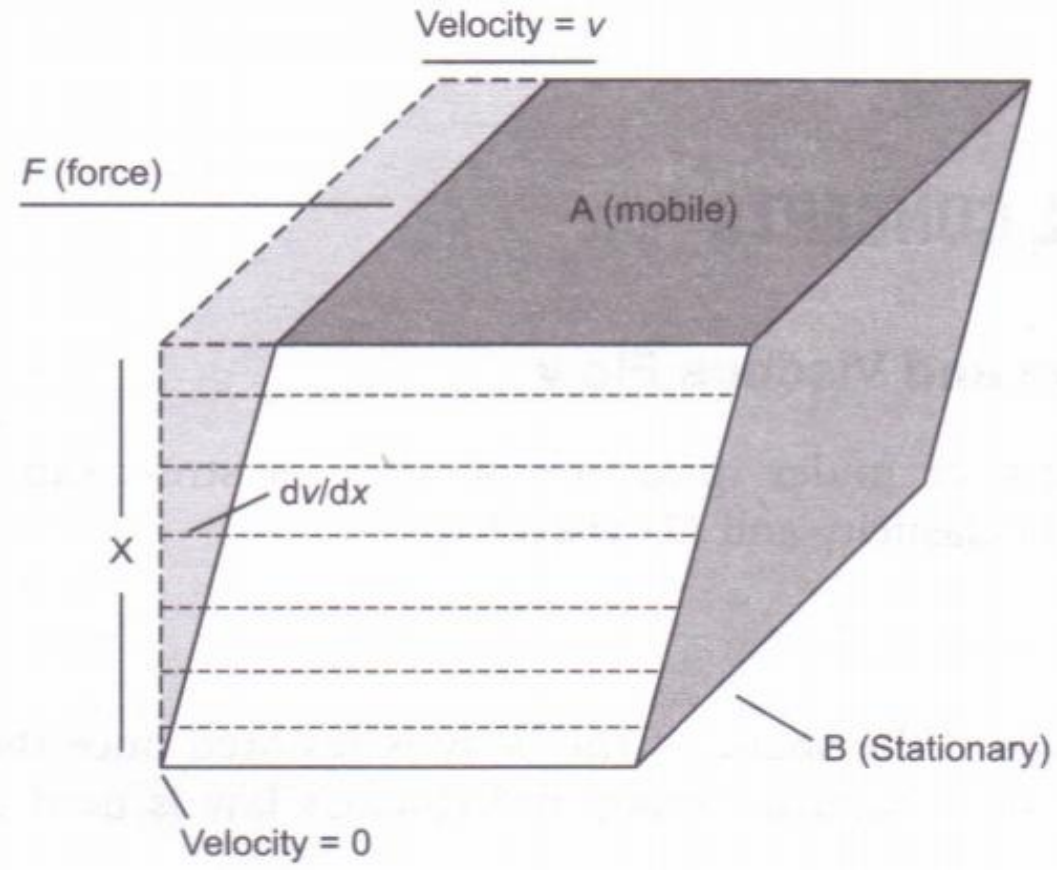


**Figure 3.1** Model demonstrating the components of classic viscous flow.

$$\frac{F}{A} \alpha \frac{dv}{dx}$$

$$\frac{F}{A} = \eta \frac{dv}{dx} \tag{3.2}$$

$$S = \eta D \tag{3.3}$$

where $\eta$ is the constant of proportionality, known as *viscosity* or *coefficient of viscosity*.

*Viscosity* is the internal friction in the fluid, i.e. resistance to the relative motion of the adjacent layers of a liquid. Conventionally, viscosity is represented by $\eta$. Then rearranging Eq. (3.3) we get:

$$\eta = \frac{S}{D}$$

Viscosity is defined as the tangential force per unit area, in dyne per $cm^2$, required to maintain a velocity difference of 1 cm/s between two parallel layers of liquid that are 1 cm apart.

The unit of viscosity can be derived as follows:

$$\eta = \frac{S}{D}$$

$$\text{Shear stress} = \frac{F}{A} = \frac{\text{dyne}}{\text{cm}^2}$$

$$\text{Rate of shear, } \frac{dv}{dx} = \frac{(\text{cm/s})}{\text{cm}} = \text{s}^{-1}$$

Therefore, the unit of viscosity in the cgs system is

$$\text{Unit of viscosity} = (\text{dyne/cm}^2)\text{s}^{-1}$$

Since dyne = g cm/$s^2$,

$$\text{Units of viscosity} = \left\{\frac{[\text{g cm/s}^2]\text{s}}{\text{cm}^2}\right\} = \text{g cm}^{-1}\text{s}^{-1} = \text{poise}$$

For dilute aqueous solutions, the common unit becomes the centipoise ($10^{-2}$ poise), cp. The viscosity of water is about 1 cp. The SI unit of viscosity is pascal second. One pascal second is equal to 10 poise.

### Example 3.1 (Rate of shear and shearing stress)

Determine the rate of shear and shearing stress if the oil is rubbed onto the skin with 15 cm/s as relative rate of motion and the film thickness of 0.01 cm. The oil had the same viscosity as that of water.

### Solution

$$\text{Rate of shear} = \frac{dv}{dx} = \frac{15 \text{ cm/s}}{0.01 \text{ cm}} = 1500 \text{ s}^{-1}$$

According to Eq. (3.3)

$$\eta = \frac{S}{D}$$

Viscosity of water = $1 \times 10^{-2}$ poise

$$1 \times 10^{-2} \text{ poise} = \frac{S}{1500} \text{ s}^{-1}$$

Then, $S = (1500)(1 \times 10^{-2})(\text{s}^{-1})(\text{poise}) = 15\ (\text{s}^{-1})(\text{dyne s cm}^{-2}) = 15 \text{ dyne cm}^{-2}$

*Fluidity* is the reciprocal of viscosity and is usually designated by the symbol $\phi$.

$$\phi = \frac{1}{\eta} \tag{3.4}$$

*Kinematic viscosity* ($v$) is the Newtonian viscosity (or absolute viscosity) divided by the density of a liquid at a particular temperature.

$$v = \frac{\eta}{\rho} \tag{3.5}$$

The units of kinematic viscosity are stoke (s) and centistoke (cs).

### Example 3.2 (Kinematic viscosity)

Determine the kinematic viscosity of the oil having viscosity $1 \times 10^{-2}$ poise and a density of 0.82.

### Solution

$$v = \frac{\eta}{\rho} = \frac{0.01}{0.82}$$

$$= 1.22 \times 10^{-2} \text{ stokes} = 1.22 \text{ centistokes}$$

## Temperature Dependence of Viscosity

Viscosity of liquids falls with rise in temperature, whereas that of gases rises with rise in temperature. In liquids, the fall in viscosity is due to decrease in the intramolecular forces of attraction. The variation of viscosity with temperature is expressed by an equation analogous to the Arrhenius equation of chemical kinetics:

$$\eta = Ae^{Ev/RT} \tag{3.6}$$

where $A$ is a constant depending on the molecular weight and molar volume of the liquid, $Ev$ the activation energy necessary to initiate flow between the molecules and $R$ the gas constant (1.9872 cal $mol^{-1}$ $K^{-1}$).

Based on Newton's law of viscous flow, fluids are classified as Newtonian and non-Newtonian. Fluids that follow Newton's law of viscous flow are called *Newtonian fluids*, whereas non-Newtonian fluids do not follow it. The classification of fluids based on their rheological behaviour is shown in Figure 3.2.

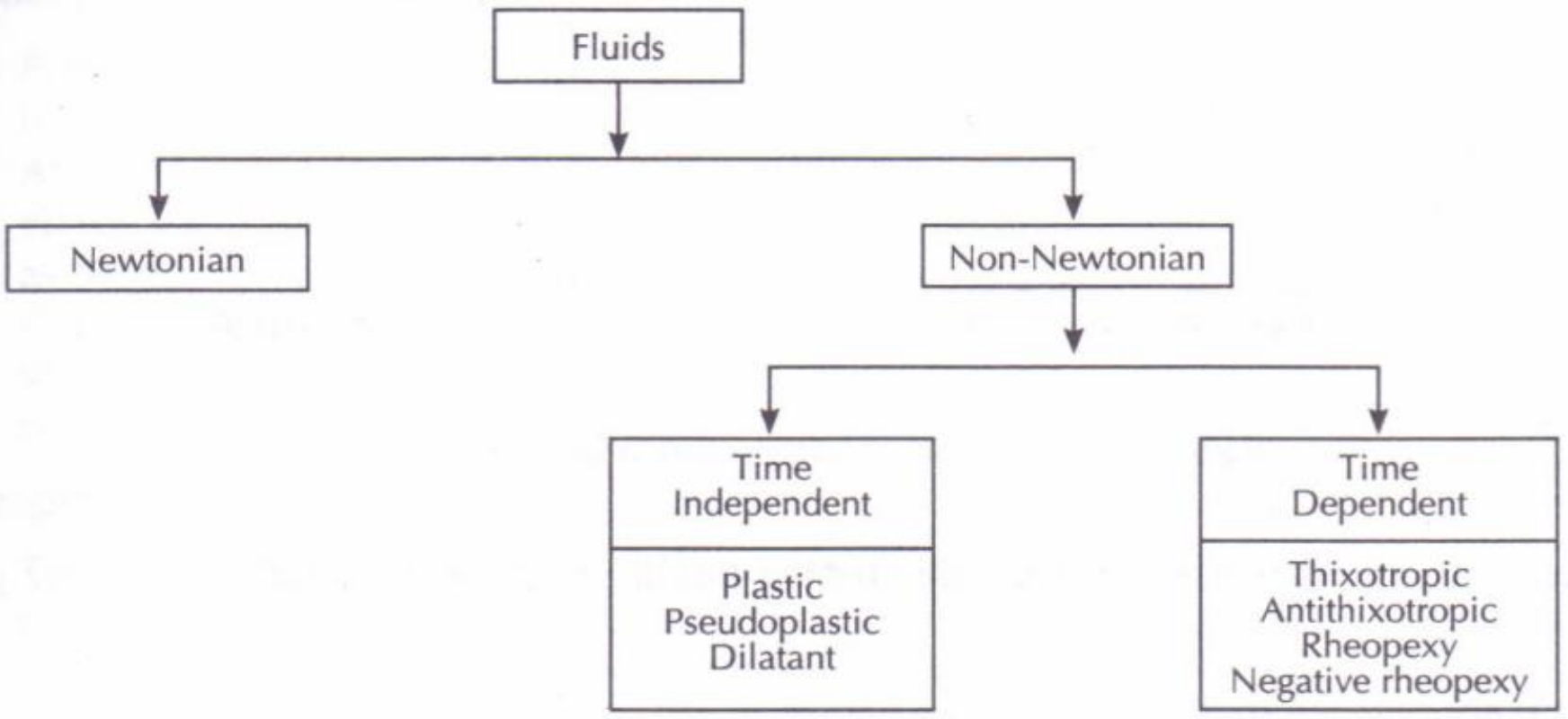


**Figure 3.2** Classification of fluids based on rheological behaviour.

## NEWTONIAN FLUIDS

**HIGHLIGHTS**

**Rheogram:** Plot of rate of shear as a function of shear stress.
**Viscogram:** Plot of rate of shear as a function of viscosity.

1. Simple liquids, either pure chemicals or solutions of lower-molecular-weight compounds, are Newtonian fluids in which a direct proportionality exists, for all values of shear, between shear stress and shear rate.
2. Viscosity of such fluids is independent of the rate of shear but depends on composition, pressure and temperature.

### Rheogram and viscogram

1. For Newtonian fluids, the rheogram is linear and passes through the origin, indicating that minimal shear applied will induce shear (see Figure 3.3a).
2. The slope of such a curve is the *fluidity* and the inverse of slope is the *viscosity* of the fluid.
3. Shear stress and shear rate are directly proportional and therefore a single viscometric point can characterize the liquid rheology.
4. For Newtonian fluids, the viscogram is a straight line parallel to the axis of rate of shear, indicating that Newtonian viscosity is independent of the rate of shear (see Figure 3.3b).

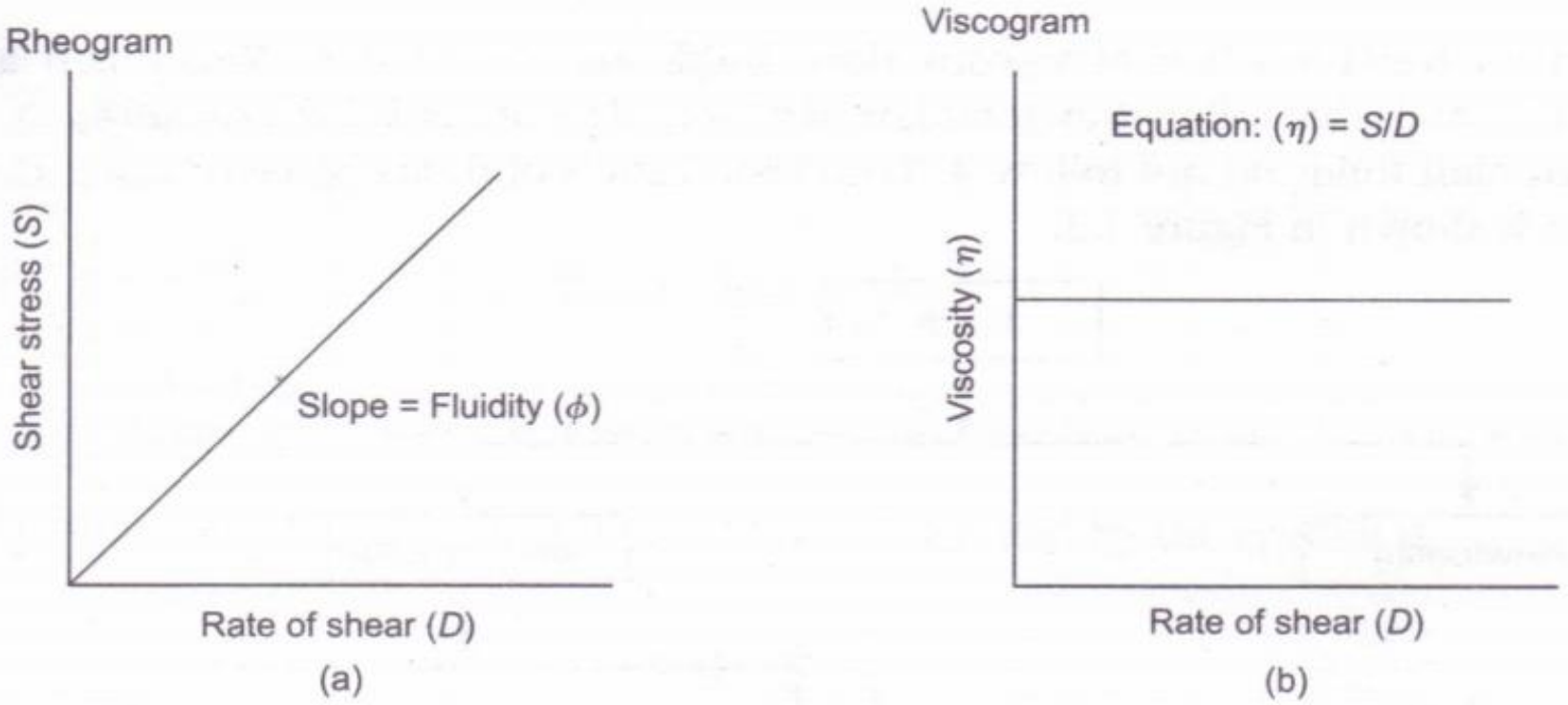


**Figure 3.3** (a) Rheogram and (b) viscogram for Newtonian fluid.

The absolute viscosities of some Newtonian liquids of pharmaceutical interest are given in Table 3.1.

**Table 3.1** Absolute viscosities of Newtonian liquids at 20°C

| Liquid | Absolute viscosity (at 20°C), centipoise |
|---|---|
| Ethyl ether | 0.24 |
| Acetone | 0.34 |
| Chloroform | 0.563 |
| Water | 1.0019 |
| Absolute ethanol | 1.20 |
| Ethanol, 40% w/w | 2.91 |
| Olive oil | 100.0 |
| Glycerin, 95% w/w | 545.0 |
| Castor oil | 1000.0 |

# NON-NEWTONIAN FLUIDS

Non-Newtonian fluids are fluids with no direct linear relationship between shear stress and shear rate, i.e. they do not follow Newton's law of flow. The rheological behaviour of non-Newtonian fluids may be characterized as either time independent or time dependent.

# TIME-INDEPENDENT NON-NEWTONIAN FLUIDS

1. These fluids instantaneously adapt to changing shear stress.
2. Time-independent non-Newtonian fluid behaviour can be of three types: plasticity, pseudoplasticity and dilatancy.

## *Plasticity*

1. Plastic materials or Bingham plastics require an initial finite force, called *yield value*, before any rheological flow can start.
2. At shear stress values below the yield value, such plastic materials substances behave as elastic solids exhibiting reversible deformation, and above the yield value, they behave as Newtonian systems.
3. Concentrated flocculated suspensions (e.g. concentrated zinc oxide suspension) and semisolid dosage forms, such as gels, creams and ointments, are examples of plastic materials.

### *Rheogram and viscogram*

1. The rheogram of a Bingham plastic is represented by a straight line or curve on the stress–shear rate plot being displaced from the origin by the yield value (see Figure 3.4a).
2. The slope of the linear portion is known as *mobility*, which is the inverse of plastic viscosity.

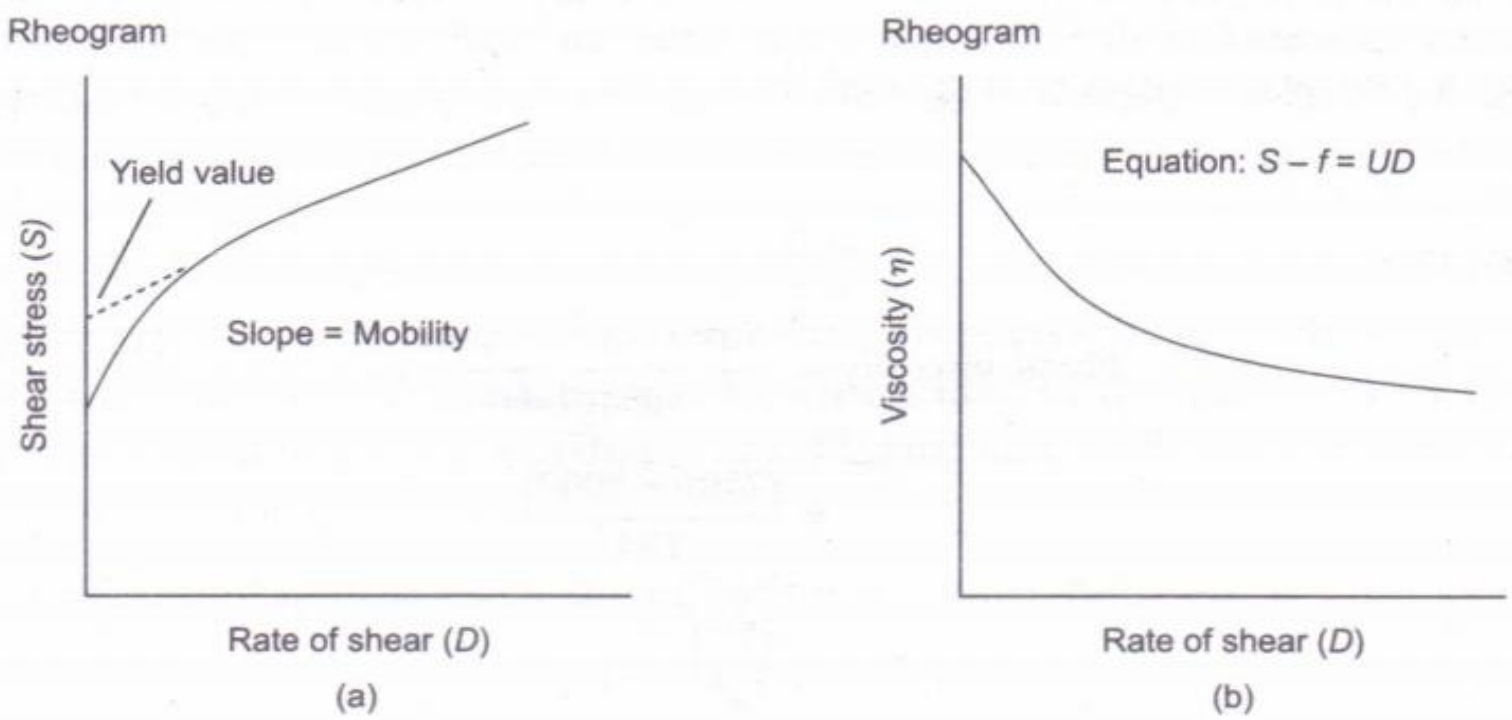


**Figure 3.4** (a) Rheogram and (b) viscogram for plastic flow.

Thus, for Newtonian behaviour at stresses ($S$) greater than the yield value ($f$), we have

$$S - f = UD \tag{3.7}$$

where $U$ is the plastic viscosity and $D$ the shear rate. Plastic viscosity is defined as the shearing stress in excess of yield value that has to be applied to induce a unit rate of shear.

### Reason

Plasticity is often exhibited by concentrated flocculated suspension where particles are attracted by the force of flocculation (van der Waals forces). The shear force required to break the force of flocculation between the particles contributes to yield value. Continued shear breaks further linkages, thus leading to decrease in apparent viscosity with increase in shear. On exceeding the yield value, the shearing stress and rate of shear become directly proportional. The diagrammatic explanation of plastic behaviour is depicted in Figure 3.5.

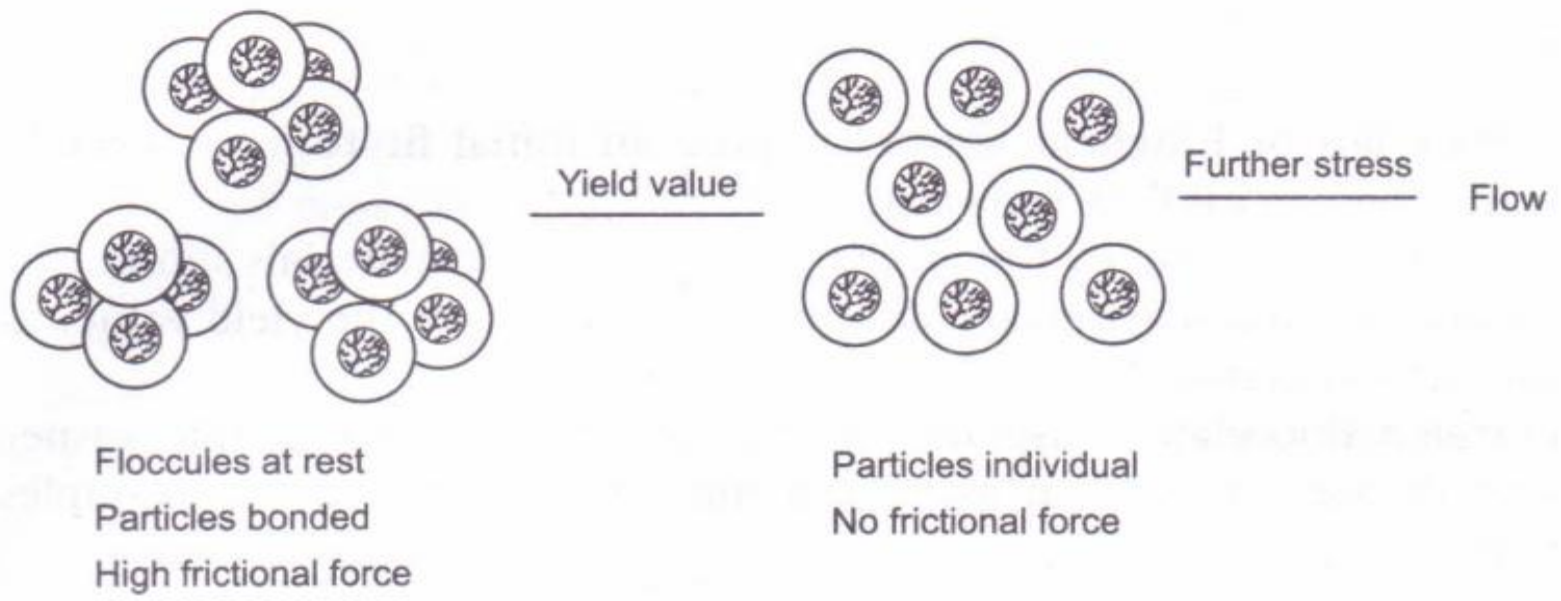


**Figure 3.5** Plastic behaviour.

## Example 3.3 (Plastic viscosity)

A plastic material was found to have yield value of 5000 dyne/cm$^2$. At shearing stress above the yield value, stress was found to increase linearly with rate of shear. If the rate of shear was 125 s$^{-1}$ when stress was 7500 dyne/cm$^2$, calculate the plastic viscosity of the sample.

### Solution

According to Eq (3.7)

$$\text{Plastic viscosity} = \frac{(\text{Stress} - \text{yield value})}{\text{shear rate}}$$

$$= \frac{(7500 - 5000)}{125}$$

$$= \frac{2500}{125}$$

$$= 20 \text{ poise}$$

### Pseudoplasticity

1. Shear-thinning behaviour is often referred to as *pseudoplasticity*.
2. Pseudoplastic material tends to become more fluid the faster they are stirred.
3. Weakly flocculated suspensions, polymeric solutions such as solution of tragacanth, sodium alginate and cellulose derivatives and semisolid systems containing polymer component are examples of pseudoplastic materials.

### Rheogram and viscogram

1. Rheogram begins at the origin, indicating that the particle–particle bonds are too weak to withstand the applied shear stresses.
2. The increase in the rate of shear is greater than the corresponding increase in shear stress, resulting in the rheogram being concave towards the shear–rate axis (Fig. 3.6a).
3. A decrease in viscosity is observed with increase in shear rate (Fig. 3.6b).

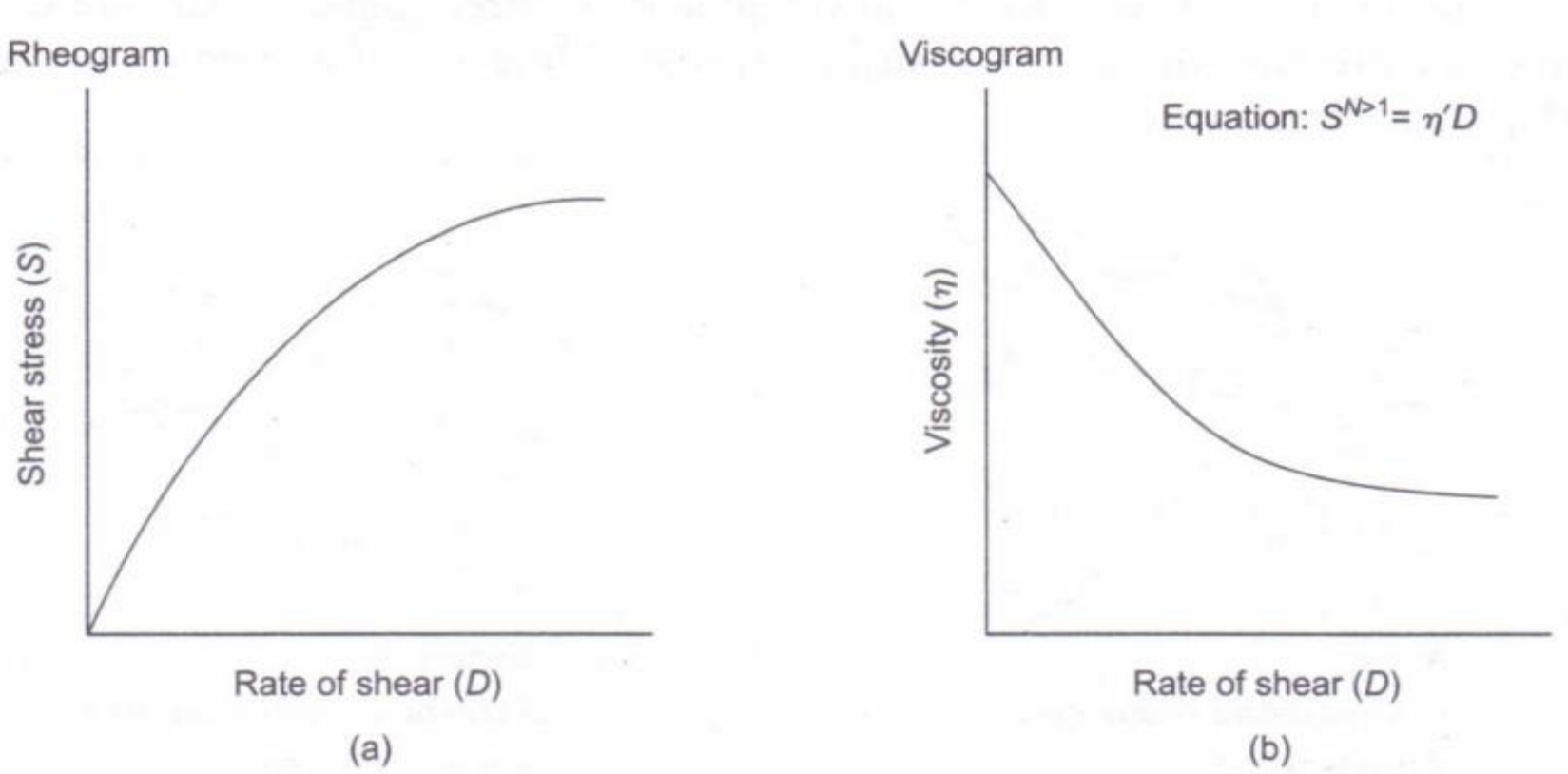


**Figure 3.6** (a) Rheogram and (b) viscogram for pseudoplastic flow.

The Ostwald-de Waele equation is used to describe pseudoplastic behaviour since a single value of viscosity cannot characterize the viscous behaviour of pseudoplastic materials.

$$S^N = \eta' D \tag{3.8}$$

where $S$ and $D$ are the shear stress and shear rate, respectively, $\eta'$ is the apparent viscosity and $N$ is the power index of deviation from Newton's law. In this equation, $N$ is greater than 1 for pseudoplastic materials and less than 1 for dilatant materials. The equation is reduced to Newton's law when $N$ is equal to 1.

When the logarithm of both sides of the equation is taken, the result is

$$\log D = N \log S - \log \eta' \tag{3.9}$$

This is equation for a straight line when log $D$ is plotted as a function of log $S$.

### Reason

Pseudoplastic flow is exhibited by polymeric solutions. In polymeric solutions, the flexible, long-chain macromolecules are in thermal agitation with water molecules. To attain the condition of minimum energy, the macromolecules tend to undergo coiling. Furthermore, intramolecular hydrogen bonding may also cause bridging between individual adjacent molecules. Both these phenomena (coiling and bridging) develop degrees of interlocking, which is responsible for the high initial viscosity of these systems. Upon the application of shear, the macromolecule chains uncoil and align themselves in the direction of flow as shown in Figure 3.7. The imposition of increasing shear rates reduces the entrapment of water, thereby offering less resistance to flow and reduction in viscosity. On removal of shear stresses, Brownian motion re-establishes the coiled conformation and interparticle links instantaneously and the system returns to its high viscosity condition. Thus, the restoration is time-independent. The pseudoplastic behaviour of weekly flocculated suspensions, such as silica or alumina gel, is due to the development of three-dimensional 'house of card' structure in the presence of water. Usually, most suspending agents exhibit similar capability for development of structure.

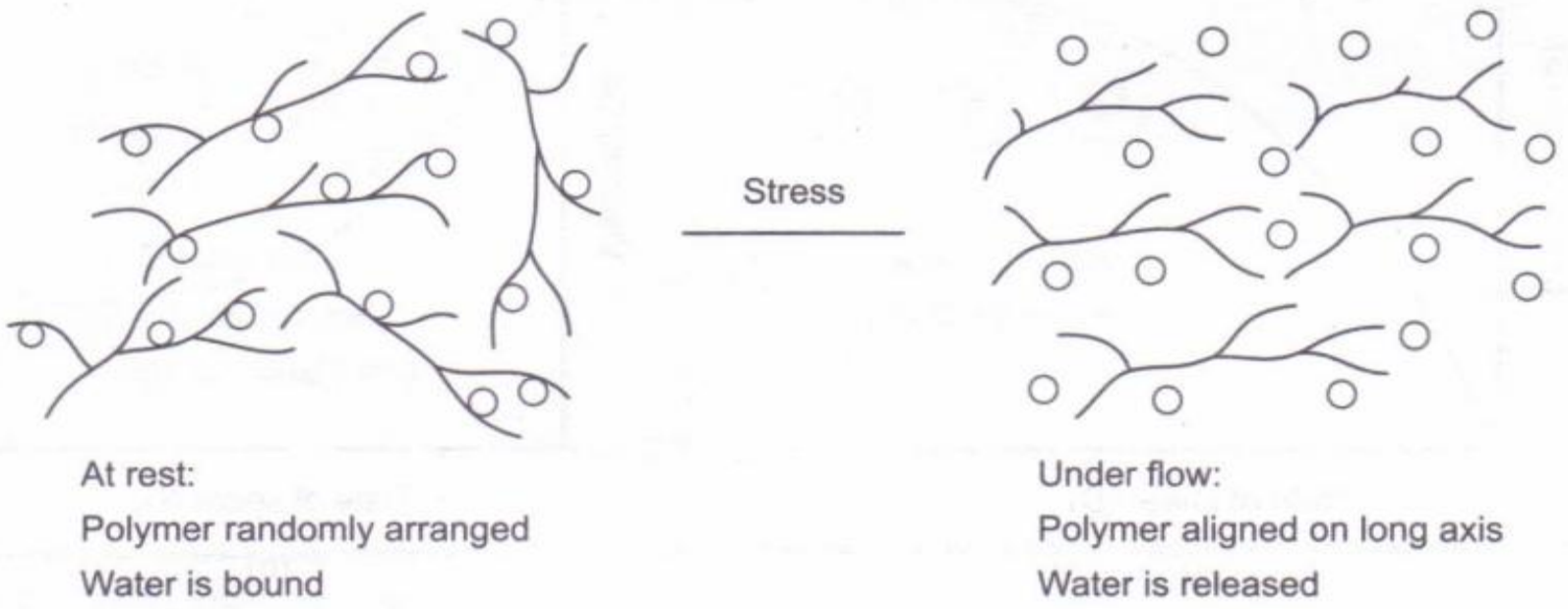


**Figure 3.7** Pseudoplastic behaviour.

### Dilatancy

1. Shear-thickening behaviour is often referred to as *dilatancy*.
2. Materials that increase in volume, i.e. dilate, when sheared are known as *dilatant*.
3. Suspensions containing high concentrations (>50% w/w) of small, deflocculated particles exhibit dilatant behaviour. Flow properties of dilatants are opposite to that of pseudoplastics.

### Rheogram and viscogram

1. Increase in the rate of shear is greater than the corresponding increment in shear stress (Fig. 3.8a).
2. Increase in viscosity is observed with increase in shear rate (Fig. 3.8b).

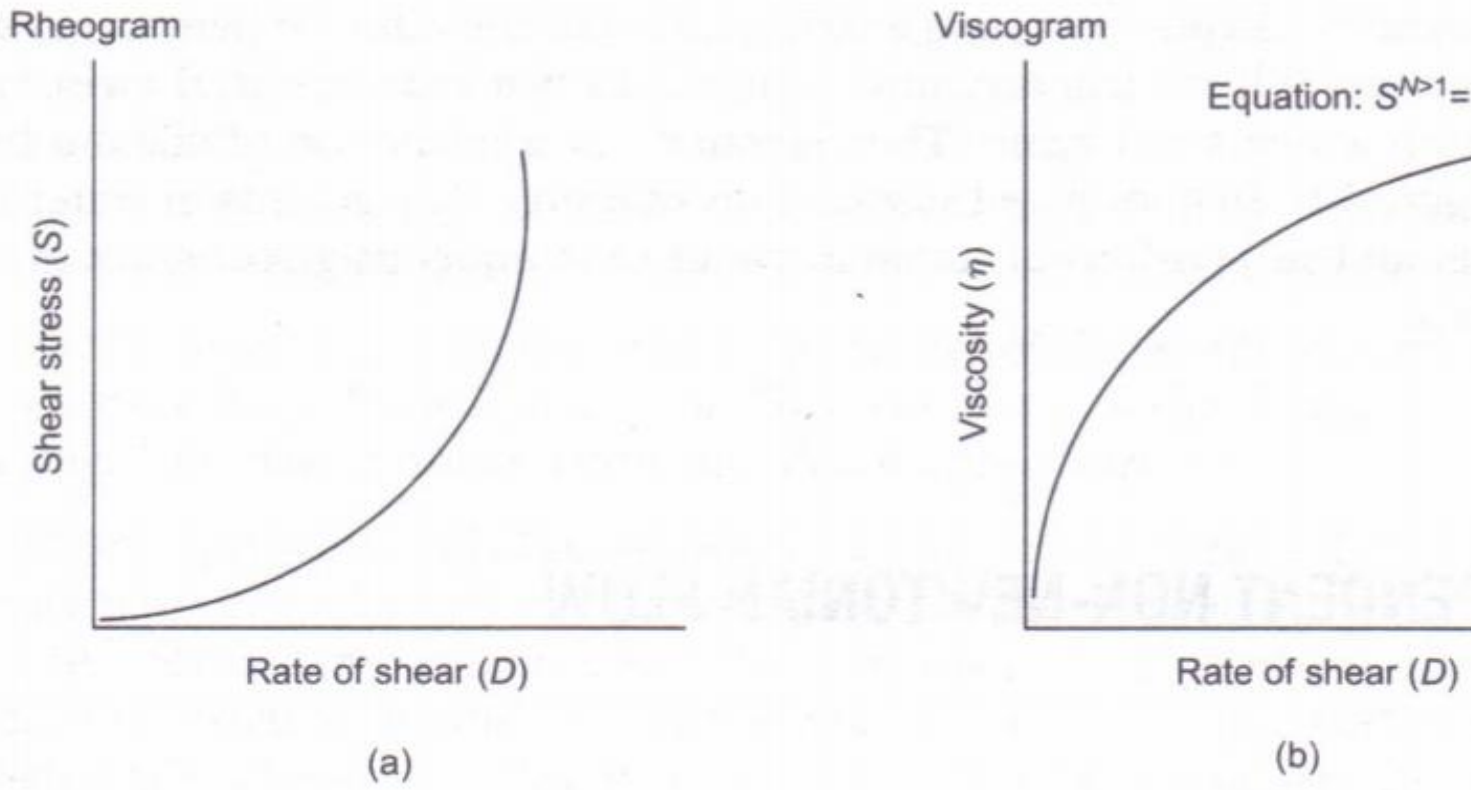


**Figure 3.8** (a) Rheogram and (b) viscogram for dilatant flow.

The Ostwald-de Waele equation used to describe pseudoplasticity is also applicable for dilatant materials.

$$S^N = \eta' D$$

where $N$ is less than 1 for dilatant materials. As the degree of dilatancy increases, the value of $N$ decreases.

### *Reason*

At rest, the deflocculated particles do not tend to aggregate but are intimately packed with minimum interparticle volume. The amount of vehicle what vehicle is sufficient to fill the volume, and to lubricate and allow the particles to slip past each other. At this stage, the material, being fluid, can be poured or stirred. On increasing shear stress, the particles bunch up together, take an open form of packing and develop large voids. Since the amount of vehicle is constant, it cannot completely fill the void spaces and the suspension appears dry as if the suspended particles had expanded or dilated. With further increase in shear rates the

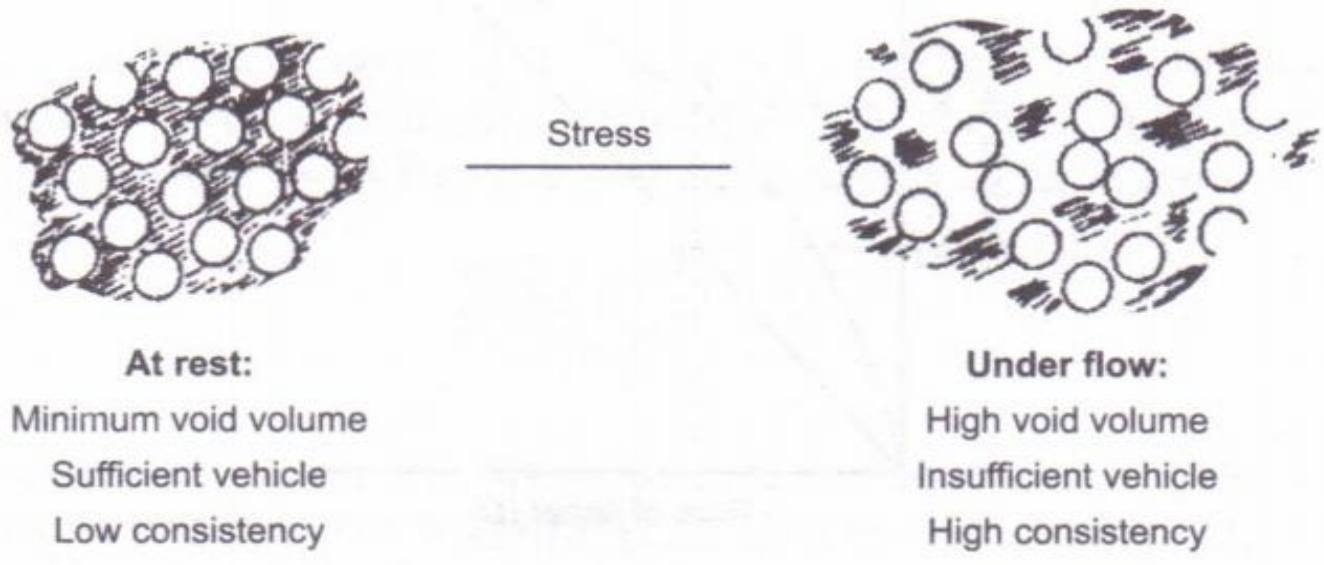


**Figure 3.9** Dilatant behaviour.

material becomes more viscous, attaining a solid-paste-like consistency; hence, it is known as *shear-thickening systems*. When shear is removed, the void volume decreases, the viscosity drops and the suspension appears wet again. The diagrammatic explanation of dilatant behaviour is depicted in Figure 3.9. Deflocculated suspensions of inorganic pigments in water (30–50% titanium dioxide) and suspensions of starch in water or in aqueous glycerin are examples of dilatants materials.

# TIME-DEPENDENT NON-NEWTONIAN FLOW

## Thixotropy

In the previous discussion for shear thinning systems, it was assumed that the system adapts itself to changing shear instantaneously, i.e. so fast that the rheogram at increasing or decreasing shear rates is a single curve. However, if the suspended particles are large or if the suspension is viscous, the Brownian motion is too slow to restore the broken interparticle links instantaneously. If the structure does not immediately recover, the descending rheogram will have lower stress values at each shear rate and the apparent viscosity will decrease even while the system is under constant shear. Such a body is said to be *thixotropic*.

1. Thixotropy is therefore time-dependent breakdown or the rebuilding of structure on standing, i.e. a reversible and isothermal transformation of gel to sol.
2. Example of thixotropic material is bentonite sodium (8% w/w) gel, which when stirred above the yield value, flows and can be poured. When kept undisturbed for an hour or two, it reverts to gel as the Brownian motion rebuilds the house of card structure.

**Thixotropy in a pseudoplastic system:** It is shown in Figure 3.10. Starting with the system at rest (O), the following facts are observed in the rheogram for pseudoplastic systems obtained by plotting shear stresses versus shear rates:

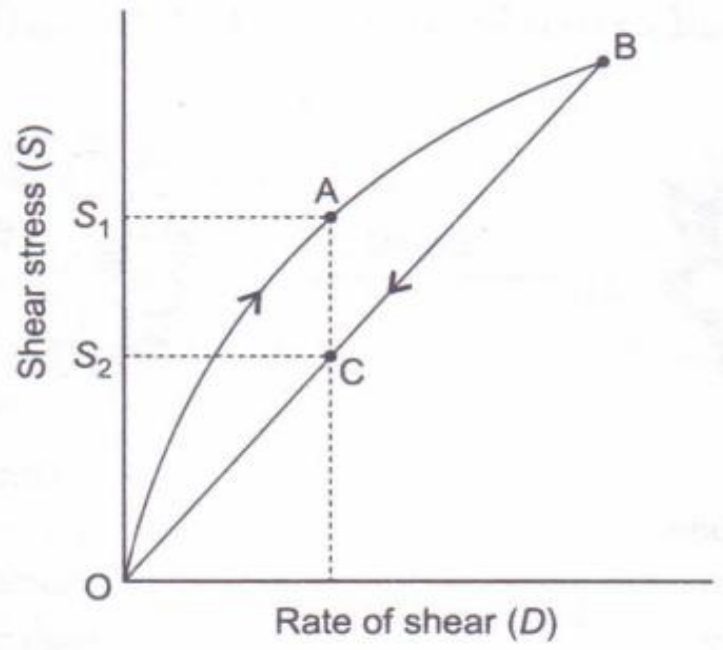


**Figure 3.10** Thixotropy in a pseudoplastic system.

1. Two curves are obtained: an up-curve (OAB) when the shear rate is increased and a down-curve (BCO) when the shear rate is reduced.
2. The up- and down-curves are nonsuper imposable.
3. The down-curve is displaced lower to the up-curve, indicating that the viscosity of the system at any rate of shear is lower on the down-curve than on the up-curve.

Thus, the shear stress required to maintain the rate of shear reduces from $S_1$ to $S_2$ and the apparent viscosity drops from $S_1/\eta$ to $S_2/\eta$. This is contrary to the rheogram of pseudoplastic materials (Fig. 3.6), where the up-curve and down-curve coincide.

If the thixotropic material is kept at rest for a sufficient time period, it retains its original high consistency (OABCO, Fig. 3.11). If no rest period is allowed and the shear cycle is repeated as soon as the down-curve is completed, the next up-curve is ODB and the down-curve is BEO. A third shear cycle without rest period will result in up-curve OEB with down-curve BCO, which might be either curved or straight (how can a curve be straight?). If the buildup of the structure is slow, there will be no structure left after the third cycle and the up-curve will coincide with the straight down-curve BCO and the liquid will turn Newtonian. This change is temporary and after a prolonged rest period, the curve BCO reverts to OAB.

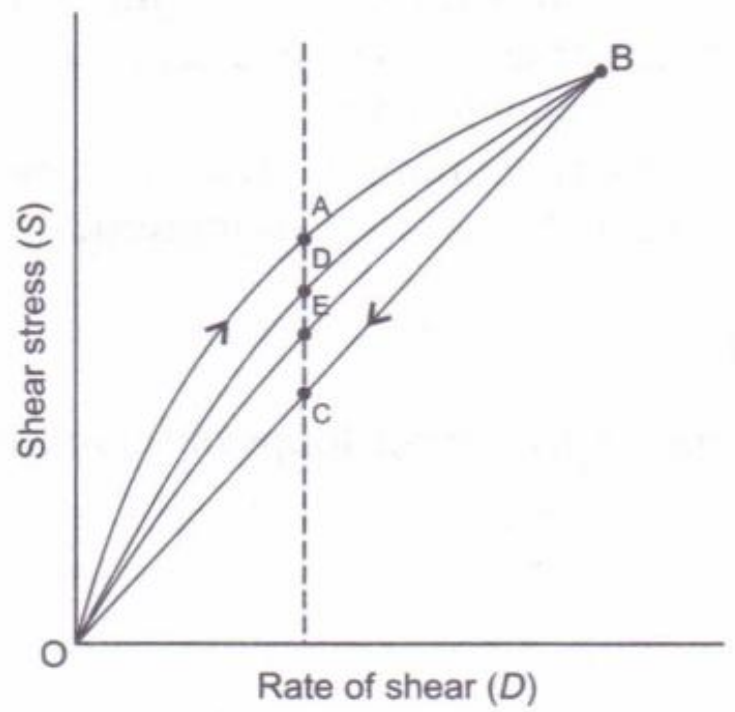


**Figure 3.11** Rheogram representing successive shear cycles for a thixotropic pseudoplastic liquid.

**Thixotropy in a plastic system:** It is shown in Figure 3.12. After imposition of one or more shear cycles, the yield value may remain unaltered as in curve A of Figure 3.12, or the yield value may reduce as in curve B (called as *false body behaviour*), or the yield value disappears as in curve C.

### *Hysteresis loop*

It measures the extent of thixotropic breakdown of the system and is the area enclosed by the up-curve and down-curve (OABCO of Fig. 3.11) or by the up-curve, down-curve and the stress axis (curves B and C of Fig. 3.12).

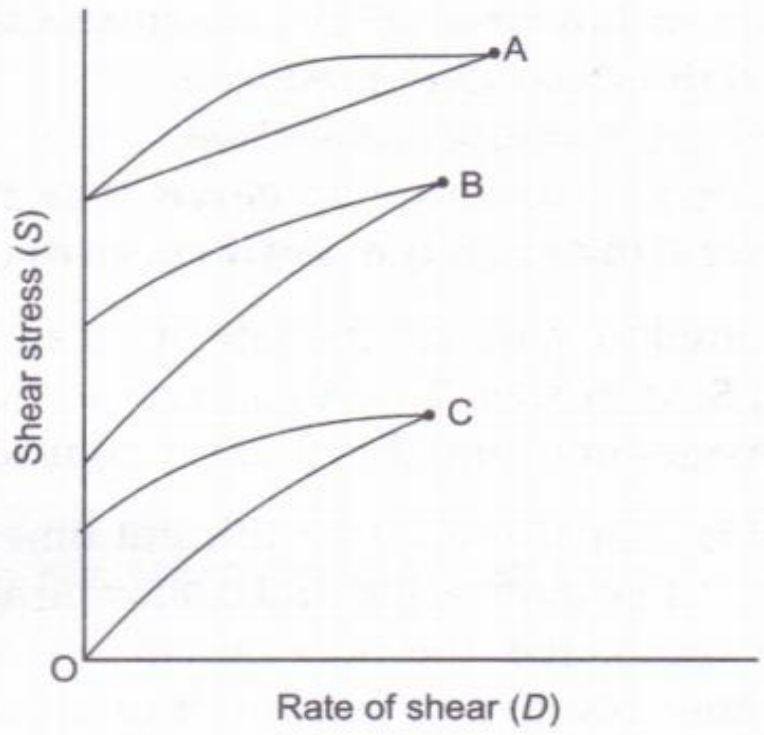


**Figure 3.12** Rheogram of plastic systems exhibiting thixotropy.

1. The magnitude of difference in the up-curve and down-curve is known as the *degree of hysteresis,* and it determines the time taken to reacquire the original structure.
2. Decrease in loop area indicates the decrease in structural breakdown.
3. Materials with no structure are Newtonian.
4. The absence of hysteresis in the rheograms of plastic and pseudoplastic systems is because of the rebuilding of structure by fast Brownian motion.

### *Bulges and spurs in thixotropy*

Bulges and spurs represent complex hysteresis loops observed in pharmaceutical dispersions (Fig. 3.13).

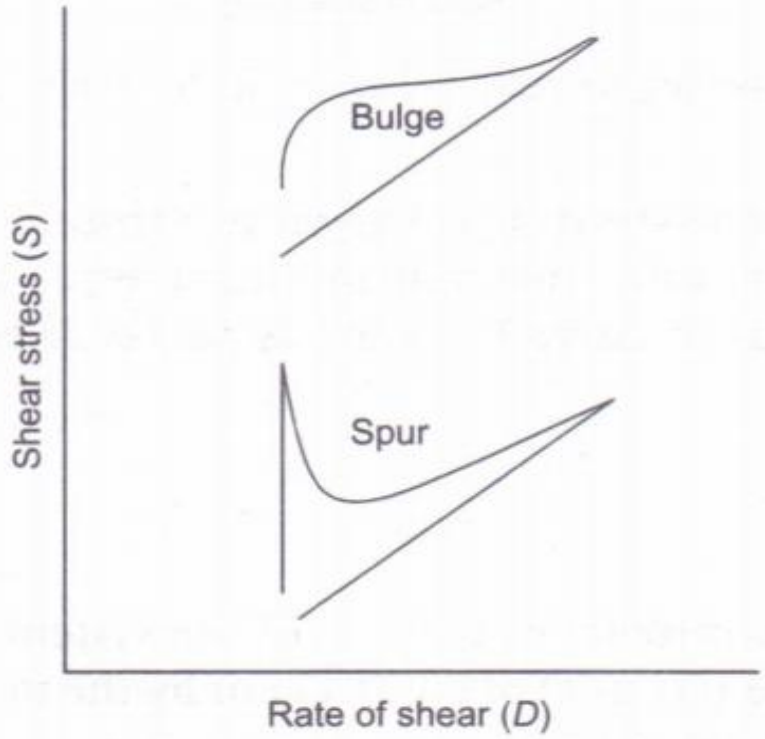


**Figure 3.13** Rheogram for a thixotropic material showing bulge and spur in the hysteresis loop.

1. Bulge is a characteristic protrusion in the up-curve observed in the hysteresis loops of concentrated bentonite gel, 10–15% w/w. The 'house-of-cards structure' formed by the crystalline plates of bentonite causes the swelling of bentonite magmas and the bulge in the rheograms.
2. Spur is a characteristic bowed up-curve protrusion observed in the hysteresis loops of highly structured systems such as procaine penicillin gel. Such systems demonstrate a high yield value, known as the *spur value*, Y, when the three-dimensional structure breaks. The spur value depicts a sharp point of structural breakdown at low shear rate.

## Rheopexy

As discussed, once the interparticle links among the macromolecule chain are broken by shear stress, their restoration by Brownian motion is slow if the particles are large or the suspension is viscous. In such cases, gentle vibration and shaking (rocking and rolling) may accelerate the restoration of interparticle links between macromolecules. The gentle movements provide mild turbulence, which helps in the dispersion of particles to acquire a random orientation and thus re-establish the network. This behaviour is known as *rheopexy*. In the case of bentonite sodium (8% w/w) gel, gentle vibration speeds up the process of re-formation of a gel.

## Negative Thixotropy or Antithixotropy

1. Defined as a reversible time-dependent increase in viscosity at a particular rate of shear.
2. In a rheogram of antithixotropic system (Fig. 3.14), the down-curve appears above the up-curve, indicating that the viscosity of the system at any rate of shear is higher on the down-curve than on the up-curve.
3. Flocculated suspensions containing low solids content (1–10%) are examples of antithixotropic systems.

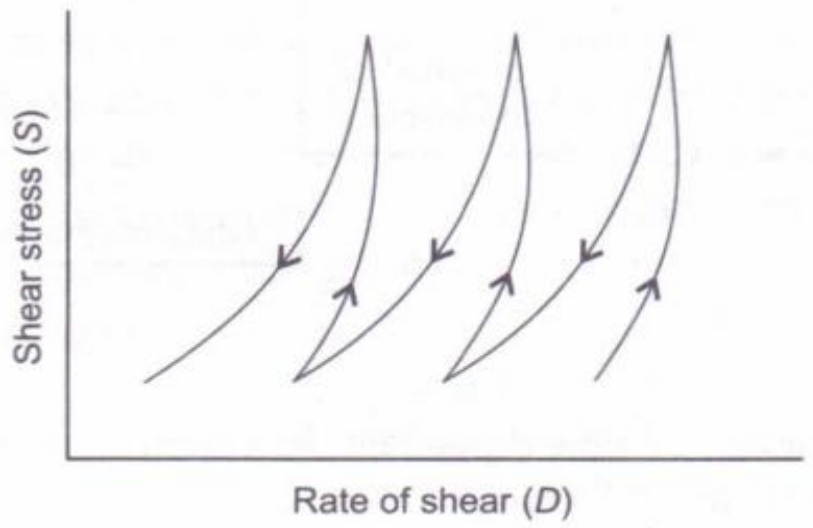


**Figure 3.14** Rheogram for magnesia magma showing antithixotropic behaviour.

In antithixotropic systems, with application of shear the original state of a large number of individual but small-sized floccules (solution state) is changed to a small number of relatively large-sized floccules (gel form), resulting in increased viscosity. On reduction of shear, the solution does not regain its original viscosity but a solution with higher viscosity is formed. This is due to the increased frequency of collision of polymer molecules in suspension or dispersed particles, leading to an increase in interparticle bonding with time upon application of shear. If the antithixotropic material is kept at rest, the large floccules break down and the original state of individual particles and small floccules (solution) is restored. If no rest period is allowed and the shear cycle is repeated as soon as the down-curve is completed, the material turns into solid gel. Magnesia magma is the classic pharmaceutical example of this behavioural type.

## Negative Rheopexy

Negative rheopexy is observed in antithixotropic systems where gentle vibration, shaking and mild turbulence speed up the reformation of solution from the gel state. In this, an antithixotropic system, such as magnesia magma, becomes more mobile under the influence of mild turbulence.

Figure 3.15 summarizes non-Newtonian behaviour depicting thixotropy, rheopexy, negative thixotropy and negative rheopexy.

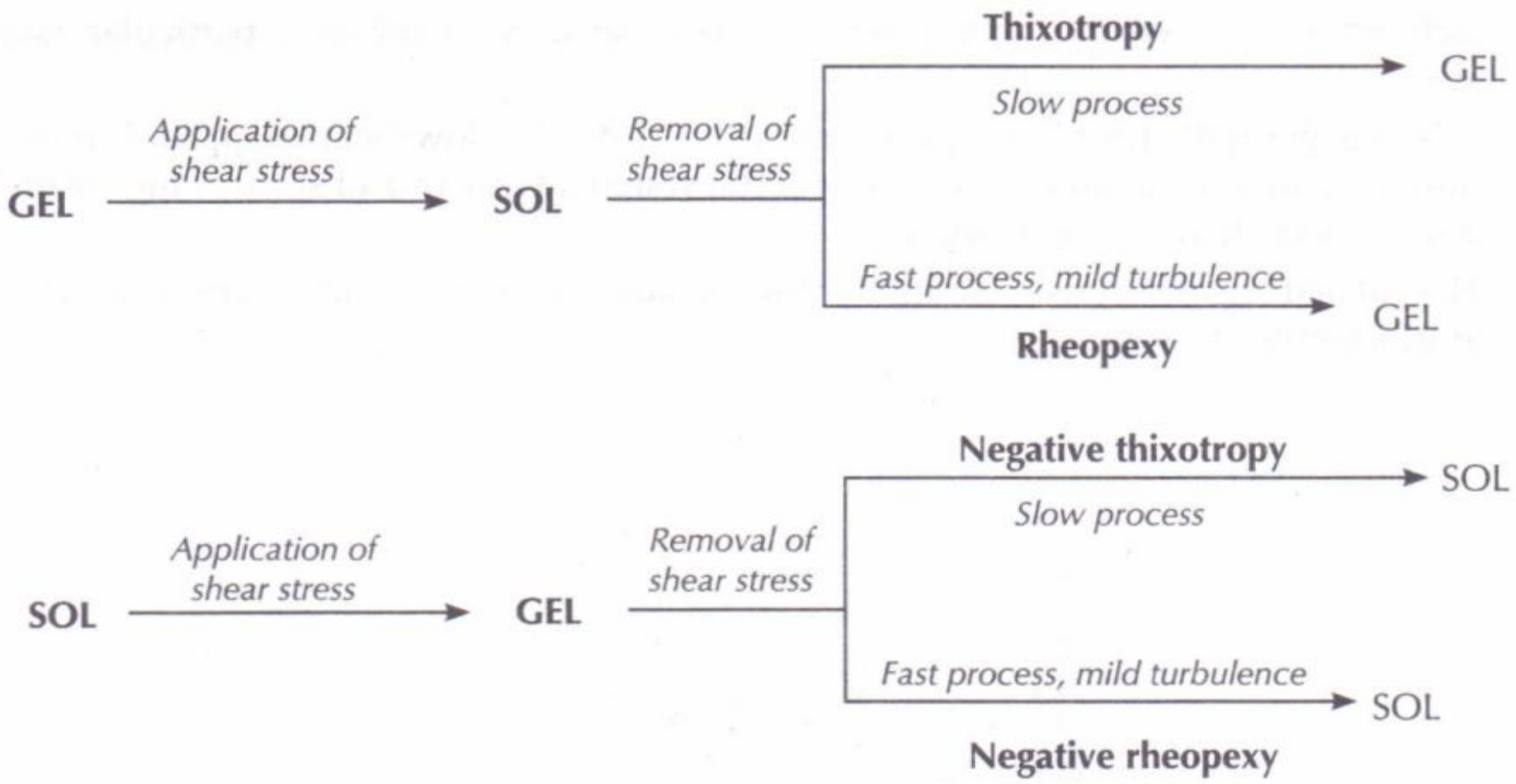


**Figure 3.15** Schematic representation of time-dependent non-Newtonian behaviour depicting thixotropy, rheopexy, negative thixotropy and negative rheopexy.

# DETERMINATION OF RHEOLOGICAL PROPERTIES: MEASUREMENT OF VISCOSITY

Two basic types of instruments are available based on the material to be analysed and/or type of the rheogram obtained.

1. **One-point instruments:** They provide a single point on a rheogram and are suitable only for Newtonian fluids. Examples include Ostwald viscometer and Hoppler viscometers.
2. **Multipoint instruments:** Complete rheogram can be obtained by characterizing the flow properties at variable rates of shear. These instruments are used to determine viscosity of non-Newtonian systems. Examples include cup and bob viscometer and cone and plate viscometers.

Based on the principle of measuring viscosity, three types of viscometers are available:

1. **Capillary viscometers:** They are based on the rate of flow of a liquid through a fine capillary or an orifice.
2. **Density-dependent viscometers:** They are based on the velocity of a falling object through a liquid under the influence of gravity.
3. **Rotational viscometers:** They are based on the resistance of a rotating element in contact with or immersed in the liquid.

## Capillary Viscometers

**Principle:** When a fluid flows through a capillary, the fluid in immediate contact with the capillary wall is motionless whereas that at the centre has the maximum velocity, and between these two limits is a velocity gradient. The driving force causing a liquid to flow is its weight whereas viscous drag of a liquid restrains the flow. Flow of liquid through capillary is depicted by Poiseuille's equation:

$$\eta = \frac{\Delta P\, t\pi\, r^4}{8LV} \tag{3.10}$$

where $V$ is volume flowing through the capillary per unit time, $r$ is the radius of the capillary, $L$ is the length of the capillary and $\Delta P$ is the pressure difference across the capillary, which provides the appropriate force to overcome the viscous drag. If $\Delta P$ in Poiseuille's equation is replaced with hydrostatic pressure, $h\rho g$ of a liquid column of height $h$ and density $\rho$; $g$ is acceleration of gravity, the equation changes to:

$$\eta = \left( \frac{hg\pi\, r^4}{8LV} \right) = \rho t \tag{3.11}$$

where

$$K = \frac{hg\pi r^4}{8LV} \tag{3.12}$$

therefore

$$\eta = K \rho t \tag{3.13}$$

## Ostwald viscometer

**Working:** As depicted in Figure 3.16a, a standard volume of liquid is introduced into a viscometer through the left arm and is then drawn up from bulb 'E' into the bulb above the mark 'A', by suction. The efflux time, *t*, required for the liquid level to fall from the upper meniscus from line A to line C of the fluid contained in upper reservoir B is measured. The diameter and length of the capillary D control the flow time. The viscosity of any unknown liquid is then determined using the following equation:

$$\eta = K \rho t \tag{3.13}$$

Generally, relative viscosity is measured by comparing a standard reference $\eta_R$ and the unknown $\eta_u$. In each case, the volume $V$ flowing is the same, but the time for flow is $t_R$ and $t_u$, respectively. Substituting this into the above equation, we obtain

$$\frac{\eta_R}{\eta_u} = \frac{t_R \rho_R}{t_u \rho_u} \tag{3.14}$$

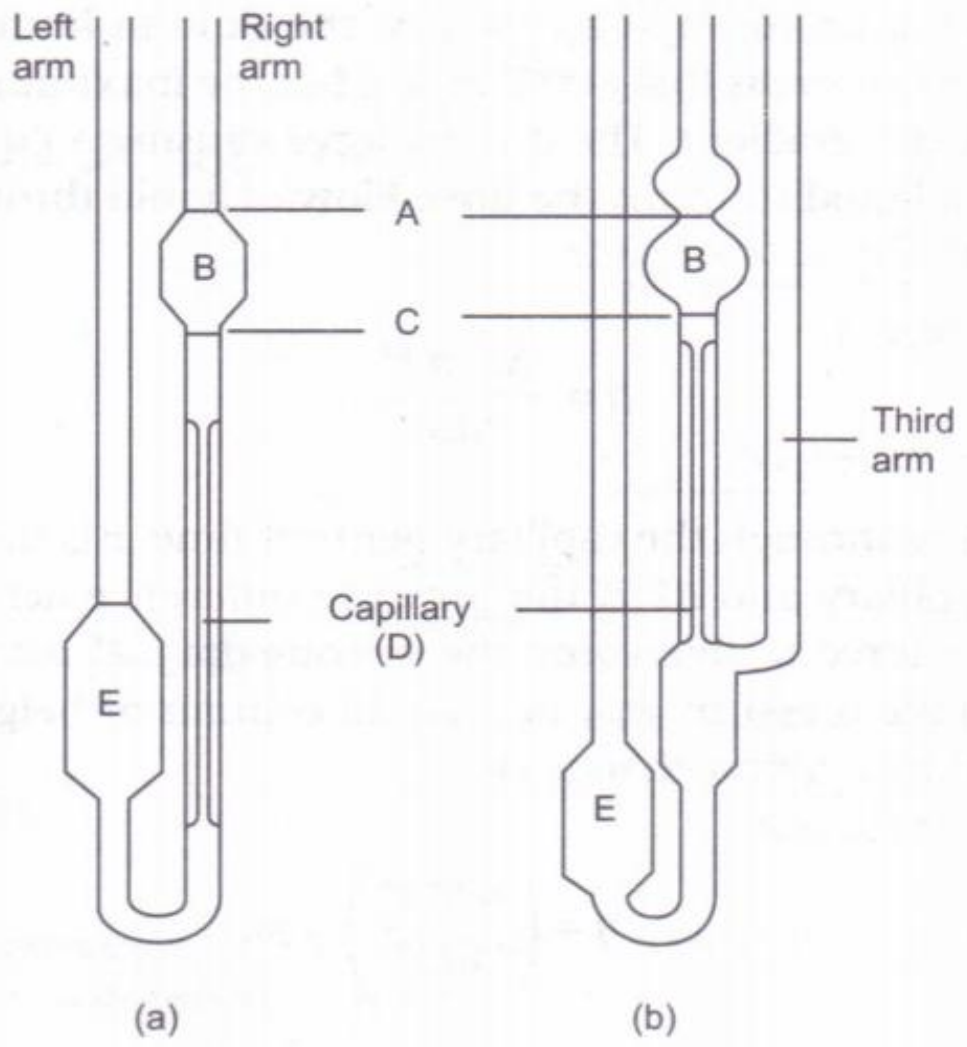


**Figure 3.16** Capillary viscometers: (a) Ostwald viscometer and (b) Ubbelohde viscometer.

Ostwald viscometer is

1. Used to measure viscosity of Newtonian liquids.
2. Restricted to 'one-shear-range' measurement.
3. Used to determine relative viscosity.

### Ubbelohde suspended level viscometer

Ubbelohde suspended level viscometer consists of an additional third vertical arm attached to the bulb below the capillary part (Fig. 3.16b). The third arm ventilates the liquid below the capillary tube and keeps the volume in the middle arm constant. This viscometer minimizes inherent problems of the Ostwald viscometer.

---

### Example 3.4 (Viscosity)

In Ostwald viscometer the flow time for water at 20°C was measured as 225 s. Similar measurements for an oil of density 0.75 g/cm³ were 450 s. What is the viscosity of the oil if the density of water at 20°C is 1.0 g/cm³, and the viscosity is 1.00 cp.

### Solution

The kinematic viscosity of water is given by

$$v = \frac{n}{d} = \frac{1.0}{1.0} = 1.0 \text{ centistokes}$$

Then, as

$$\frac{v_{\text{lia}}}{v} = \frac{t_{\text{lia}}}{t}$$

$$\frac{v_{\text{lia}}}{1.0} = \frac{450}{225}$$

$$v_{\text{lia}} = 2.0 \text{ centistokes}$$

Then, $\eta_{\text{lia}} = d_{\text{lia}} v_{\text{lia}} = (0.75)(2.0) = 1.50$ cp

---

### Extrusion rheometer

**Working:** A sample storage chamber is loaded with the sample to be investigated. The sample is extruded through a capillary tube attached to one end. The chamber contents are forced through this exit capillary by the force of the piston. This system is shown schematically in Figure 3.17.

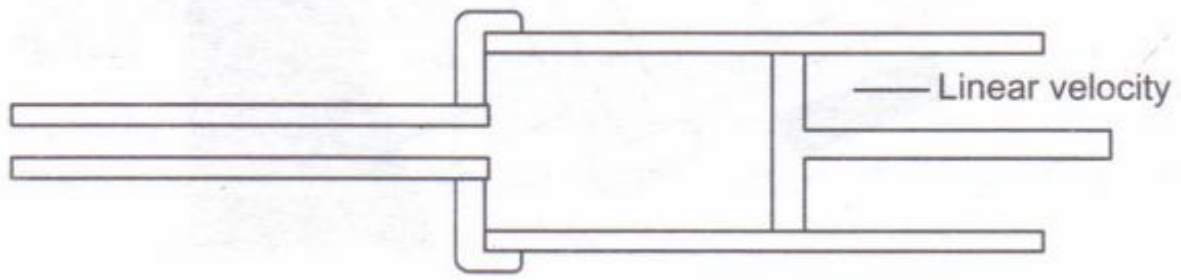


**Figure 3.17** Extrusion rheometer.

Under test conditions, a constant force is applied to the piston, and the resultant displacement of piston or sample extruded is measured. Extrusion is performed through a calibrated orifice into containers at geometrically increasing pressures (5, 10, 20, 40 and 80 psi). Typically, the constant force is applied from gas cylinders with a good pressure regulation system. The rate of flow in cubic centimetres per second is calculated from the density, weight and the elapsed time of each extrusion.

- Capable of performing rheological studies of pastes, ointments and creams.

## Density-Dependent Viscometers

### *Falling sphere viscometer*

**Principle:** Falling sphere viscometer is based on the Stokes' law, according to which motion of a body through a viscous medium is resisted by viscous drag. Initially, the body experiences acceleration due to gravity, but soon this acceleration is balanced by the viscous drag and the body falls with uniform terminal velocity.

**Working:** In a falling ball viscometer, time $t$ for a ball of density $\rho_B$ to fall through a fixed distance of liquid of density $\rho_L$ and of viscosity $\eta$ is determined using the Stokes' equation:

$$\eta = K(\rho_B - \rho_L)t \tag{3.15}$$

The constant $K$ includes wall interaction factors since the equation is based on the assumption that the ball falls freely in an ocean of liquid, i.e. there is no effect from the container walls. A liquid of known viscosity is used to calibrate the instruments for general use, in a manner analogous to that with Ostwald viscometers. *Hoppler viscometer* is the commercial example of a falling sphere viscometer (Fig. 3.18).

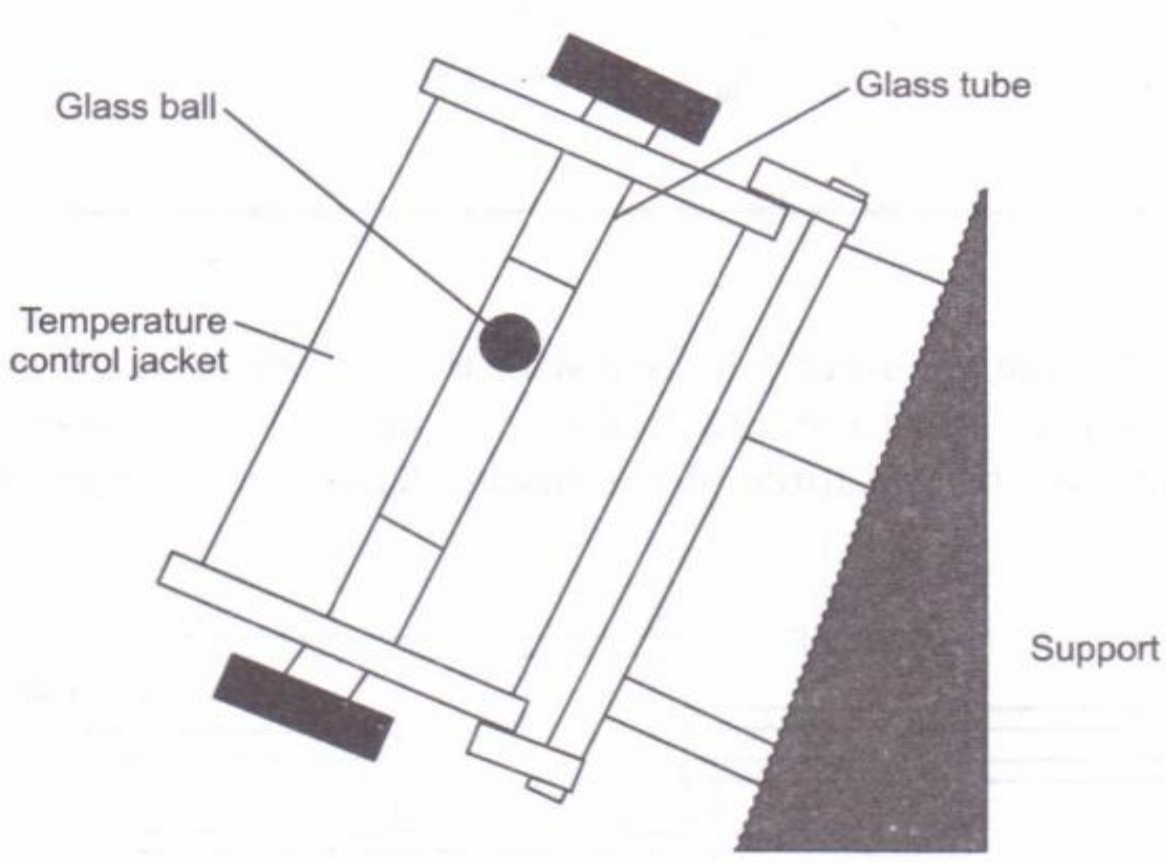


**Figure 3.18** Hoppler falling sphere viscometer.

### *Bubble viscometer*

This is based on a similar principle. A series of sealed standard tubes have calibrated oils covering a range of viscosities. Each has a small air bubble of exact geometry. The unknown sample is placed in an empty tube and stoppered so that it is identical in bubble content to the standards. The unknown and standard tubes are inverted, and the bubble rise times are compared to determine the standard most resembling the unknown.

---

*Example 3.5 (Viscosity)*

A ball of density 3.0 takes 100 s to fall the fixed distance of an inclined tube viscometer when a calibrating liquid of density 1.0 and viscosity 8.0 poise is used. (A) Calculate the instrumental constant. (B) What would be the viscosity of a sample oil of density 0.8 if the fall time under similar conditions was 125 s?

*Solution*

A. $\eta = K(\rho_B - \rho_L)t$

$$K = \frac{\eta}{(\rho_B - \rho_L)t} = \frac{8.0}{(3.0-1.0)(100)}\frac{\text{poise}}{(\text{g/mL})(\text{s})} = 0.04\,\text{poise}\,\text{g}^{-1}\,\text{mL}\,\text{s}^{-1}$$

B. $\eta = 0.04\,(\rho_B - \rho_{oil})t$

$= (0.04)(3.0 - 0.8)(125)$

$= 11$ poise

---

## Rotational Viscometers

**Principle:** These instruments are based on the fact that a solid rotating body immersed in a liquid is subjected to a retarding force due to the viscous drag, which is directly proportional to the viscosity of the liquid.

### *Cup and bob viscometers*

As represented by Figure 3.19, the cup and bob viscometer comprise two members, a central bob or cylinder and a coaxial or concentric cup. One or both are free to rotate in relation to each other. Between these is the test substance, in the annulus. Three basic configurations have been utilized.

1. **Couette type:** Rotating outer cup with strain measurement on the central bob. For example, the *MacMichael viscometer*.
2. **Searle type:** Rotating central bob with strain measurement on the cup. For example, the *Stormer viscometer* and the *Brookfield viscometer*.
3. Fixed cup with both rotation and strain measured on the bob. For example, the *Contraves viscometer, Epprecht viscometer* and *Rotovisko*.

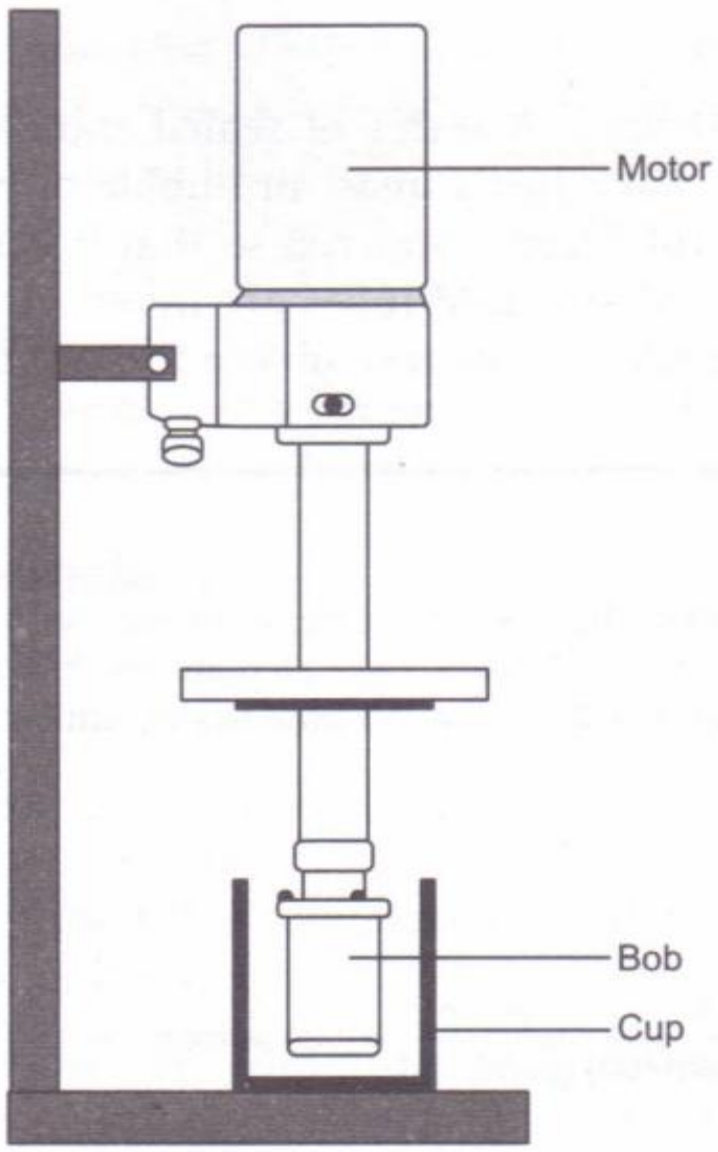


**Figure 3.19** Representation of cup and bob viscometer

The sample is placed in the space between the bob and the cup. A known weight is placed and the time taken by the bob to rotate a specific number of times is determined and converted into revolutions per minute (rpm). The procedure is repeated by increasing the weights and a rheogram is obtained by plotting rpm versus weight added. The rpm value can be considered as shear rates and weights as shear stress. The viscosity of the material can be calculated using the following equation:

$$\eta = K\left(\frac{w}{v}\right) \tag{3.16}$$

where $w$ is the weight in grams, $v$ is rpm and $K$ is instrument constant.

- Large volume of sample is required for rheological studies.
- Variable shear stress across the sample between the cup and the bob results in plug flow in case of plastic materials.

**HIGHLIGHTS**

**Plug flow:** During the analysis of plastic material, the shear stress close to the rotating surface is sufficient to exceed the yield value but the material away from the rotating surface experiences shear stress less than the yield value. The material in this region will remain solid and measured viscosity would be erroneous.

### Cone and plate viscometers

In this type of viscometer, the cone is a slightly bevelled plate such that ideally the angle $\psi$ between the cone and the plate is only a few degrees; even in cruder forms, it is less than 10° (Fig. 3.20).

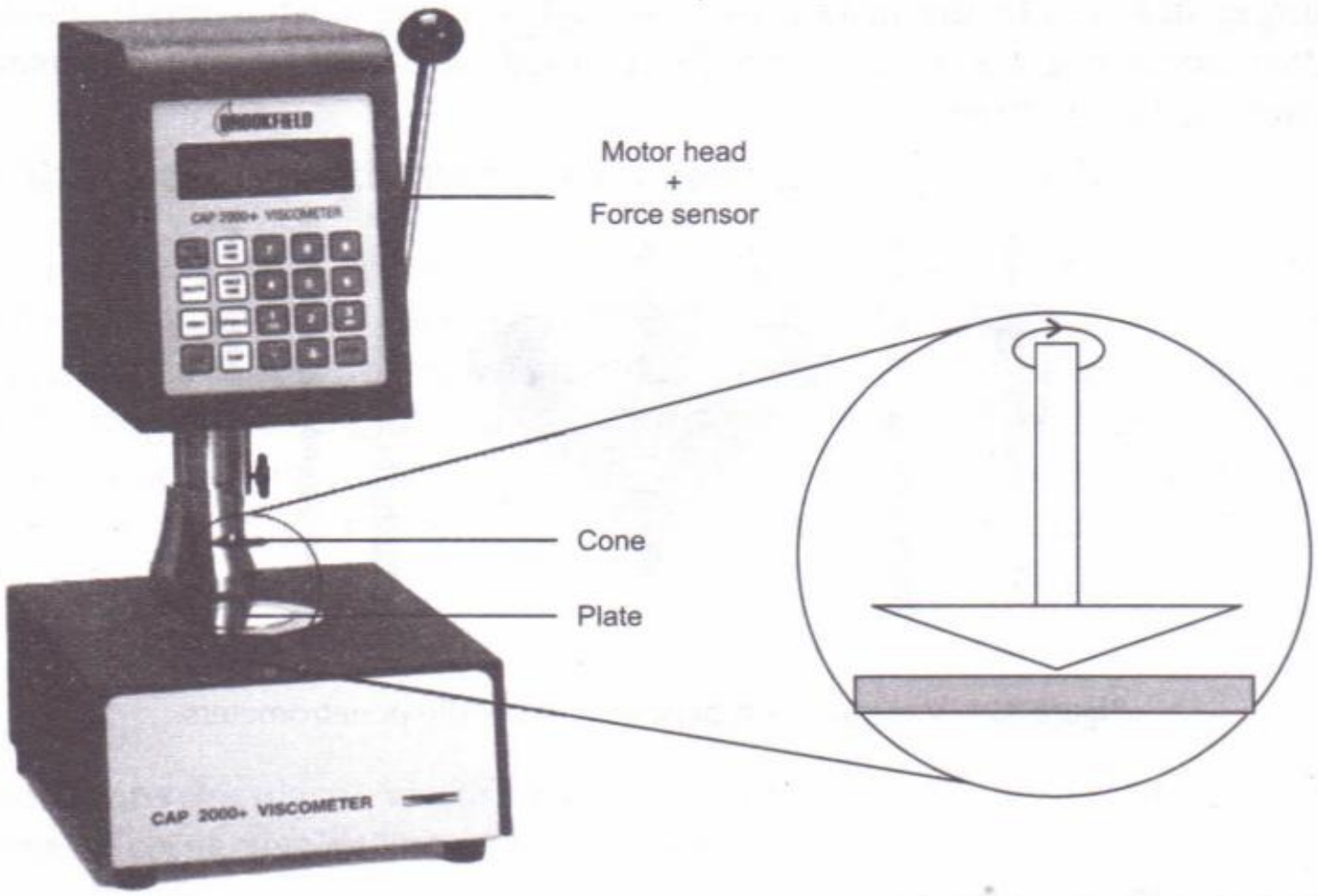


**Figure 3.20** Cone and plate viscometer. (Source: Brookfield High Shear CAP-2000 + L Cone/Plate Viscometer; url: http://www.labsource.co.uk/shop/brookfield-high-shear-cap2000l-coneplate-viscometers-p-1398.html)

The linear velocity at any point on the cone $r$ from the apex is $r\Omega$, where $\Omega$ is the angular velocity, and the separation is $r\psi$; hence, the shear rate is given by

$$D = \frac{r\Omega}{r\psi} = \frac{\Omega}{\psi} \tag{3.17}$$

It should be noted in the above equation that the shear rate at any point is the same and uniform throughout the gap when the cone angle is small, thereby avoiding plug formation.

In operation, the sample is placed at the centre of the plate and is sheared in the narrow gap between the stationary plate and the rotating cone. The viscosity in poise measured in the cone and plate viscometer is calculated using the following equation:

$$\eta = K\left(\frac{T}{v}\right) \tag{3.18}$$

where $T$ is torque reading, $v$ is rpm and $K$ is instrument constant.

The classic example of this instrument of this category is the *Ferranti–Shirley viscometer,* whose use in a wide range of pharmaceutical and cosmetic literature testifies to its general versatility.

## Penetrometers

Penetrometers measure the consistency or hardness of relatively rigid semisolids. The cone and the needle forms are the most commonly used (Fig. 3.21). In use, the cone is mounted on an instrument that measures its movement with time. The tip is set at the surface, and a spring tension is attached to the top of the cone. At time zero, the cone is released. Usually, the penetration occurring in a fixed time is determined. The travel distance is usually reported in decimillimetres, $10^{-4}$ metres.

**Figure 3.21** Various types of cone and needle penetrometers.

## Non-Newtonian Corrections

All of the previous equations related to viscometers have been derived considering Newtonian behaviour. It means that shear rate is constant throughout the viscometer. Comparison of non-Newtonian fluid requires correction to a shear rate term in reference to a fixed point in the viscometer. In general, the correction takes the following form:

$$\gamma_{\text{corrected}} = \gamma F(n) \tag{3.19}$$

where $F$ is the correction factor and $n$ is constant and is determined from the slope of a log–log plot of shear stress versus shear rate. Correction factors for the common viscometers are tabulated in Table 3.2.

**Table 3.2** Non-Newtonian correction factors for viscometers

| Viscometer | Correction factor, F($n$) |
|---|---|
| Capillary | $3n + 1/4n$ |
| Falling sphere | $1 - 2.104\ d/D + 2.09\ d^3/D^3$<br>where $d$ is sphere diameter and $D$ is tube diameter |
| Cup and bob (infinite gap) | $1/n$ |
| Cone and plate | 1 |

# MEASUREMENT OF THIXOTROPY

Thixotropy can be quantitatively estimated by estimating the area of hysteresis, which is a measure of thixotropic breakdown. It can be obtained using a planimeter. Several coefficients of thixotropic breakdown can be used to quantify thixotropic behaviour in plastic systems.

## Structural Breakdown with Increasing Rates of Shear (*M*)

Thixotropic coefficient, *M*, is the loss in shearing stress per unit increase in rate of shear. A plastic material is subjected to increasing rates of shear until it reaches the highest rate of shear value $v_1$ (Fig. 3.22). On decreasing the rate of shear, a down-curve is obtained, from the slope of which plastic viscosity $U_1$ can be calculated. Without disturbing, the rate of shear is increased to another higher value $v_2$; a down-curve is obtained for it as well, from the slope of which plastic viscosity $U_2$ can be calculated. The value of *M* can be calculated from the following formula:

$$M = \frac{(U_1 - U_2)}{\ln (v_2/v_1)} \tag{3.20}$$

where $U_1$ and $U_2$ are the plastic viscosities of the two down-curves having maximum rates of shear of $v_1$ and $v_2$, respectively. The unit of *M* is dyne s $cm^{-2}$.

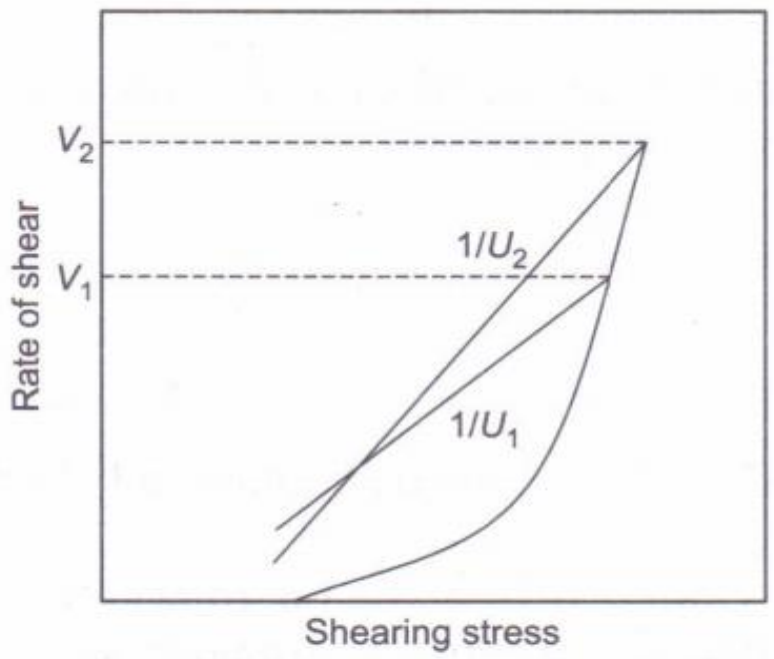


**Figure 3.22** Structural breakdown of a plastic system with increasing rate of shear.

## Structural Breakdown with Time at Constant Rate of Shear (*B*)

When the shear rate of a thixotropic material is increased (up-curve AB) and then decreased (down-curve BE) keeping the rate constant, a typical hysteresis loop ABE is obtained (Fig. 3.23). However, if the sample is taken up to point B and then the rate of shear is

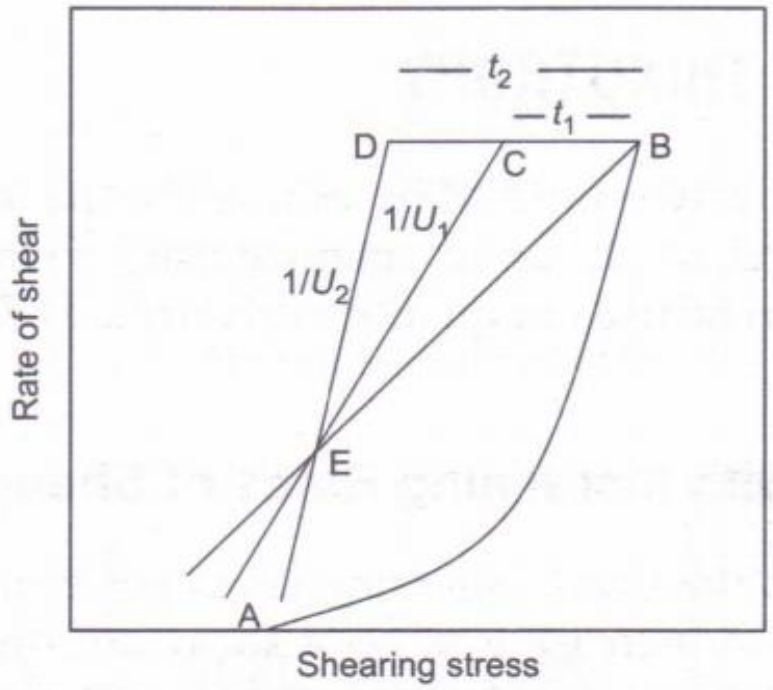


**Figure 3.23** Structural breakdown of a plastic system at constant rate of shear with time.

maintained constant for time $t_1$ seconds, the shearing stress and hence the consistency of the material would decrease depending on the time for shear, rate of shear and degree of structure in the material. Then a hysteresis loop ABCE is obtained. If the same sample is held for time $t_2$ seconds at the same rate of shear, a hysteresis loop ABCDE is obtained. Based on these rheograms, thixotropic coefficient $B$, the rate of breakdown of system at a constant rate of shear, can be calculated using the following formula:

$$B = \frac{U_1 - U_2}{\ln (t_2/t_1)} \tag{3.21}$$

where $U_1$ and $U_2$ are the plastic viscosities of the two down-curves, after shearing at a constant rate of shear for $t_1$ and $t_2$ seconds, respectively.

## VISCOELASTICITY

1. Viscoelastic materials exhibit both viscous fluidity and elastic solidity when undergoing deformation.
2. Viscoelastic property is exhibited by most pharmaceutical semisolids such as creams, lotions, ointments, colloidal dispersions and suppositories.
3. Amorphous and semicrystalline polymers, carbopol gel and aqueous solution of high molecular weight poly(ethylene oxide) also exhibit viscoelasticity.
4. Biological fluids such as blood, sputum and cervical fluid also exhibit viscoelasticity.

Viscous materials resist shear flow and strain linearly with time when a stress is applied.

Elastic materials strain instantaneously when stress is applied and quickly return to their original state on removal of stress.

Viscoelastic materials exhibit both pure viscous flow and elastic deformation. Such behaviour is called *viscoelastic flow.*

## Viscoelasticity Mechanism

When a stress is applied to a polymer (viscoelastic material), parts of the long polymer chain rearrange. The rearrangement occurs to accompany the stress. This rearrangement is called *creep*. During rearrangement, the polymers remain a solid material. However, rearrangement creates a back stress in the material. If the magnitude of the back stress is equal to the applied stress, the material no longer creeps. On removal of applied stress, the accumulated back stresses will cause the polymer to return to its original form.

The rearrangement or creep gives the prefix *visco-* and the recovery to its original form gives the suffix *-elasticity*. Thus, viscoelasticity is a molecular rearrangement.

A viscoelastic material possesses the following three properties:

1. Hysteresis in the stress–strain curve,
2. Time-dependent strain at constant stress (creep) and
3. Time-dependent stress at constant strain (stress relaxation).

## Viscoelastic Models

The viscoelastic material is composed of both elastic and viscous components. The mechanical models made up of combinations of springs (elastic component) and dashpots (viscous component) are used to represent viscoelastic behaviour. The spring represents the elastic component, whereas the dashpot represents the viscous component.

The elastic property can be represented by the Hookean spring given by the following formula:

$$\sigma = E\varepsilon \tag{3.22}$$

where $\sigma$ is the stress, $E$ is the elastic modulus of the material and $\varepsilon$ is the strain that occurs under the given stress.

The viscous property can be represented by movement of a piston inside a cylinder filled with a fluid (dashpot) such that the stress–strain rate relationship can be given as

$$\sigma = \eta \frac{\mathrm{d}\epsilon}{\mathrm{d}t} \tag{3.23}$$

where $\sigma$ is the stress, $\eta$ is the viscosity of the material and $\mathrm{d}\varepsilon/\mathrm{d}t$ is the time derivative of strain.

When stress is applied, the piston moves through the fluid and produces a shear proportional to the viscosity of fluid and when stress is removed the piston does not return to its original position, indicating a viscous nature.

The Maxwell model, the Kelvin–Voigt model, the standard linear solid model and the Weichert model are examples of viscoelastic models. Each of these models differs in the arrangement of springs and dashpots.

### Maxwell model

The Maxwell model is a mechanical model in which a Hookean spring and Newtonian dashpot are connected in series, as shown in Figure 3.24.

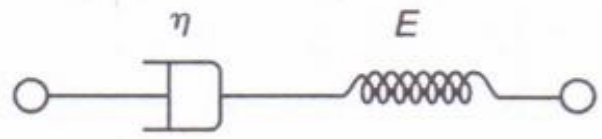


**Figure 3.24** Diagrammatic representation of the Maxwell model.

When a displacing force is applied, the spring stretches immediately, and the dashpot slowly moves independently. When the force is removed, there is an immediate rebound of the elastic displacement, but no viscous flow occurs after elastic recovery. The spring returns to its original conformation, but the dashpot remains in its new location because there is no force for restoration.

1. In the Maxwell model, the stress on each element is same and equal to the imposed stress, whereas the total strain is the sum of the strain in each element.

$$\sigma = \sigma_s = \sigma_d \tag{3.24}$$

$$\varepsilon = \varepsilon_s + \varepsilon_d \tag{3.25}$$

2. The Maxwell model predicts stress relaxation property (stress decays exponentially with time).
3. The Maxwell model does not predict creep accurately.

### Kelvin–Voigt model

The Kelvin–Voigt model, also known as the Voigt model, consists of a Hookean spring and a Newtonian dashpot connected in parallel, as shown in Figure 3.25.

When a displacing force is applied to a Kelvin element and held constant, a viscous flow occurs that decreases with time. The viscous flow occurs because of the displacing force, and the net magnitude of that force decreases since the spring stretches to balance the force. When the displacing force is removed, there is a slow return to the original position as the internal force of the spring drives the dashpot back to its original position. Thus, the elastic element has a time component to reach steady state.

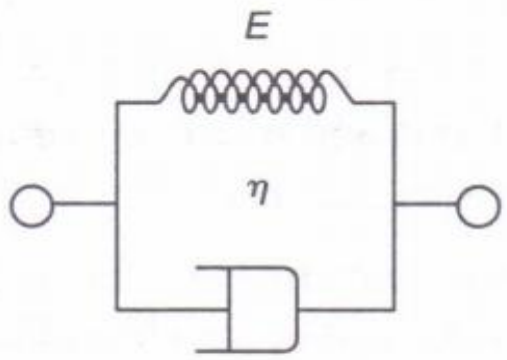


**Figure 3.25** Diagrammatic representation of the Kelvin–Voigt model.

1. The Voigt model explains the creep behaviour of polymers.

$$\sigma(t) = E\varepsilon(t) + \eta \frac{d\varepsilon(t)}{dt} \tag{3.26}$$

2. The Voigt model represents a solid undergoing reversible, viscoelastic strain.
3. The Voigt model does not predict creep accurately.

### Standard linear solid model (Maxwell form)

The standard linear solid model consists of a Hookean spring in parallel with the Maxwell unit, as shown in Figure 3.26.

- The standard linear solid model describes the property of polymers whose conformational change is eventually limited by the network of entanglements.

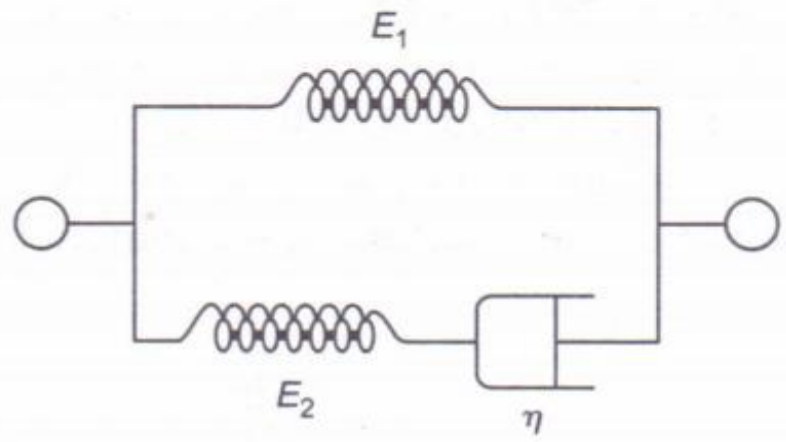


**Figure 3.26** Diagrammatic representation of the standard linear solid model.

### Weichert model

The Weichert model consists of many spring–dashpot Maxwell elements as shown in Figure 3.27.

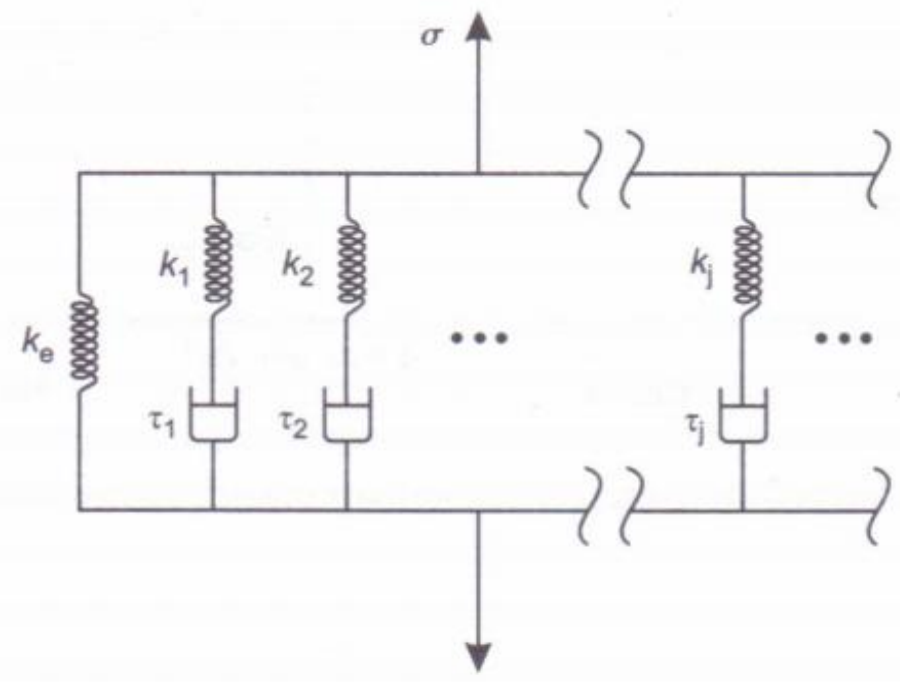


**Figure 3.27** Diagrammatic representation of the Weichert model.

1. A real polymer does not relax with a single relaxation time. Molecular segments of varying length contribute to the relaxation, with the simpler and shorter segments relaxing much more quickly than the longer ones.
2. The Weichert model takes into account the fact that relaxation does not occur at a single time, but at a distribution of times.

## Viscoelastic Creep

When subjected to a constant stress, viscoelastic materials experience a time-dependent increase in strain, known as *viscoelastic creep*. Its curve can be obtained by plotting the creep modulus (constant applied stress divided by total strain at a particular time) as a function of time as shown in Figure 3.28. The creep curve illustrates the viscoelastic properties of the material. The portion AB of the curve represents the elastic behaviour followed by the curve BC representing viscoelastic behaviour. The linear portion CD corresponds to the time when bonds in the material rupture under the influence of continuous stress, leading to viscous flow. When the stress is removed, the recovery curve DEF is obtained. The portion DE represents instantaneous elastic recovery equivalent to AB followed by slow elastic recovery region EF equivalent to BC. In the recovery curve, no portion corresponds to CD, since viscous flow occurs by irreversible destruction of the structure of the material.

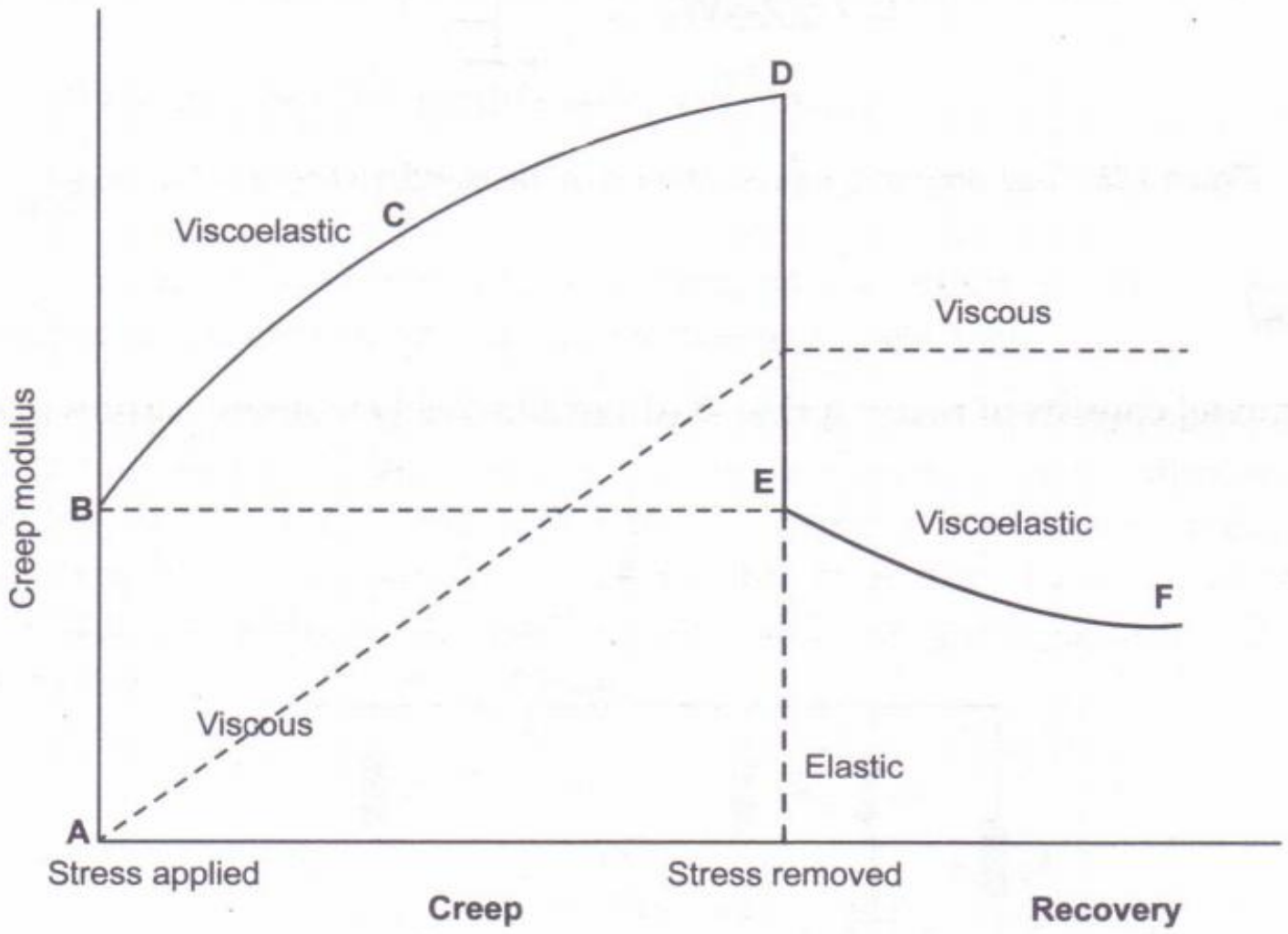


**Figure 3.28** Creep curve for a viscoelastic material.

# SPECIALIZED PHARMACEUTICAL APPLICATIONS OF RHEOLOGY

Table 3.3 depicts some shear rates corresponding to pharmaceutical use.

**Table 3.3** Shear rates value for different applications

| Parameter | Shear rate value ($s^{-1}$) |
|---|---|
| Squeezing from a tube | 10–1000 |
| Pouring from bottle | 100 |
| Topical application | 120 |
| Rubbing on ointment tile | 150 |
| Rubbing into skin | 100–10,000 |
| Nasal spray | 1000 |
| Pumping of products | 1000–100,000 |
| High-speed filling | 5000–100,000 |

## Yield Value and Suspensions

The rheological yield value theoretically permits the preparation of permanent suspensions. The theoretic yield value (YV) for suspension must balance or exceed the force of gravitational settlement. Hence, for spherical objects:

$$YV = \frac{gV(\rho_p - \rho_m)}{A} \tag{3.27}$$

where $g$ is the acceleration due to gravity, $V$ is the particle volume, $\rho_p$ is the particle density, $\rho_m$ is the suspending medium density and $A$ is the cross-sectional area of the particle ($\pi R^2$ for round particles of radius $R$). Based on this equation, to suspend sand of density 2.60 and radius 0.030 cm, theoretic yield value of 65 dyne $cm^{-2}$ is required, whereas to suspend marbles of density 2.55 and radius 0.8 cm, theoretic yield value of 1620 dyne $cm^{-2}$ is required.

## Plug Flow—Artifactual Observations

In the case of plastic material, a body may remain motionless against the motionless wall of a viscosity measuring device (such as in case of cup and bob viscometer), whereas the rest of the material moves as a unit down a tube or with a rotating bob. This behaviour is characteristic of *plug flow*. Such behaviour disrupts rheological measurements. Use of special star-shaped and ribbed bobs and/or cone and plate viscometer minimizes this effect.

## Rheological Use of Mixing Equipment

A major engineering use of rheological measurements is power requirements in mixers and blenders. Application of such measurements determines the end point of the granulation process. This can be particularly important when further mixing may create an intractable solid mass or an undesirable fluidizing.

## Biorheology

The study of flow and deformation in a biological system is called *biorheology*. Understanding the rheological properties of biological fluid is important for successful drug delivery to the body and also for understanding the general state of health. The rheological nature of various biological fluids is tabulated in Table 3.4.

**Table 3.4** Rheologic characteristics of biological fluids

| Rheological behaviour | Organ/fluid | Utility |
|---|---|---|
| Newtonian | Cerebrospinal fluid | Act as water cushion to protect the spinal cord and brain from physical impact |
| | Bronchial mucus | Viscosity increases in cystic fibrosis |
| Pseudoplastic | Synovial fluid | High viscosity at low shear maintains clearance between articular surfaces, whereas when the joint moves (at high shear) viscosity is lowered and protects the cartilage from wear |
| | Tear fluid | Allows tear fluid to form a continuous layer over the eye |
| | Blood | Viscosity increases in arteriosclerosis, coronary heart disease, angina and myocardial infarction |
| | GIT mucus | Altered rheology of the GI mucus barrier results in ulcerative processes |
| Viscoelastic | Nasal mucus | Increase in mucus viscosity indicates sinusitis and chronic inflammation |
| | Semen/cervical mucus | Transfer of spermatozoa |
| | Vitreous humour | Change in rheology from gel to liquid indicates pathological conditions |

## Questions

1. Give proper justification for the following:
   a. Single viscometric point can characterize the rheology of Newtonian fluids.
   b. Cone and plate viscometers have advantage over cup and bob viscometers.
   c. Polymer solution tends to become more fluid, the faster it is stirred.
   d. Concentrated flocculated suspensions do not flow at low shear rates.
   e. Ubbelohde viscometer is more accurate than Ostwald's U-tube viscometer.
2. Write short notes on the following:
   a. Rheopexy and negative rheopexy
   b. Plug flow
   c. Creep curve
   d. Penetrometers
   e. Bulges and spurs
3. Explain time-independent non-Newtonian flow of fluids with suitable examples, rheograms and mechanism.
4. Explain the thixotropy in plastic and pseudoplastic system. Describe procedure to measure thixotropy.
5. Define viscoelasticity and describe various viscoelastic models.

# 17 COARSE DISPERSIONS

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

1. Describe what pharmaceutical suspensions are and what roles they play in the pharmaceutical sciences.
2. Discuss the desirable qualities of pharmaceutical suspensions.
3. Discuss the factors that affect the stability of suspensions and explain flocculation.
4. Describe settling and sedimentation theory and calculate sedimentation rates.
5. Define and calculate the two useful sedimentation parameters, sedimentation volume and degree of flocculation.
6. Describe the approaches commonly used in the preparation of physically stable suspensions.
7. Define pharmaceutical emulsion and emulsifying agent and identify the main types of emulsions.
8. Discuss the four classifications of pharmaceutical emulsion instability.
9. Understand semisolids, thixotropic properties, syneresis, and swelling.
10. Classify pharmaceutical semisolids.
11. Describe coarse dispersions and give examples.

Particulate systems have been classified on the basis of size into molecular dispersions (Chapter 5), colloidal systems (Chapter 16), and coarse dispersions (this chapter). This chapter attempts to provide the pharmacist with an insight into the role of physics and chemistry in the research and development of the several classes of coarse dispersions. The theory and technology of these important pharmaceutical classes are based on interfacial and colloidal principles, micromeritics, and rheology (Chapters 15, 16, 18, and 19, respectively).

## SUSPENSIONS

A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium. The particles have diameters for the most part greater than 0.1 $\mu$m, and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity.

Examples of oral suspensions are the oral antibiotic syrups, which normally contain 125 to 500 mg per 5 mL of solid material. When formulated for use as pediatric drops, the concentration of suspended material is correspondingly greater. Antacid and radiopaque suspensions generally contain high concentrations of dispersed solids. Externally applied suspensions for topical use are legion and are designed for dermatologic, cosmetic, and protective purposes. The concentration of dispersed phase may exceed 20%. Parenteral suspensions contain from 0.5% to 30% of solid particles. Viscosity and particle size are significant factors because they affect the ease of injection and the availability of the drug in depot therapy.

An acceptable suspension possesses certain desirable qualities, including the following. The suspended material should not settle rapidly; the particles that do settle to the bottom of the container must not form a hard cake but should be readily redispersed into a uniform mixture when the container is shaken; and the suspension must not be too viscous to pour freely from the orifice of the bottle or to flow through a syringe needle. In the case of an external lotion, the product must be fluid enough to spread easily over the affected area and yet must not be so mobile that it runs off the surface to which it is applied; the lotion must dry quickly and provide an elastic protective film that will not rub off easily; and it must have an acceptable color and odor.

It is important that the characteristics of the dispersed phase be chosen with care so as to produce a suspension having optimum physical, chemical, and pharmacologic properties. Particle-size distribution, specific surface area, inhibition of crystal growth, and changes in polymorphic form are of special significance, and the formulator must ensure that these and other properties[1–3] do not change sufficiently

### KEY CONCEPT SUSPENSIONS

Suspensions contribute to pharmacy and medicine by supplying insoluble and what often would otherwise be distasteful substances in a form that is pleasant to the taste, by providing a suitable form for the application of dermatologic materials to the skin and sometimes to the mucous membranes, and for the parenteral administration of insoluble drugs. Therefore, pharmaceutical suspensions can be classified into three groups: orally administered mixtures, externally applied lotions, and injectable preparations.

during storage to adversely affect the performance of the suspension. Finally, it is desirable that the product contain readily obtainable ingredients that can be incorporated into the mixture with relative ease by the use of standard methods and equipment.

The remainder of this section will be devoted to a discussion of some of the properties that provide the desirable characteristics just enumerated.

For pharmaceutical purposes, *physical stability* of suspensions may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion. Because this ideal situation is seldom realized, it is appropriate to add that if the particles do settle, they should be easily resuspended by a moderate amount of agitation.

## INTERFACIAL PROPERTIES OF SUSPENDED PARTICLES

Little is known about energy conditions at the surfaces of solids, yet knowledge of the thermodynamic requirements is needed for the successful stabilization of suspended particles.

Work must be done to reduce a solid to small particles and disperse them in a continuous medium. The large surface area of the particles that results from the comminution is associated with a surface free energy that makes the system *thermodynamically unstable*, by which we mean that the particles are highly energetic and tend to regroup in such a way as to decrease the total area and reduce the surface free energy. The particles in a liquid suspension therefore tend to *flocculate*, that is, to form light, fluffy conglomerates that are held together by weak van der Waals forces. Under certain conditions—in a compacted cake, for example—the particles may adhere by stronger forces to form what are termed *aggregates*. Caking often occurs by the growth and fusing together of crystals in the precipitates to produce a solid aggregate.

The formation of any type of agglomerate, either floccules or aggregates, is taken as a measure of the system's tendency to reach a more thermodynamically stable state. An increase in the work, $W$, or surface free energy, $\Delta G$, brought about by dividing the solid into smaller particles and consequently increasing the total surface area, $\Delta A$, is given by

$$\Delta G = \gamma SL \cdot \Delta A \qquad (17\text{–}1)$$

where $\gamma_{SL}$ is the interfacial tension between the liquid medium and the solid particles.

**EXAMPLE 17–1**

**Surface Free Energy**

**Compute the change in the surface free energy of a solid in a suspension if the total surface is increased from $10^3$ to $10^7$ cm$^2$. Assume that the interfacial tension between the solid and the liquid medium, $\gamma_{SL}$, is 100 dynes/cm.**

**The initial free energy is**

$$G_1 = 100 \times 10^3 = 10^5 \text{ ergs/cm}^2$$

**When the surface area is $10^7$ cm$^2$,**

$$G_2 = 100 \times 10^7 = 10^9 \text{ ergs/cm}^2$$

**The change in the free energy, $\Delta G_{21}$, is $10^9 - 10^5 \cong 10^9$ erg/cm$^2$. The free energy has been increased by $10^9$, which makes the system more thermodynamically unstable.**

To approach a stable state, the system tends to reduce the surface free energy; equilibrium is reached when $\Delta G = 0$. This condition can be accomplished, as seen from equation (17–1), by a reduction of interfacial tension, or it can be approached by a decrease of the interfacial area. The latter possibility, leading to flocculation or aggregation, can be desirable or undesirable in a pharmaceutical suspension, as considered in a later section.

The interfacial tension can be reduced by the addition of a surfactant but cannot ordinarily be made equal to zero. A suspension of insoluble particles, then, usually possesses a finite positive interfacial tension, and the particles tend to flocculate. An analysis paralleling this one could also be made for the breaking of an emulsion.

The forces at the surface of a particle affect the degree of flocculation and agglomeration in a suspension. Forces of attraction are of the London–van der Waals type; the repulsive forces arise from the interaction of the electric double layers surrounding each particle. The formation of the electric double layer is considered in detail in Chapter 15, which deals with interfacial phenomena. The student is advised to review, at this point, the section dealing with the electrical properties of interfaces because particle charge, electric double-layer formation, and zeta potential are all relevant to the present topic.

The potential energy of two particles is plotted in **Figure 17–1** as a function of the distance of separation. Shown are the curves depicting the energy of attraction, the energy of repulsion, and the net energy, which has a peak and two minima. When the repulsion energy is high, the potential barrier is also high, and collision of the particles is opposed. The system remains deflocculated, and, when sedimentation is complete, the particles form a close-packed arrangement with the smaller particles filling the voids between the larger ones. Those particles lowest in the sediment are gradually pressed together by the weight of the ones above; the energy barrier is thus overcome, allowing the particles to come into close contact with each other. To resuspend and redisperse these particles, it is again necessary to overcome the high-energy barrier. Because this is not easily achieved by agitation, the particles tend to remain strongly attracted to each other and form a hard cake. When the particles are flocculated, the energy barrier is still too large to be surmounted, and so the approaching particle resides in the second energy minimum, which is at a distance of separation of perhaps 1000 to 2000 Å. This distance is sufficient to form the loosely structural flocs. These concepts evolve from the Derjaguin and Landau, Verwey and Overbeek (DLVO) theory for the stability of lyophobic sols. Schneider et al.[4] prepared a computer program for

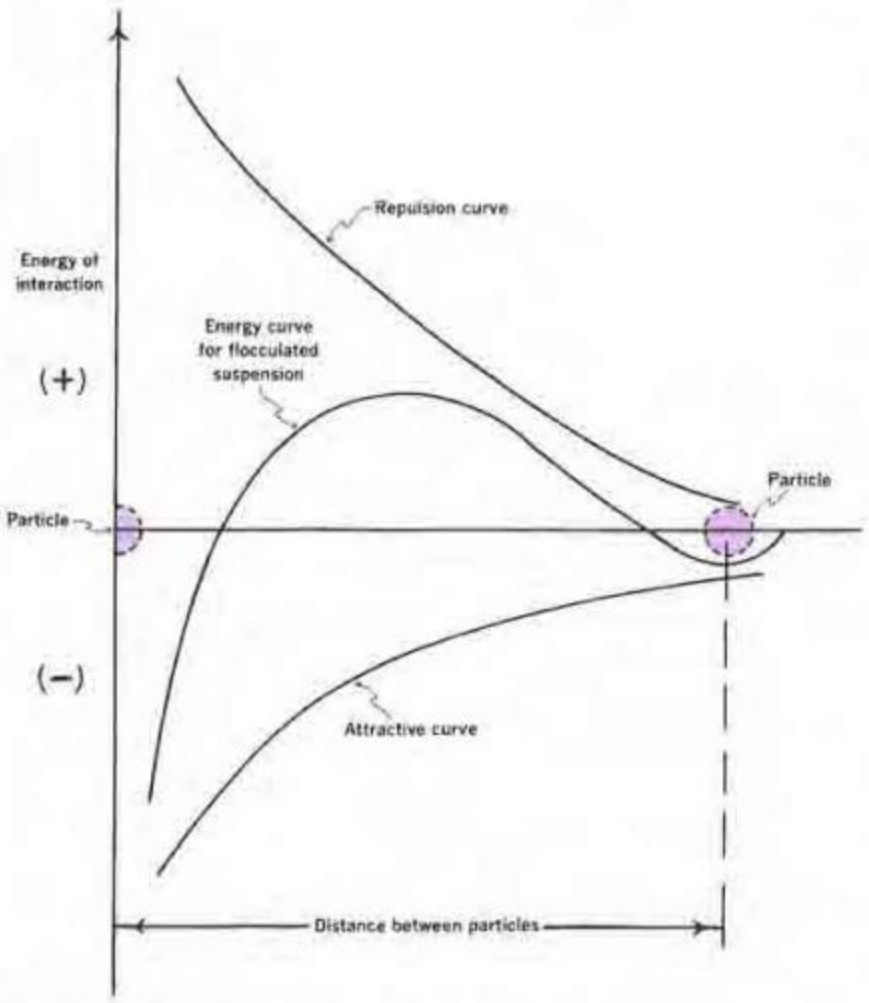


Fig. 17–1. Potential energy curves for particle interactions in suspension. (From A. Martin, J. Pharm. Sci. **50**, 514, 1961. With permission.)

calculating the repulsion and attraction energies in pharmaceutical suspensions. They showed the methods of handling the DLVO equations and the careful consideration that must be given to the many physical units involved. Detailed examples of calculations were given.

To summarize, flocculated particles are weakly bonded, settle rapidly, do not form a cake, and are easily resuspended; deflocculated particles settle slowly and eventually form a sediment in which aggregation occurs with the resultant formation of a hard cake that is difficult to resuspend.

## SETTLING IN SUSPENSIONS

As mentioned earlier, one aspect of physical stability in pharmaceutical suspensions is concerned with keeping the particles uniformly distributed throughout the dispersion. Although it is seldom possible to prevent settling completely over a prolonged period of time, it is necessary to consider the factors that influence the velocity of sedimentation.

### Theory of Sedimentation

The velocity of sedimentation is expressed by Stokes's law:

$$v = \frac{d^2(\rho_s - \rho_o)g}{18\eta_o} \qquad (17\text{–}2)$$

where $v$ is the terminal velocity in cm/sec, $d$ is the diameter of the particle in cm, $\rho_s$ and $\rho_o$ are the densities of the dispersed phase and dispersion medium, respectively, $g$ is the acceleration due to gravity, and $\eta_o$ is the viscosity of the dispersion medium in poise.

Dilute pharmaceutical suspensions containing less than about 2 g of solids per 100 mL of liquid conform roughly to these conditions. (Some feel that the concentration must be less than 0.5 g/100 mL before Stokes's equation is valid.) In dilute suspensions, the particles do not interfere with one another during sedimentation, and *free settling* occurs. In most pharmaceutical suspensions that contain dispersed particles in concentrations of 5%, 10%, or higher percentages, the particles exhibit *hindered settling*. The particles interfere with one another as they fall, and Stokes's law no longer applies.

Under these circumstances, some estimation of physical stability can be obtained by diluting the suspension so that it contains about 0.5% to 2.0% w/v of dispersed phase. This is not always recommended, however, because the stability picture obtained is not necessarily that of the original suspension. The addition of a diluent may affect the degree of flocculation (or deflocculation) of the system, thereby effectively changing the particle-size distribution.

To account for the nonuniformity in particle shape and size invariably encountered in real systems. We can write Stokes's equation in other forms. One of the proposed modifications is[5]

$$v' = v\epsilon^n \qquad (17\text{–}3)$$

where $v'$ is the rate of fall at the interface in cm/sec and $v$ is the velocity of sedimentation according to Stokes's law. The term $\varepsilon$ represents the initial porosity of the system, that is, the initial volume fraction of the uniformly mixed suspension, which varies from zero to unity. The exponent $n$ is a measure of the "hindering" of the system. It is a constant for each system.

**EXAMPLE 17–2**

**The average particle diameter of calcium carbonate in aqueous suspension is 54 $\mu$m. The densities of $CaCO_3$ and water, respectively, are 2.7 and 0.997 g/cm$^3$. The viscosity of water is 0.009 poise at 25°C. Compute the rate of fall $v'$ for $CaCO_3$ samples at two different porosities, $\epsilon_1 = 0.95$ and $\epsilon_2 = 0.5$. The $n$ value is 19.73.**

**From Stokes's law, equation (17–2),**

$$v = \frac{(54 \times 10^{-4})^2(2.7 - 0.997)981}{18 \times 0.009} = 0.30 \text{ cm/sec}$$

**Taking logarithms on both sides of equation (17–3), we obtain $\ln v' = \ln v + n \ln \epsilon$.**

**For $\epsilon_1 = 0.95$,**

$$\ln v' = -1.204 + [19.73(-0.051)] = -2.210$$

$$v' = 0.11 \text{ cm/sec}$$

**Analogously, for $\epsilon_2 = 0.5$, $v' = 3.5 \times 10^{-7}$ cm/sec. Note that at low porosity values (i.e., 0.5, which corresponds to a high concentration of solid in suspension), the sedimentation is hindered, leading to small $v'$ values. On the other hand, when the suspension becomes infinitely diluted (i.e., $\epsilon = 1$), the rate of fall is given by $v' = v$. In**

the present example, if $\epsilon = 1$,

$$v' = 0.3 \times 1^{19.73} = 0.3 \text{ cm/sec}$$

which is the Stokes-law velocity.

## Effect of Brownian Movement

For particles having a diameter of about 2 to 5 $\mu$m (depending on the density of the particles and the density and viscosity of the suspending medium), Brownian movement counteracts sedimentation to a measurable extent at room temperature by keeping the dispersed material in random motion. The *critical radius, r,* below which particles will be kept in suspension by kinetic bombardment of the particles by the molecules of the suspending medium (Brownian movement) was worked out by Burton.[6]

It can be seen in the microscope that Brownian movement of the smallest particles in a field of particles of a pharmaceutical suspension is usually eliminated when the sample is dispersed in a 50% glycerin solution, having a viscosity of about 5 centipoise. Hence, it is unlikely that the particles in an ordinary pharmaceutical suspension containing suspending agents are in a state of vigorous Brownian motion.

## Sedimentation of Flocculated Particles

When sedimentation is studied in flocculated systems, it is observed that the flocs tend to fall together, producing a distinct boundary between the sediment and the supernatant liquid. The liquid above the sediment is clear because even the small particles present in the system are associated with the flocs. Such is not the case in deflocculated suspensions having a range of particle sizes, in which, in accordance with Stokes's law, the larger particles settle more rapidly than the smaller particles. No clear boundary is formed (unless only one size of particle is present), and the supernatant remains turbid for a considerably longer period of time. Whether the supernatant liquid is clear or turbid during the initial stages of settling is a good indication of whether the system is flocculated or deflocculated, respectively.

According to Hiestand,[7] the initial rate of settling of flocculated particles is determined by the floc size and the porosity of the aggregated mass. Subsequently, the rate depends on compaction and rearrangement processes within the sediment. The term *subsidence* is sometimes used to describe settling in flocculated systems.

## Sedimentation Parameters

Two useful parameters that can be derived from sedimentation (or, more correctly, subsidence) studies are *sedimentation volume, V,* or *height, H,* and *degree of flocculation.*

The sedimentation volume, $F$, is defined as the ratio of the final, or ultimate, volume of the sediment, $V_u$, to the original volume of the suspension, $V_o$, before settling. Thus,

$$F = V_u / V_o \qquad (17\text{–}4)$$

The sedimentation volume can have values ranging from less than 1 to greater than 1. $F$ is normally less than 1, and in this case, the ultimate volume of sediment is smaller than the original volume of suspension, as shown in **Figure 17–2*a***, in which $F = 0.5$. If the volume of sediment in a flocculated suspension equals the original volume of suspension, then $F = 1$ (**Fig. 17–2*b***). Such a product is said to be in "flocculation equilibrium" and shows no clear supernatant on standing. It is therefore pharmaceutically acceptable. It is possible for $F$ to have values greater than 1, meaning that the final volume of sediment is greater than the original suspension volume. This comes about because the network of flocs formed in the suspension is so loose and fluffy that the volume they

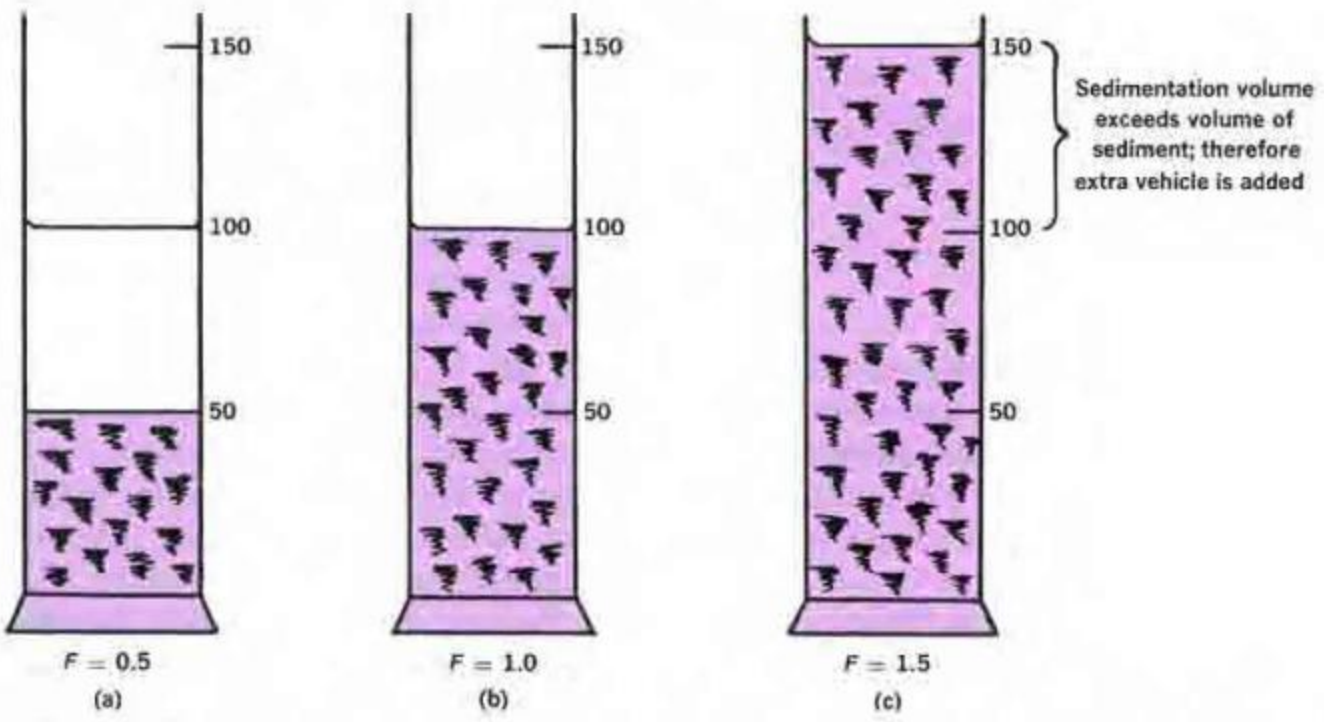


Fig. 17–2. Sedimentation volumes produced by adding varying amounts of flocculating agent. Examples (*b*) and (*c*) are pharmaceutically acceptable.

are able to encompass is greater than the original volume of suspension. This situation is illustrated in **Figure 17–2*c***, in which sufficient extra vehicles have been added to contain the sediment. In example shown, $F = 1.5$.

The sedimentation volume gives only a qualitative account of flocculation because it lacks a meaningful reference point.[7] A more useful parameter for flocculation is $\beta$, the *degree of flocculation*.

If we consider a suspension that is completely deflocculated, the ultimate volume of the sediment will be relatively small. Writing this volume as $V_\infty$, based on equation **(17–4)**, we have

$$F_\infty = V_\infty / V_o \qquad \textbf{(17–5)}$$

where $F_\infty$ is the sedimentation volume of the deflocculated, or peptized, suspension. The degree of flocculation, $\beta$, is therefore defined as the ratio of $F$ to $F_\infty$, or

$$\beta = F/F_\infty \qquad \textbf{(17–6)}$$

Substituting equations **(17–4)** and **(17–5)** in equation **(17–6)**, we obtain

$$\beta = \frac{V_u/V_o}{V_\infty/V_o} = V_u/V_\infty \qquad \textbf{(17–7)}$$

The degree of flocculation is a more fundamental parameter than $F$ because it relates the volume of flocculated sediment to that in a deflocculated system. We can therefore say that

$$\beta = \frac{\text{Ultimate sediment volume of } \textit{flocculated} \text{ suspension}}{\text{Ultimate sediment volume of } \textit{deflocculated} \text{ suspension}}$$

**EXAMPLE 17–3**

**Compute the sedimentation volume of a 5% w/v suspension of magnesium carbonate in water. The initial volume is $V_o = 100$ mL and the final volume of the sediment is $V_u = 30$ mL. If the degree of flocculation is $\beta = F/F_\infty = 1.3$, what is the deflocculated sedimentation volume, $F_\infty$?**

We have

$$F = 30/100 = 0.30$$

$$F_\infty = F/\beta = 0.30/1.3 = 0.23$$

## FORMULATION OF SUSPENSIONS

The approaches commonly used in the preparation of physically stable suspensions fall into two categories—the use of a structured vehicle to maintain deflocculated particles in suspension, and the application of the principles of flocculation to produce flocs that, although they settle rapidly, are easily resuspended with a minimum of agitation.

*Structured vehicles* are pseudoplastic and plastic in nature; their rheologic properties are discussed in Chapter 19. As we shall see in a later section, it is frequently desirable that thixotropy be associated with these two types of flow. Structured vehicles act by entrapping the particles (generally deflocculated) so that, ideally, no settling occurs. In reality, some degree of sedimentation will usually take place. The "shear-thinning" property of these vehicles does, however, facilitate the re-formation of a uniform dispersion when shear is applied.

A disadvantage of deflocculated systems, mentioned earlier, is the formation of a compact cake when the particles eventually settle. It is for this reason that the formulation of flocculated suspensions has been advocated.[8] Optimum physical stability and appearance will be obtained when the suspension is formulated with flocculated particles in a structured vehicle of the hydrophilic colloid type. Consequently, most of the subsequent discussion will be concerned with this approach and the means by which controlled flocculation can be achieved. Whatever approach is used, the product must (*a*) flow readily from the container and (*b*) possess a uniform distribution of particles in each dose.

### Wetting of Particles

The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process and requires further consideration. Powders sometimes are added to the vehicle, particularly in large-scale operations, by dusting on the surface of the liquid. It is frequently difficult to disperse the powder owing to an adsorbed layer of air, minute quantities of grease, and other contaminants. The powder is not readily wetted, and although it may have a high density, it floats on the surface of the liquid. Finely powdered substances are particularly susceptible to this effect because of entrained air, and they fail to become wetted even when forced below the surface of the suspending medium. The *wettability* of a powder can be ascertained easily by observing the contact angle that powder makes with the surface of the liquid. The angle is approximately 90° when the particles are floating well out of the liquid. A powder that floats low in the liquid has a lesser angle, and one that sinks obviously shows no contact angle. Powders that are not easily wetted by water and accordingly show a large contact angle, such as sulfur, charcoal, and magnesium stearate, are said to be *hydrophobic*. Powders that are readily wetted by water when free of adsorbed contaminants are called *hydrophilic*. Zinc oxide, talc, and magnesium carbonate belong to the latter class.

Surfactants are quite useful in the preparation of a suspension in reducing the interfacial tension between solid particles and a vehicle. As a result of the lowered interfacial tension, the advancing contact angle is lowered, air is displaced from the surface of particles, and wetting and deflocculation are promoted. Schott et al.[9] studied the deflocculating effect of octoxynol, a nonionic surfactant, in enhancing the dissolution rate of prednisolone from tablets. The tablets break up into fine granules that are deflocculated in suspension. The deflocculating effect is proportional to the surfactant concentration. However, at very high surfactant concentration, say, 15 times the critical micelle concentration, the surfactant produces extensive flocculation. Glycerin and similar

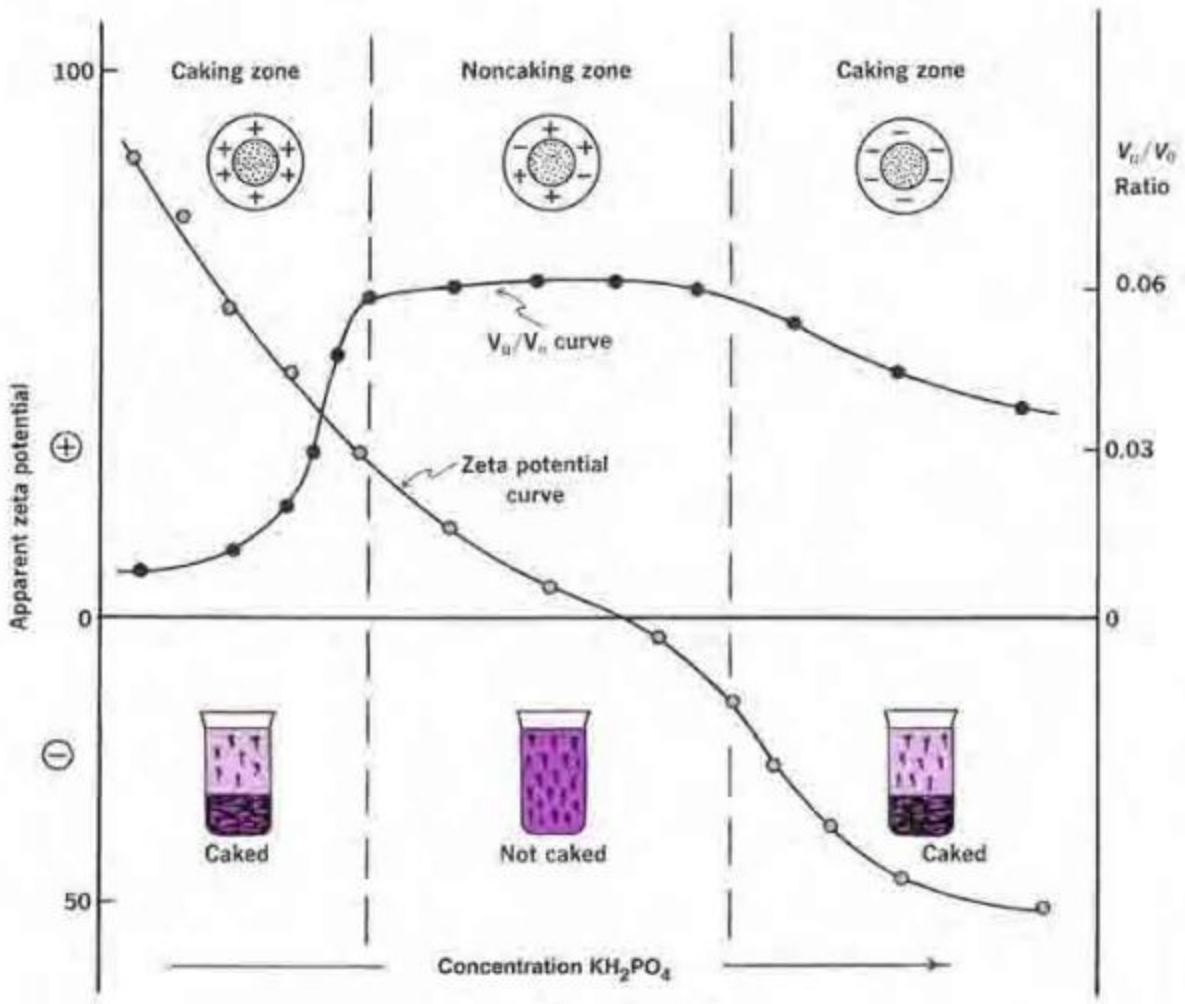


Fig. 17–3. Caking diagram, showing the flocculation of a bismuth subnitrate suspension by means of the flocculating agent monobasic potassium phosphate. (From A. Martin and J. Swarbrick, in *Sprowls' American Pharmacy*, 6th Ed., Lippincott, Philadelphia, 1966, p. 205. With permission.)

hygroscopic substances are also valuable in levigating the insoluble material. Apparently, glycerin flows into the voids between the particles to displace the air and, during the mixing operation, coats and separates the material so that water can penetrate and wet the individual particles. The dispersion of particles of colloidal gums by alcohol, glycerin, and propylene glycol, allowing water to subsequently penetrate the interstices, is a well-known practice in pharmacy.

To select suitable wetting agents that possess a well-developed ability to penetrate the powder mass, Hiestand[7] used a narrow trough, several inches long and made of a hydrophobic material, such as Teflon, or coated with paraffin wax. At one end of the trough is placed the powder and at the other end the solution of the wetting agent. The rate of penetration of the latter into the powder can then be observed directly.

## Controlled Flocculation

Assuming that the powder is properly wetted and dispersed, we can now consider the various means by which controlled flocculation can be produced so as to prevent formation of a compact sediment that is difficult to redisperse. The topic, described in detail by Hiestand,[7] is conveniently discussed in terms of the materials used to produce flocculation in suspensions, namely electrolytes, surfactants, and polymers.

*Electrolytes* act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta potential and the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

If we disperse particles of bismuth subnitrate in water, we find that, based on electrophoretic mobility studies, they possess a large positive charge, or zeta potential. Because of the strong forces of repulsion between adjacent particles, the system is peptized or deflocculated. By preparing a series of bismuth subnitrate suspensions containing increasing concentrations of monobasic potassium phosphate, Haines and Martin[10] were able to show a correlation between apparent zeta potential and sedimentation volume, caking, and flocculation. The results are summarized in **Figure 17–3** and are explained in the following manner.

The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of the negatively charged phosphate anion. With the continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in the negative direction, as shown in **Figure 17–3**. Microscopic examination of the various suspensions shows that at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again. The onset of flocculation coincides with the maximum sedimentation volume determined. $F$ remains reasonably constant while flocculation persists, and only when the zeta potential becomes sufficiently negative to effect repeptization does the sedimentation volume start to fall. Finally, the absence of caking in the suspensions correlates with the maximum sedimentation volume, which, as stated previously,

## KEY CONCEPT WHAT IS A POLYMER?

*Polymers* are long-chain, high–molecular-weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.

reflects the amount of flocculation. At less than maximum values of $F$, caking becomes apparent.

These workers[10] also demonstrated a similar correlation when aluminum chloride was added to a suspension of sulfamerazine in water. In this system, the initial zeta potential of the sulfamerazine particles is negative and is progressively reduced by adsorption of the trivalent aluminum cation. When sufficient electrolyte is added, the zeta potential reaches zero and then increases in a positive direction. Colloidal and coarse dispersed particles can possess surface charges that depend on the pH of the system. An important property of the pH-dependent dispersions is the zero point of charge, that is, the pH at which the net surface charge is zero. The desired surface charge can be achieved through adjusting the pH by the addition of HCl or NaOH to produce a positive, zero, or negative surface charge. The negative zeta potential of nitrofurantoin decreases considerably when the pH values of the suspension are charged from basic to acidic.[11]

*Surfactants*, both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical because these compounds can also act as wetting and deflocculating agents to achieve dispersion.

Felmeister and others[12] studied the influence of a xanthan gum (an anionic heteropolysaccharide) on the flocculation characteristics of sulfaguanidine, bismuth subcarbonate, and other drugs in suspension. Addition of xanthan gum resulted in increased sedimentation volume, presumably by a polymer-bridging phenomenon. Hiestand[13] reviewed the control of floc structure in coarse suspensions by the addition of polymeric materials.

Hydrophilic polymers also act as protective colloids, and particles coated in this manner are less prone to cake than are uncoated particles. These polymers exhibit pseudoplastic flow in solution, and this property serves to promote physical stability within the suspension. Gelatin, a polyelectrolytic polymer, exhibits flocculation that depends on the pH and ionic strength of the dispersion medium. Sodium sulfathiazole, precipitated from acid solution in the presence of gelatin, was shown by Blythe[14] to be free-flowing in the dry state and not to cake when suspended. Sulfathiazole normally carries a negative charge in aqueous vehicles. The coated material, precipitated from acid solution in the presence of gelatin, however, was found to carry a positive charge. This is due to gelatin being positively charged at the pH at which precipitation was carried out. It has been suggested[8] that the improved properties result from the positively charged gelatin-coated particles being partially flocculated in suspension, presumably because the high negative charge has been replaced by a smaller, albeit positive, charge. Positively charged liposomes have been used as flocculating agents to prevent caking of negatively charged particles. Liposomes are vesicles of phospholipids having no toxicity and that can be prepared in various particle sizes.[15] They are adsorbed on the negatively charged particles.

### Flocculation in Structured Vehicles

Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if $F$, the sedimentation volume, is not close or equal to 1. Consequently, in practice, a suspending agent is frequently added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose, Carbopol 934, Veegum, tragacanth, and bentonite have been employed, either alone or in combination.

This can lead to incompatibilities, depending on the initial particle charge and the charge carried by the flocculating agent and the suspending agent. For example, suppose we prepare a dispersion of positively charged particles that is then flocculated by the addition of the correct concentration of an anionic electrolyte such as monobasic potassium phosphate. We can improve the physical stability of this system by adding a minimal amount of one of the hydrocolloids just mentioned. No physical incompatibility will be observed because the majority of hydrophilic colloids are themselves negatively charged and are thus compatible with anionic flocculating agents. If, however, we flocculate a suspension of negatively charged particles with a cationic electrolyte (aluminum chloride), the subsequent addition of a hydrocolloid may result in an incompatible product, as evidenced by the formation of an unsightly stringy mass that has little or no suspending action and itself settles rapidly.

Under these circumstances, it becomes necessary to use a protective colloid to change the sign on the particle from negative to positive. This is achieved by the adsorption onto the particle surface of a fatty acid amine (which has been checked to ensure its nontoxicity) or a material such as gelatin, which is positively charged below its isoelectric point. We are then able to use an anionic electrolyte to produce flocs that are compatible with the negatively charged suspending agent.

This approach can be used regardless of the charge on the particle. The sequence of events is depicted in **Figure 17–4**, which is self-explanatory.

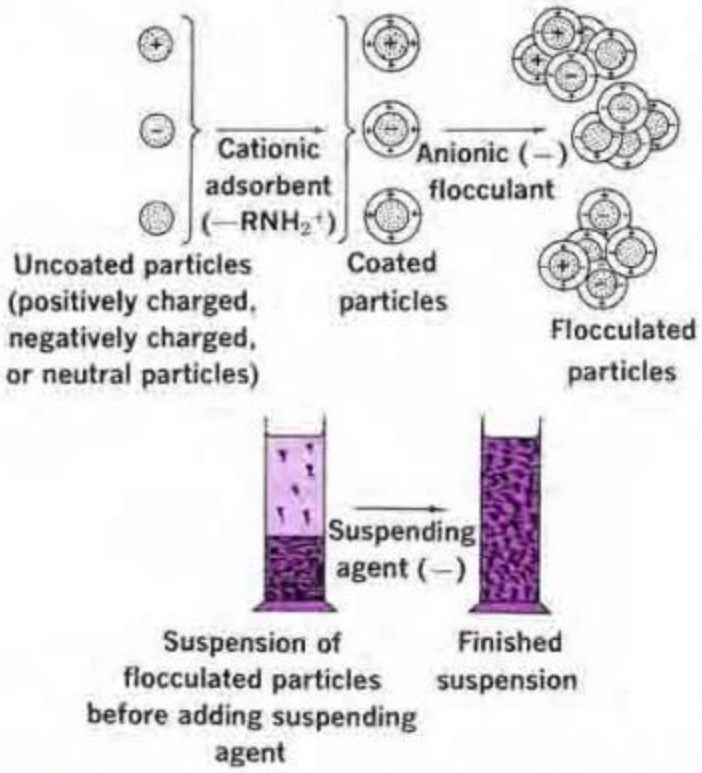


Fig. 17–4. The sequence of steps involved in the formation of a stable suspension. (From A. Martin and J. Swarbrick, in *Sprowls' American Pharmacy*, 6th Ed., Lippincott, Philadelphia, 1966, p. 206. With permission.)

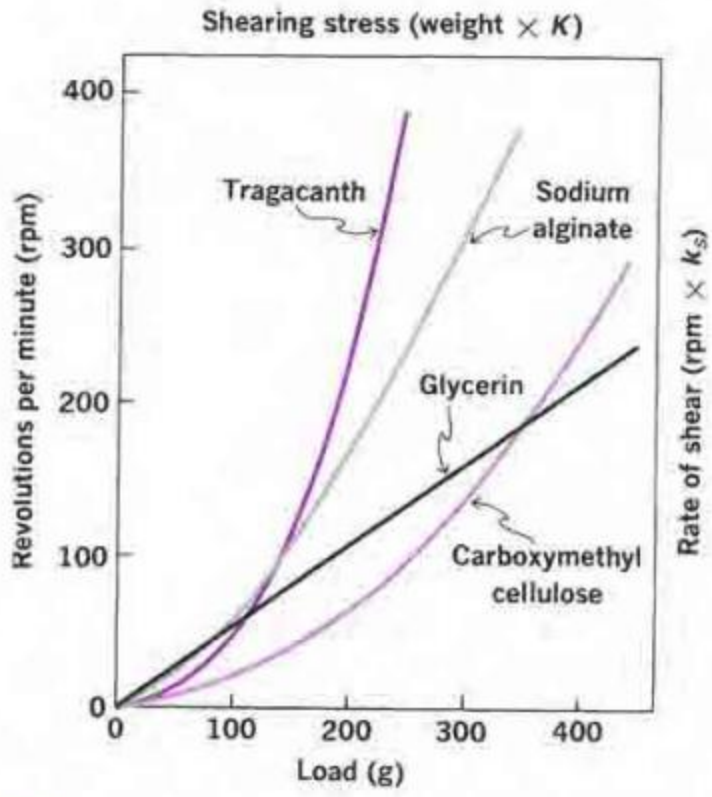


Fig. 17–5. Rheologic flow curves of various suspending agents analyzed in a modified Stormer viscometer.

## Rheologic Considerations

The principles of rheology can be applied to a study of the following factors: the viscosity of a suspension as it affects the settling of dispersed particles, the change in flow properties of the suspension when the container is shaken and when the product is poured from the bottle, and the spreading qualities of the lotion when it is applied to an affected area. Rheologic considerations are also important in the manufacture of suspensions.

The only shear that occurs in a suspension in storage is due to a settling of the suspended particles; this force is negligible and may be disregarded. When the container is shaken and the product is poured from the bottle, however, a high shearing rate is manifested. As suggested by Mervine and Chase,[16] the ideal suspending agent should have a *high* viscosity at negligible shear, that is, during shelf storage; and it should have a *low* viscosity at high shearing rates, that is, it should be free-flowing during agitation, pouring, and spreading. As seen in **Figure 17–5**, pseudoplastic substances such as tragacanth, sodium alginate, and sodium carboxymethylcellulose show these desirable qualities. The Newtonian liquid glycerin is included in the graph for comparison. Its viscosity is suitable for suspending particles but is too high to pour easily and to spread on the skin. Furthermore, glycerin shows the undesirable property of tackiness (stickiness) and is too hygroscopic to use in undiluted form. The curves in **Figure 17–5** were obtained by use of the modified Stormer viscometer.

A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful because it forms a gel on standing and becomes fluid when disturbed. **Figure 17–6** shows the consistency curves for bentonite, Veegum (Vanderbilt Co.), and a combination of bentonite and sodium carboxymethylcellulose. The hysteresis loop of bentonite is quite marked. Veegum also shows considerable thixotropy, both when tested by inverting a vessel containing the dispersion and when analyzed in a rotational viscometer. When bentonite and carboxymethylcellulose dispersions are mixed, the resulting curve shows both pseudoplastic and thixotropic characteristics. Such a combination should produce an excellent suspending medium.

## Preparation of Suspensions

The factors entering into the preparation and stabilization of suspensions involve certain principles of interest to physical pharmacy and are briefly discussed here. The physical

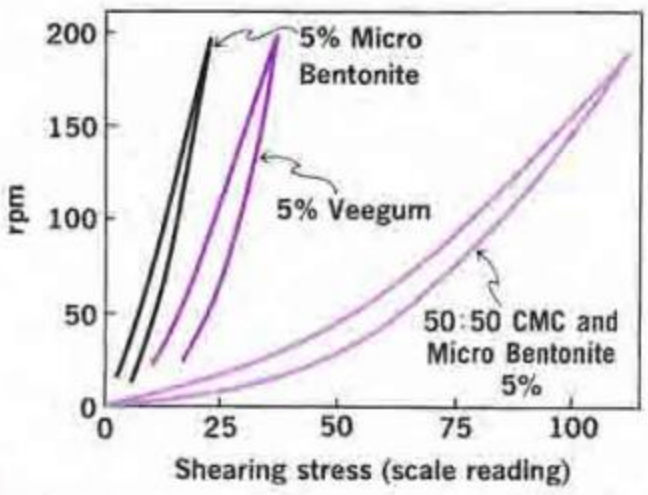


Fig. 17–6. Flow curves for 5% suspending agents in water, showing thixotropy. The curves were obtained with the Ferranti–Shirley cone–plate viscometer.

principles involved in the dispersion of solids by different types of equipment were discussed by Oldshue.[17]

A suspension is prepared on the small scale by grinding or levigating the insoluble material in the mortar to a smooth paste with a vehicle containing the dispersion stabilizer and gradually adding the remainder of the liquid phase in which any soluble drugs may be dissolved. The slurry is transferred to a graduate, the mortar is rinsed with successive portions of the vehicle, and the dispersion is finally brought to the final volume.

On a large scale, dispersion of solids in liquids is accomplished by the use of ball, pebble, and colloid mills. Dough mixers, pony mixers, and similar apparatus are also employed. Only the colloid mill is described here; a discussion of the other mills can be found in the book by Fischer.[18a] Dry grinding in ball mills is treated by Fischer,[18a] Berry and Kamack,[18b] and Prasher.[18c]

The colloid mill is based on the principle of a high-velocity, cone-shaped rotor that is centered with respect to a stator at a small adjustable clearance. The suspension is fed to the rotor by gravity through a hopper, sheared between the rotor and the stator, and forced out below the stator, where it may be recycled or drawn off.

The efficiency of the mill is based on the clearance between the disks, the peripheral velocity of the rotor, and the non-Newtonian viscosity of the suspension. The mill breaks down the large aggregates and flocs so that they can be dispersed throughout the liquid vehicle and then protected by the dispersion stabilizer. The shearing action that leads to disaggregation occurs at the surfaces of the rotating and stationary disks and between the particles themselves in a concentrated suspension. If the yield value is too great, the material fails to flow; if the viscosity is low, a loss in effectiveness of shearing action occurs. Therefore, the yield value should be low, and the plastic or apparent viscosity of the material should be at a maximum consistent with the optimum rate of flow through the mill. If the material is highly viscous or if the plates are adjusted to a clearance that is too narrow, the temperature rises rapidly, and cooling water must be circulated around the stator to dissipate the heat that is produced. Dilatant materials—for example, deflocculated suspensions containing 50% or more of solids—are particularly troublesome. They flow freely into the mill but set up a high shearing rate and produce overheating and stalling of the motor. Beginning any milling process with the plates set at a wide clearance minimizes this danger. If this technique fails, however, the material must be milled in another type of equipment or the paste must be diluted with a vehicle until dilatancy is eliminated.

## Physical Stability of Suspensions

Raising the temperature often leads to flocculation of *sterically stabilized* suspensions, that is, suspensions stabilized by nonionic surfactants. Repulsion due to steric interactions depends on the nature, thickness, and completeness of the surfactant-adsorbed layers on the particles. When the suspension is heated, the energy of repulsion between the particles can be reduced owing to dehydration of the polyoxyethylene groups of the surfactant. The attractive energy is increased and the particles flocculate.[19] Zapata et al.[20] studied the mechanism of freeze–thaw instability in aluminum hydrocarbonate and magnesium hydroxide gels as model suspensions because of their well-known sensitivity to temperature changes. During the freezing process, particles can overcome the repulsive barrier caused by ice formation, which forces the particles close enough to experience the strong attractive forces present in the primary minimum and form aggregates according to the DLVO theory. When the ice melts, the particles remain as aggregates unless work is applied to overcome the primary energy peak. Aggregate size was found to be inversely related to the freezing rate. The higher the freezing rate, the smaller is the size of ice crystals formed. These small crystals do not result in the aggregation of as many suspension particles as do large ice crystals.

In addition to particle aggregation, particle growth is also a destabilizing process resulting from temperature fluctuations or *Ostwald ripening* during storage. Fluctuations of temperature can change the particle size distribution and polymorphic form of a drug, altering the absorption rate and drug bioavailability.[21] Particle growth is particularly important when the solubility of the drug is strongly dependent on the temperature. Thus, when temperature is raised, crystals of drug may dissolve and form supersaturated solutions, which favor crystal growth. This can be prevented by the addition of polymers or surfactants. Simonelli et al.[3] studied the inhibition of sulfathiazole crystal growth by polyvinylpyrrolidone. These authors suggested that the polymer forms a noncondensed netlike film over the sulfathiazole crystal, allowing the crystal to grow out only through the openings of the net. The growth is thus controlled by the pore size of the polymer network at the crystal surface. The smaller the pore size, the higher is the supersaturation of the solution required for the crystals to grow. This can be shown using the Kelvin equation as applied to a particle suspended in a saturated solution[3]:

$$\ln \frac{c}{c_o} = \frac{2\gamma M}{NkT\rho R} \qquad (17\text{–}8)$$

where $c$ is the solubility of a small particle of radius $R$ in an aqueous vehicle and $c_o$ is the solubility of a very large crystalline particle; $\gamma$ is the interfacial tension of the crystal, $\rho$ is the density of the crystal, and $M$ is the molecular weight of the solute. $N$ is Avogadro's number, $k$ is the Boltzmann constant, and $N \times k = 8.314 \times 10^7$ ergs$^{-1}$ mole$^{-1}$. The ratio $c/c_o$ defines the supersaturation ratio that a large crystal requires in the aqueous solution saturated with respect to the small particle. According to equation (17–8), as the radius of curvature of a protruding crystal decreases, the protrusion will require a correspondingly larger supersaturation ratio before it can grow. The radius of curvature of a protrusion must equal that of the pore of the polymer on the crystal surface.

**EXAMPLE 17–4**

**Supersaturation Ratio**

Assume that the interfacial tension of a particle of drug in an aqueous vehicle is 100 ergs/cm$^2$, its molecular weight is 200 g/mole, and the temperature of the solution is 30°C or 303 K. (*a*) Compute the supersaturation ratio, $c/c_o$, that is required for the crystal to grow. The radius, $R$, of the particle is 5 $\mu$m, or $5 \times 10^{-4}$ cm, and its density is 1.3 g/cm$^3$. (*b*) Compute the supersaturation ratio when the particle is covered by a polymer and the pore radius, $R$, of the polymer at the crystal surface is $6 \times 10^{-7}$ cm.

Using the Kelvin equation, we obtain

(*a*)

$$\ln \frac{c}{c_o} = \frac{2 \times 100 \times 200}{8.314 \times 10^7 \times 1.3 \times 303 \times 5 \times 10^{-4}} = 0.0024$$

(*b*)

$$\ln \frac{c}{c_o} = \frac{2 \times 100 \times 200}{8.314 \times 10^7 \times 1.3 \times 303 \times 6 \times 10^{-7}} = 2.036$$

$$c/c_o = \text{antiln}(2.036) = 7.66$$

Notice that $c/c_o$ in part (*a*) represents slight oversaturation, whereas in (*b*) the supersaturation concentration must be 7.6 times larger than the solubility of the drug molecule for the crystalline particle to grow. In other words, the addition of a polymer greatly increases the point at which supersaturation occurs and makes it more difficult for the drug crystal to grow.

Ziller and Rupprecht[22] designed a control unit to monitor crystal growth and studied the inhibition of growth by poly (vinylpyrrolidone) (PVP) in acetaminophen suspensions. According to these workers, some of the segments of the polymer PVP attach to the free spaces on the drug crystal lattice and the polymer is surrounded by a hydration shell (**Fig. 17–7**). The adsorbed segments of the polymer inhibit crystal growth of acetaminophen because they form a barrier that impedes the approach of the drug molecules from the solution to the crystal surface. High–molecular-weight polymers of PVP are more effective than low–molecular-weight polymers because the adsorption of the polymer on the crystal surface becomes more irreversible as the chain length increases.

The stability of suspensions may also decrease owing to interaction with excipients dissolved in the dispersion medium. Zatz and Lue[19] studied the flocculation by sorbitol in sulfamerazine suspensions containing nonionic surfactants as wetting agents. The flocculation by sorbitol depends on the cloud point of the surfactant. Thus, the lower the cloud point, the less sorbitol was needed to induce flocculation. The fact that the cloud point can be lowered by preservatives such as methylparaben shows that the choice of additives may change the resistance to caking of a suspension containing nonionic surfactants. Zatz and Lue[19] suggested that the cloud point can be used to estimate the critical flocculation concentration of sorbitol. Lucks et al.[23] studied the adsorption of preservatives such as cetylpyridinium chloride on zinc oxide particles in suspension. Increasing amounts of this preservative led to charge reversal of the suspension. Cetylpyridinium chloride, a cationic surfactant, has a positive charge and is strongly adsorbed at the particle surface. The positive end of the preservative molecule adsorbs on the negatively charged surface of the zinc oxide particles, forming a layer with the hydrocarbon chains oriented outward toward the dispersion medium. A second layer of preservative adsorbs at this monolayer, with the positively charged groups now directed toward the dispersion medium. Thus, the physical stability of the suspension may be enhanced owing to the repulsion of like-charged particles. However, the strong adsorption of the preservative on the zinc oxide particles reduces the biologically active free fraction of preservative in the dispersion medium, and the microbiologic activity is diminished.

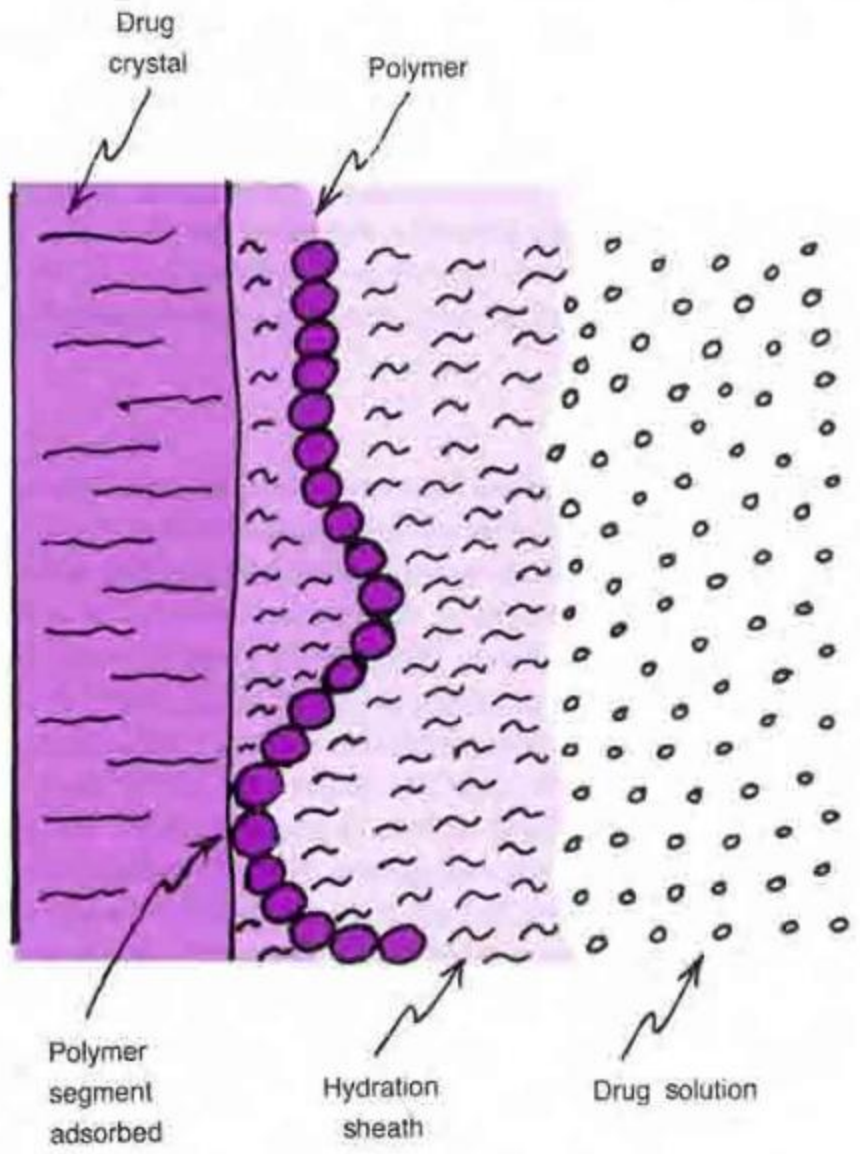


**Fig. 17–7.** Dissolution and crystallization of a drug in the presence of a polymer adsorbed on the drug crystal. (From H. K. Ziller and H. Rupprecht, Drug Dev. Ind. Pharm. **14**, 2341, 1988. With permission.)

## EMULSIONS

An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules (the dispersed phase) in the other liquid phase (the continuous phase), stabilized by the presence of an *emulsifying agent*. The various types of emulsifying agents

are discussed later in this section. Either the dispersed phase or the continuous phase may range in consistency from that of a mobile liquid to a semisolid. Thus, emulsified systems range from lotions of relatively low viscosity to ointments and creams, which are semisolid in nature. The particle diameter of the dispersed phase generally extends from about 0.1 to 10 $\mu$m, although particle diameters as small as 0.01 $\mu$m and as large as 100 $\mu$m are not uncommon in some preparations.

### Emulsion Types

Invariably, one liquid phase in an emulsion is essentially polar (e.g., aqueous), whereas the other is relatively nonpolar (e.g., an oil). When the oil phase is dispersed as globules throughout an aqueous continuous phase, the system is referred to as an *oil-in-water* (o/w) emulsion. When the oil phase serves as the continuous phase, the emulsion is spoken of as a *water-in-oil* (w/o) product. Medicinal emulsions for oral administration are usually of the o/w type and require the use of an o/w emulsifying agent. These include synthetic nonionic surfactants, acacia, tragacanth, and gelatin. Not all emulsions that are consumed, however, belong to the o/w type. Certain foods such as butter and some salad dressings are w/o emulsions.

Externally applied emulsions may be o/w or w/o, the former employing the following emulsifiers in addition to the ones mentioned previously: sodium lauryl sulfate, triethanolamine stearate, monovalent soaps such as sodium oleate, and self-emulsifying glyceryl monostearate, that is, glyceryl monostearate mixed with a small amount of a monovalent soap or an alkyl sulfate. Pharmaceutical w/o emulsions are used almost exclusively for external application and may contain one or several of the following emulsifiers: polyvalent soaps such as calcium palmitate, sorbitan esters (Spans), cholesterol, and wool fat.

Several methods are commonly used to determine the type of an emulsion. A small quantity of a water-soluble dye such as methylene blue or brilliant blue FCF may be dusted on the surface of the emulsion. If water is the external phase (i.e., if the emulsion is of the o/w type), the dye will dissolve and uniformly diffuse throughout the water. If the emulsion is of the w/o type, the particles of dye will lie in clumps on the surface. A second method involves dilution of the emulsion with water. If the emulsion mixes freely with the water, it is of the o/w type. Another test uses a pair of electrodes connected to an external electric source and immersed in the emulsion. If the external phase is water, a current will pass through the emulsion and can be made to deflect a voltmeter needle or cause a light in the circuit to glow. If the oil is the continuous phase, the emulsion fails to carry the current.

### Pharmaceutical Applications

An o/w emulsion is a convenient means of orally administering water-insoluble liquids, especially when the dispersed phase has an unpleasant taste. More significant in contemporary pharmacy is the observation that some oil-soluble compounds, such as some vitamins, are absorbed more completely when emulsified than when administered orally as an oily solution. The use of intravenous emulsions has been studied as a means of maintaining debilitated patients who are unable to assimilate materials administered orally. Tarr et al.[24] prepared emulsions of taxol, a compound with antimitotic properties, for intravenous administration as an alternative method to the use of cosolvents in taxol administration. Davis and Hansrani[25] studied the influence of droplet size and emulsifying agents on the phagocytosis of lipid emulsions. When the emulsion is administered intravenously, the droplets are normally rapidly taken up by the cells of the reticuloendothelial system, in particular the fixed macrophages in the liver. The rate of clearance by the macrophages increases as the droplet size becomes larger or the surface charge, either positive or negative, increases. Therefore, emulsion droplets stabilized by a nonionic surfactant (zero surface charge) were cleared much more slowly than the droplets stabilized by negatively charged phospholipids. Radiopaque emulsions have found application as diagnostic agents in x-ray examinations.

Emulsification is widely used in pharmaceutical and cosmetic products for external use. This is particularly so with dermatologic and cosmetic lotions and creams because a product that spreads easily and completely over the affected area is desired. Such products can now be formulated to be water washable and nonstaining and, as such, are obviously more acceptable to the patient and the physician than some of the greasy products used a decade or more ago. Emulsification is used in aerosol products to produce foams. The propellant that forms the dispersed liquid phase within the container vaporizes when the emulsion is discharged from the container. This results in the rapid formation of a foam.

## THEORIES OF EMULSIFICATION

There is no universal theory of emulsification because emulsions can be prepared using several different types of emulsifying agent, each of which depends for its action on a different principle to achieve a stable product. For a theory to be meaningful, it should be capable of explaining (*a*) the stability of the product and (*b*) the type of emulsion formed. Let us consider what happens when two immiscible liquids are agitated together so that one of the liquids is dispersed as small droplets in the other. Except in the case of very dilute oil-in-water emulsions (oil hydrosols), which are somewhat stable, the liquids separate rapidly into two clearly defined layers. Failure of two immiscible liquids to remain mixed is explained by the fact that the *cohesive* force between the molecules of each separate liquid is greater than the *adhesive* force between the two liquids. The cohesive force of the individual phases is manifested as an interfacial energy or tension at the boundary between the liquids, as explained in Chapter 15.

When one liquid is broken into small particles, the interfacial area of the globules constitutes a surface that is enormous

**TABLE 17–1**
**SOME TYPICAL EMULSIFYING AGENTS***

| Name | Class | Type of Emulsion Formed |
|---|---|---|
| Triethanolamine oleate | Surface-active agent (anionic) | o/w (HLB = 12) |
| *N*-cetyl *N*-ethyl morpholinium ethosulfate (Atlas G-263) | Surface-active agent (cationic) | o/w (HLB = 25) |
| Sorbitan monooleate (Atlas Span 80) | Surface-active agent (nonionic) | w/o (HLB = 4.3) |
| Polyoxyethylene sorbitan monooleate (Atlas Tween 80) | Surface-active agent (nonionic) | o/w (HLB = 15) |
| Acacia (salts of *d*-glucuronic acid) | Hydrophilic colloid | o/w |
| Gelatin (polypeptides and amino acids) | Hydrophilic colloid | o/w |
| Bentonite (hydrated aluminum silicate) | Solid particle | o/w (and w/o) |
| Veegum (magnesium aluminum silicate) | Solid particle | o/w |
| Carbon black | Solid particle | w/o |

*Key: o/w = oil in water; w/o = water in oil; HLB = hydrophilic–lipophilic balance value.

compared with the surface area of the original liquid. If 1 $cm^3$ of mineral oil is dispersed into globules having a volume–surface diameter, $d_{vs}$ of 0.01 $\mu$m ($10^{-6}$ cm) in 1 $cm^3$ of water so as to form a fine emulsion, the surface area of the oil droplets becomes 600 $m^2$. The surface free energy associated with this area is about $34 \times 10^7$ ergs, or 8 calories. The total volume of the system, however, has not increased; it remains at 2 $cm^3$. The calculations are made by use of equations **(18–15)** and **(18–17)** from which

$$S_v = \frac{6}{d_{vs}}$$

$$S_v = \frac{6}{10^{-6}} = 6 \times 10^6 \text{ cm}^2 = 600 \text{ m}^2$$

The work input or surface free energy increase is given by the equation $W = \gamma_{ow} \times \Delta A$, and the interfacial tension, $\gamma_{ow}$, between mineral oil and water is 57 dynes/cm (erg/$cm^2$). Thus,

$$W = 57 \text{ ergs/cm}^2 \times (6 \times 10^6 \text{ cm}^2)$$
$$= 34 \times 10^7 \text{ ergs} = 34 \text{ joules}$$

and because 1 cal = 4.184 joules,

$$34 \text{ joules } 4.184 = 8 \text{ calories}$$

In summary, if 1 $cm^3$ of mineral oil is mixed with 1 $cm^3$ of water to produce fine particles ($d_{vs} = 0.01$ $\mu$m), the total surface is equivalent to an area slightly greater than that of a basketball court, or about 600 $m^2$. (In real emulsions, the particles are ordinarily about 10 to 100 times larger than this, and the surface area is proportionately smaller.) The increase in energy, 8 calories, associated with this enormous surface is sufficient to make the system thermodynamically unstable, hence the droplets have a tendency to coalesce.

To prevent coalescence or at least to reduce its rate to negligible proportions, it is necessary to introduce an emulsifying agent that will form a film around the dispersed globules. Emulsifying agents can be divided into three groups, as follows:

(*a*) Surface-active agents, which are adsorbed at oil–water interfaces to form monomolecular films and reduce interfacial tension. These agents are discussed in detail in Chapter 15, dealing with interfacial phenomena.

(*b*) Hydrophilic colloids (discussed in Chapter 16), which form a *multi*molecular film around the dispersed droplets of oil in an o/w emulsion.[26,27]

(*c*) Finely divided solid particles, which are adsorbed at the interface between two immiscible liquid phases and form what amounts to a film of particles around the dispersed globules. The factor common to all three classes of emulsifying agent is the formation of a film, whether it be monomolecular, multimolecular, or particulate.

On this basis, we can now discuss some of the more important theories relating to the stability and type of emulsion formed.

Examples of typical emulsifying agents are given in **Table 17–1**.

## Monomolecular Adsorption

Surface-active agents, or amphiphiles, reduce interfacial tension because of their adsorption at the oil–water interface to form monomolecular films. Because the surface free energy increase, $W$, equals $\gamma_{o/w} \times \Delta A$ and we must, of necessity, retain a high surface area for the dispersed phase, any reduction in $\gamma_{o/w}$, the interfacial tension, will reduce the surface free energy and hence the tendency for coalescence. It is not unusual for a good emulsifying agent of this type to reduce the interfacial tension to 1 dyne/cm; we can therefore reduce the surface free energy of the system to approximately 1/60 of that calculated earlier.

The reduction in surface free energy is of itself probably not the main factor involved. Of more likely significance is

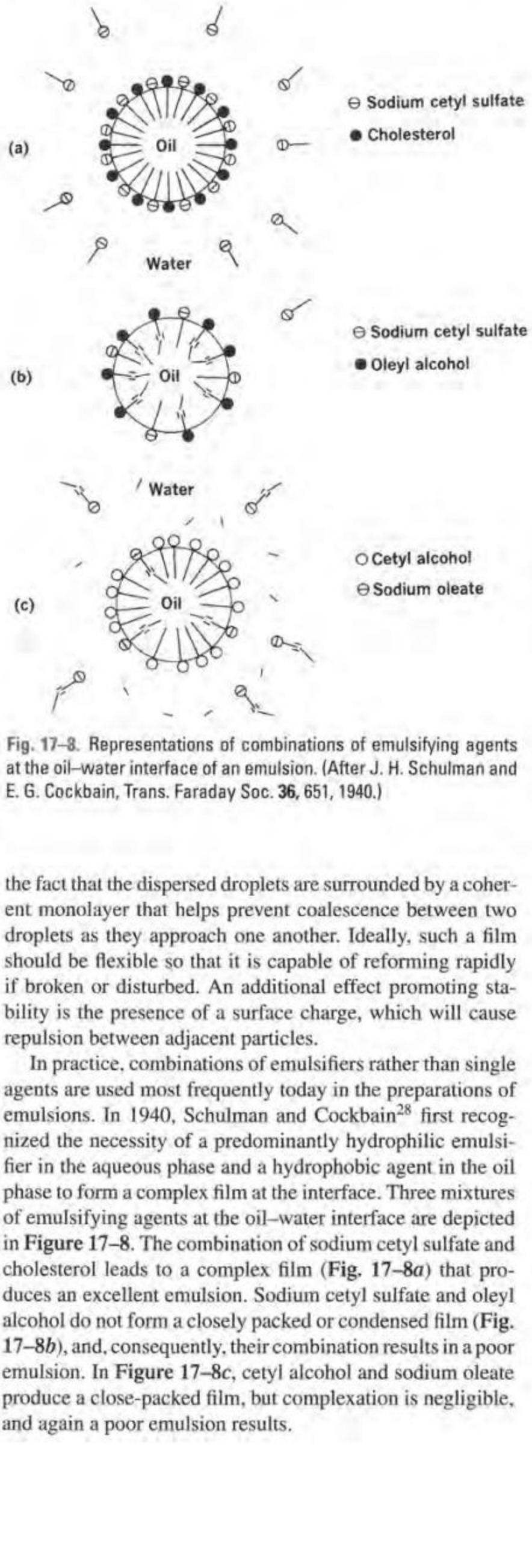


Fig. 17–8. Representations of combinations of emulsifying agents at the oil–water interface of an emulsion. (After J. H. Schulman and E. G. Cockbain, Trans. Faraday Soc. **36,** 651, 1940.)

the fact that the dispersed droplets are surrounded by a coherent monolayer that helps prevent coalescence between two droplets as they approach one another. Ideally, such a film should be flexible so that it is capable of reforming rapidly if broken or disturbed. An additional effect promoting stability is the presence of a surface charge, which will cause repulsion between adjacent particles.

In practice, combinations of emulsifiers rather than single agents are used most frequently today in the preparations of emulsions. In 1940, Schulman and Cockbain[28] first recognized the necessity of a predominantly hydrophilic emulsifier in the aqueous phase and a hydrophobic agent in the oil phase to form a complex film at the interface. Three mixtures of emulsifying agents at the oil–water interface are depicted in **Figure 17–8**. The combination of sodium cetyl sulfate and cholesterol leads to a complex film (**Fig. 17–8***a*) that produces an excellent emulsion. Sodium cetyl sulfate and oleyl alcohol do not form a closely packed or condensed film (**Fig. 17–8***b*), and, consequently, their combination results in a poor emulsion. In **Figure 17–8***c*, cetyl alcohol and sodium oleate produce a close-packed film, but complexation is negligible, and again a poor emulsion results.

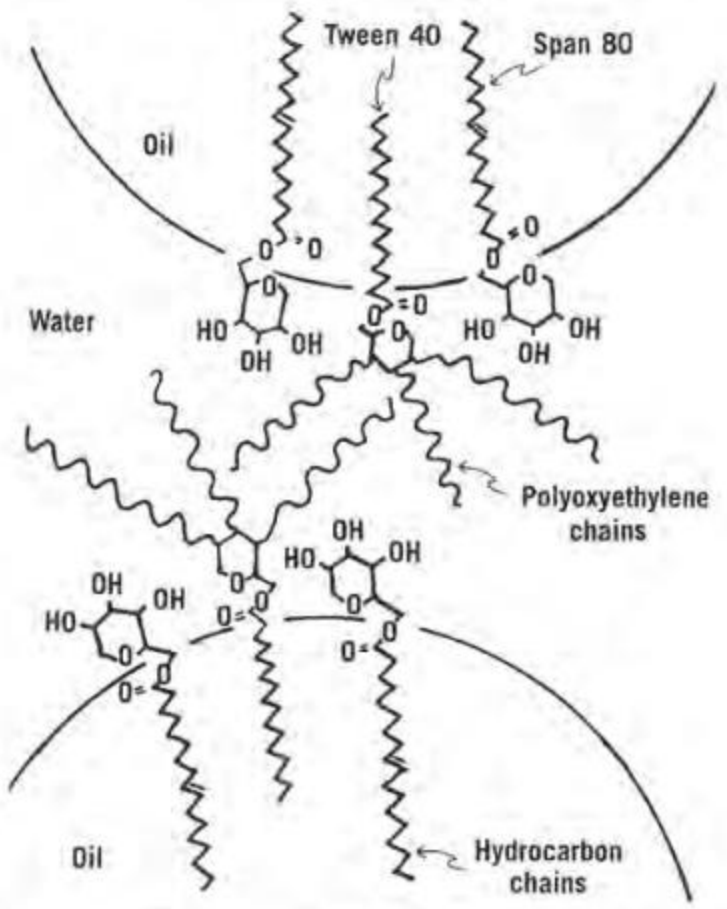


Fig. 17–9. Schematic of oil droplets in an oil–water emulsion, showing the orientation of a Tween and a Span molecule at the interface. (From J. Boyd, C. Parkinson, and P. Sherman, J. Coll. Interface Sci. **41,** 359, 1972. With permission.)

A hydrophilic Tween can be combined with a lipophilic Span, varying the proportions so as to produce the desired o/w or w/o emulsion.[29] Boyd et al.[30] discussed the molecular association of Tween 40 and Span 80 in stabilizing emulsions. In **Figure 17–9**, the hydrocarbon portion of the Span 80 (sorbitan monooleate) molecule lies in the oil globule and the sorbitan radical lies in the aqueous phase. The bulky sorbitan heads of the Span molecules prevent the hydrocarbon tails from associating closely in the oil phase. When Tween 40 (polyoxyethylene sorbitan monopalmitate) is added, it orients at the interface such that part of its hydrocarbon tail is in the oil phase and the remainder of the chain, together with the sorbitan ring and the polyoxyethylene chains, is located in the water phase. It is observed that the hydrocarbon chain of the Tween 40 molecule is situated in the oil globule between the Span 80 chains, and this orientation results in effective van der Waals attraction. In this manner, the interfacial film is strengthened and the stability of the o/w emulsion is increased against particle coalescence. The same principle of mixed emulsifying agents can be applied in the use of combinations such as sodium stearate and cholesterol, sodium lauryl sulfate and glyceryl monostearate, and tragacanth and Span. Chun et al.[31] determined the hydrophile–lipophile balance (HLB) of some natural agents and further discussed the principle of mixed emulsifiers.

The type of emulsion that is produced, o/w or w/o, depends primarily on the property of the emulsifying agent. This characteristic is referred to as the *hydrophile–lipophile* balance, that is, the polar–nonpolar nature of the emulsifier. In fact,

whether a surfactant is an emulsifier, wetting agent, detergent, or solubilizing agent can be predicted from a knowledge of the HLB, as discussed in a previous chapter. In an emulsifying agent such as sodium stearate, $C_{17}$ $H_{35}COONa$, the nonpolar hydrocarbon chain, $C_{17}H_{35}-$, is the lipophilic or "oil-loving" group; the carboxyl group, $-COONa$, is the *hydrophilic* or "water-loving" portion. The balance of the hydrophilic and lipophilic properties of an emulsifier (or combination of emulsifiers) determines whether an o/w or w/o emulsion will result. In general, o/w emulsions are formed when the HLB of the emulsifier is within the range of about 9 to 12, and w/o emulsions are formed when the range is about 3 to 6. An emulsifier with a high HLB, such as a blend of Tween 20 and Span 20, will form an o/w emulsion. On the other hand, Span 60 alone, having an HLB of 4.7, tends to form a w/o emulsion.

It would appear, therefore, that the type of emulsion is a function of the relative solubility of the surfactant, the phase in which it is more soluble being the continuous phase. This is sometimes referred to as the *rule of Bancroft*, who observed this phenomenon in 1913. Thus, an emulsifying agent with a high HLB is preferentially soluble in water and results in the formation of an o/w emulsion. The reverse situation is true with surfactants of low HLB, which tend to form w/o emulsions. Beerbower, Nixon, and Hill[32] suggested an explanation for emulsion type and stability and devised a general scheme for emulsion formulation based on the Hildebrand and Hansen solubility parameters.

### Multimolecular Adsorption and Film Formation

Hydrated lyophilic colloids have been used for many years as emulsifying agents, although their use is declining because of the large number of synthetic surfactants now available. In a sense, they can be regarded as surface active because they appear at the oil–water interface. They differ, however, from the synthetic surface-active agents in that (*a*) they do not cause an appreciable lowering of interfacial tension and (*b*) they form a multi- rather than a monomolecular film at the interface. Their action as emulsifying agents is due mainly to the latter effect because the films thus formed are strong and resist coalescence. An auxiliary effect promoting stability is the significant increase in the viscosity of the dispersion medium. Because the emulsifying agents that form multilayer films around the droplets are invariably hydrophilic, they tend to promote the formation of o/w emulsions.

### Solid-Particle Adsorption

Finely divided solid particles that are wetted to some degree by both oil and water can act as emulsifying agents. This results from their being concentrated at the interface, where they produce a particulate film around the dispersed droplets so as to prevent coalescence. Powders that are wetted preferentially by water form o/w emulsions, whereas those more easily wetted by oil form w/o emulsions.

## PHYSICAL STABILITY OF EMULSIONS

Probably the most important consideration with respect to pharmaceutical and cosmetic emulsions is the stability of the finished product. The stability of a pharmaceutical emulsion is characterized by the absence of coalescence of the internal phase, absence of creaming, and maintenance of elegance with respect to appearance, odor, color, and other physical properties. Some workers define instability of an emulsion only in terms of agglomeration of the internal phase and its separation from the product. Creaming, resulting from flocculation and concentration of the globules of the internal phase, sometimes is not considered as a mark of instability. An emulsion is a dynamic system, however, and flocculation and resultant creaming represent potential steps toward complete coalescence of the internal phase. Furthermore, in the case of pharmaceutical emulsions, creaming results in a lack of uniformity of drug distribution and, unless the preparation is thoroughly shaken before administration, leads to variable dosage. Certainly, the visual appeal of an emulsion is affected by creaming, and this is just as real a problem to the pharmaceutical compounder as is separation of the internal phase.

Another phenomenon important in the preparation and stabilization of emulsions is *phase inversion*, which can be an aid or a detriment in emulsion technology. Phase inversion involves the change of emulsion type from o/w to w/o or vice versa. Should phase inversion occur following preparation, it may logically be considered as an instance of instability.

In the light of these considerations, the instability of pharmaceutical emulsions may be classified as follows:

(*a*) Flocculation and creaming
(*b*) Coalescence and breaking
(*c*) Miscellaneous physical and chemical changes
(*d*) Phase inversion

### Creaming and Stokes's Law

Those factors that find importance in the creaming of an emulsion are related by Stokes's law, equation **(17–2)**. The limitations of this equation to actual systems have been discussed previously for suspensions, and these apply equally to emulsified systems.

Analysis of the equation shows that if the dispersed phase is less dense than the continuous phase, which is generally the case in o/w emulsions, the velocity of sedimentation becomes negative, that is, an upward *creaming* results. If the internal phase is heavier than the external phase, the globules settle, a phenomenon customarily noted in w/o emulsions in which the internal aqueous phase is denser than the continuous oil phase. This effect can be referred to as *creaming in a downward direction*. The greater the difference between the density of the two phases, the larger the oil globules, and the less viscous the external phase, the greater is the rate of creaming.

By increasing the force of gravity through centrifugation, the rate of creaming can also be increased. The diameter of the globules is seen to be a major factor in determining the rate of creaming. Doubling the diameter of the oil globules increases the creaming rate by a factor of 4.

**EXAMPLE 17–5**

**Velocity of Creaming**

**Consider an o/w emulsion containing mineral oil with a specific gravity of 0.90 dispersed in an aqueous phase having a specific gravity of 1.05. If the oil particles have an average diameter of 5 $\mu$m, or $5 \times 10^{-4}$ cm, the external phase has a viscosity of 0.5 poise (0.5 dyne sec/cm$^2$ or 0.5 g/cm sec), and the gravity constant is 981 cm/sec$^2$, what is the velocity of creaming in cm/day?**

We have

$$v = \frac{(5 \times 10^{-4})^2 \times (0.90 - 1.05) \times 981}{18 \times 0.5}$$

$$= -4.1 \times 10^{-6} \text{ cm/sec}$$

**and because a 24-hr day contains 86,400 sec, the rate of upward creaming, $-v$, is**

$$-v = 4.1 \times 10^{-6} \text{ cm/sec} \times 86{,}400 \text{ sec/day} = 0.35 \text{ cm/day}$$

The factors in Stokes's equation can be altered to reduce the rate of creaming in an emulsion. The viscosity of the external phase can be increased without exceeding the limits of acceptable consistency by adding a *viscosity improver* or *thickening agent* such as methylcellulose, tragacanth, or sodium alginate. The particle size of the globules can be reduced by homogenization; this, in fact, is the basis for the stability against creaming of homogenized milk. If the average particle size of the emulsion in the example just given is reduced to 1 $\mu$m, or one fifth of the original value, the rate of creaming is reduced to 0.014 cm/day or about 5 cm/year. Actually, when the particles are reduced to a diameter below 2 to 5 $\mu$m, Brownian motion at room temperature exerts sufficient influence so that the particles settle or cream more slowly than predicted by Stokes's law.

Little consideration has been given to the adjustment of densities of the two phases in an effort to reduce the rate of creaming. Theoretically, adjusting the external and internal phase densities to the same value should eliminate the tendency to cream. This condition is seldom realized, however, because temperature changes alter the densities. Some research workers have increased the density of the oil phase by the addition of oil-soluble substances such as $\alpha$-bromonaphthalene, bromoform, and carbon tetrachloride, which, however, cannot be used in medicinal products. Mullins and Becker[33] added a food grade of a brominated oil to adjust the densities in pharmaceutical emulsions.

Equation (17–2) gives the rate of creaming of a single droplet of the emulsion, whereas one is frequently interested in the rate of creaming at the center of gravity of the mass of the disperse phase. Greenwald[34] developed an equation for the mass creaming rate, to which the interested reader is referred for details.

## Coalescence and Breaking

Creaming should be considered as separate from breaking because creaming is a reversible process, whereas breaking is irreversible. The cream floccules can be redispersed easily, and a uniform mixture is reconstituted from a creamed emulsion by agitation because the oil globules are still surrounded by a protective sheath of emulsifying agent. When breaking occurs, simple mixing fails to resuspend the globules in a stable emulsified form because the film surrounding the particles has been destroyed and the oil tends to coalesce. Considerable work has been devoted to the study of breaking instability. The effects of certain factors on breaking are summarized in the following paragraphs.

King[35] showed that reduction of particle size does not necessarily lead to increased stability. Rather, he concluded that an optimum degree of dispersion for each particular system exists for maximum stability. As in the case of solid particles, if the dispersion is nonuniform, the small particles wedge between larger ones, permitting stronger cohesion so that the internal phase can coalesce easily. Accordingly, a moderately coarse dispersion of uniform-sized particles should have the best stability. Viscosity alone does not produce stable emulsions; however, viscous emulsions may be more stable than mobile ones by virtue of the retardation of flocculation and coalescence. Viscous or "tacky" emulsifiers seem to facilitate shearing of the globules as the emulsion is being prepared in the mortar, but this bears little or no relationship to stability. Knoechel and Wurster[36] showed that viscosity plays only a minor role in the gross stability of o/w emulsions. Probably an *optimum* rather than a *high* viscosity is needed to promote stability.

The *phase–volume* ratio of an emulsion has a secondary influence on the stability of the product. This term refers to the relative volumes of water and oil in the emulsion. As shown in the section on powders, uniform spherical particles in loose packing have a porosity of 48% of the total bulk volume. The volume occupied by the spheres must then be 52%.

If the spheres are arranged in closest packing, theoretically they cannot exceed 74% of the total volume regardless of their size. Although these values do not consider the distortions of size and shape and the possibility of small particles lying between larger spheres, they do have some significance with respect to real emulsions. Ostwald and Kolloid[37] showed that if one attempts to incorporate more than about 74% of oil in an o/w emulsion, the oil globules often coalesce and the emulsion breaks. This value, known as the *critical point*, is defined as the concentration of the internal phase above which the emulsifying agent cannot produce a stable emulsion of the desired type. In some stable emulsions, the value may be higher than 74% owing to the irregular shape and size of the globules. Generally speaking, however, a phase–volume ratio of 50:50 (which approximates loose packing) results in about the most stable emulsion. This fact was discovered empirically by pharmacists many years ago, and most

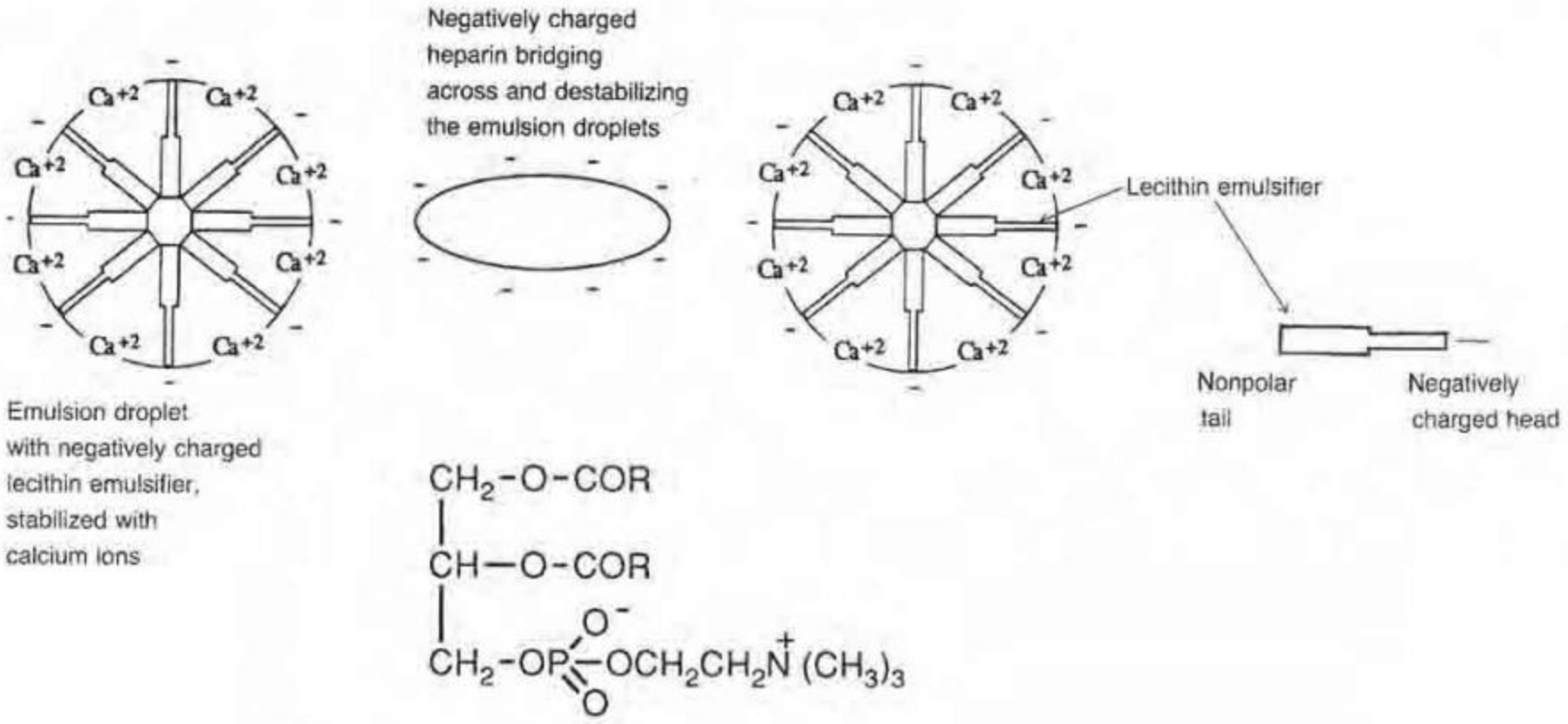


Fig. 17–10. Parental emulsion droplets in the presence of the negatively charged emulsifier lecithin and stabilized by electrostatic repulsion by calcium ions. The emulsion may be flocculated and destabilized by the bridging effect of heparin, a negatively charged polyelectrolyte, which overcomes the stabilizing electrostatic repulsion of the $Ca^{2+}$ ions. (From O. L. Johnson, C. Washington, S. S. Davis, and K. Schaupp, Int. J. Pharm. **53**, 237, 1989. With permission.)

medicinal emulsions are prepared with a volume ratio of 50 parts of oil to 50 parts of water.

Emulsions can be stabilized by electrostatic repulsion between the droplets, that is, by increasing their zeta potential. Magdassi and Siman-Tov[38] used lecithin to stabilize perfluorocarbon emulsions, which appear to be a good blood substitute. Lecithin is a mixture of phospholipids having a negative charge at physiologic pH. The stabilizing effect is due to the adsorption of lecithin at the droplet surface, which creates a negative charge and consequently electrostatic repulsion. Lecithin produces very stable emulsions of triglyceride acids in water for intravenous administration. However, the stability of these emulsions may be poor because in clinical practice they are mixed with electrolytes, amino acids, and other compounds for total parenteral nutrition. The addition of positively charged species such as sodium and calcium ions or cationic amino acids—the charge on the latter depending on the pH—reduces the zeta potential and may cause flocculation. Johnson et al.[39] studied the effect of heparin and various electrolytes, frequently used clinically, on the stability of parenteral emulsions. Heparin, an anticoagulant, is a negatively charged polyelectrolyte that causes rapid flocculation in emulsions containing calcium and lecithin. The critical flocculation concentration occurs at a specific zeta potential. The value of this zeta potential can be determined by plotting the flocculation rate against the surface potential and extrapolating to zero flocculation rate.[40] Johnson et al.[39] explained the destabilizing effect of heparin as follows. Divalent electrolytes such as calcium bind strongly to the surface of droplets stabilized with lecithin to form 1:2 ion–lipid complexes. This causes a charge reversal on the droplets, leading to positively charged particles. The droplets are then flocculated by a bridging of the negatively charged heparin molecules across the positively charged particles, as depicted in **Figure 17–10**.

When the oil particles, which usually carry a negative charge, are surrounded in an o/w emulsion by a film of emulsifier, particularly a nonionic agent, the electrokinetic effects are probably less significant than they are in suspensions in maintaining the stability of the system. The effect of electrolytes in these systems has been studied by Schott and Royce.[41] Probably the most important factors in the stabilization of an emulsion are the physical properties of the emulsifier film at the interface. To be effective, an emulsifier film must be both tough and elastic and should form rapidly during emulsification. Serrallach et al.[42] measured the strength of the film at the interface. They found that a good emulsifying agent or emulsifier combination brings about a preliminary lowering of the interfacial tension to produce small uniform globules and forms rapidly to protect the globules from reaggregation during manufacture. The film then slowly increases in strength over a period of days or weeks.

## Evaluation of Stability

According to King and Mukherjee,[43] the only precise method for determining stability involves a size–frequency analysis of the emulsion from time to time as the product ages. For

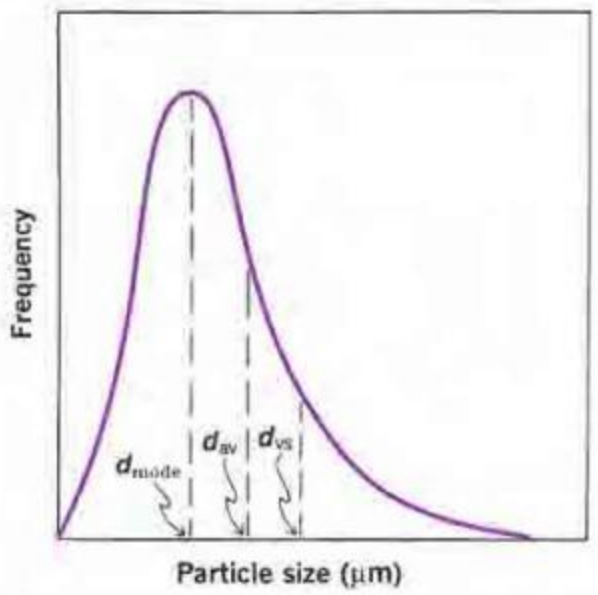


Fig. 17–11. Particle-size distribution of an emulsion. Such curves ordinarily are skewed to the right as shown in the figure, and the mode diameter, that is, the highest point on the curve or the most frequent value, is seen to occur at the lower end of the scale of diameters. The arithmetic mean diameter, $d_{av}$, will be found somewhat to the right of the mode in a right-skewed distribution, and the mean volume–surface diameter, $d_{vs}$, is to the right of the arithmetic mean.

rapidly breaking emulsions, macroscopic observation of separated internal phase is adequate, although the separation is difficult to read with any degree of accuracy. In the microscopic method, the particle diameters are measured, and a size–frequency distribution of particles ranging from 0.0 to 0.9 $\mu$m, 1.0 to 1.9 $\mu$m, 2.0 to 2.9 $\mu$m, and so on, is made as shown in **Figure 17–11**. The particle size or diameter of the globules in micrometers is plotted on the horizontal axis against the frequency or number of globules in each size range on the vertical axis. Finkle et al.[44] were probably the first workers to use this method to determine the stability of emulsions. Since that time, many similar studies have been made. Schott and Royce[45] showed that the experimental problems involved in microscopic size determinations are Brownian motion, creaming, and field flow. Brownian motion affects the smallest droplets, causing them to move in and out of focus so that they are not consistently counted. Velocity of creaming is proportional to the square of the droplet diameter, and creaming focuses attention on the largest droplets because they move faster toward the cover glass than do smaller ones. *Field flow* is the motion of the entire volume of emulsion in the field due to the pressure exerted by the immersion objective on the cover glass, evaporation of the continuous phase, or convection currents resulting from heating by the light source. These workers[45] described an improved microscopic technique that overcomes these experimental problems and gives a more accurate measure of the droplet size.

An initial frequency distribution analysis on an emulsion is not an adequate test of stability because stability is not related to initial particle size. Instead, one should perhaps consider the coalescence of the dispersed globules of an aging emulsion or the separation of the internal phase from the emulsion over a period of time. Boyd et al.,[30] however, deemed this method unsatisfactory because the globules can undergo considerable coalescence before the separation becomes visible. These workers conducted particle-size analyses with a Coulter centrifugal photosedimentometer. Mean volume diameters were obtained, and these were converted to number of globules per milliliter. King and Mukherjee[43] determined the specific interfacial area, that is, the area of interface per gram of emulsified oil, of each emulsion at successive times. They chose the reciprocal of the decrease of specific interfacial area with time as a measure of the stability of an emulsion.

Other methods used to determine the stability of emulsions are based on accelerating the separation process, which normally takes place under storage conditions. These methods employ freezing, thaw–freeze cycles, and centrifugation.

Merrill[46] introduced the centrifuge method for evaluating the stability of emulsions. Garrett, Vold, and others[47] used the ultracentrifuge as an analytic technique in emulsion technology. Coulter counting, turbidimetric analysis, and temperature tests have also been used in an effort to evaluate new emulsifying agents and determine the stability of pharmaceutical emulsions. Garti et al.[48] developed a method for evaluating the stability of oil–water viscous emulsions (ointments and cosmetic creams) containing nonionic surfactants. The method is based on electric conductivity changes during nondestructive short heating–cooling–heating cycles. Conductivity curves are plotted during the temperature cycling. A stability index is defined as $\Delta/h$, where $h$ is the change in the conductivity between 35°C and 45°C and $\Delta$ is the conductivity interval within the two heating curves at 35°C, as shown in **Figure 17–12**. The *stability index* indicates the relative change in conductivity between two cycles. The smaller the conductivity, the greater is the stability of the emulsion. The method was applied in a series of emulsions at different HLBs, emulsifier concentrations, and oil-phase

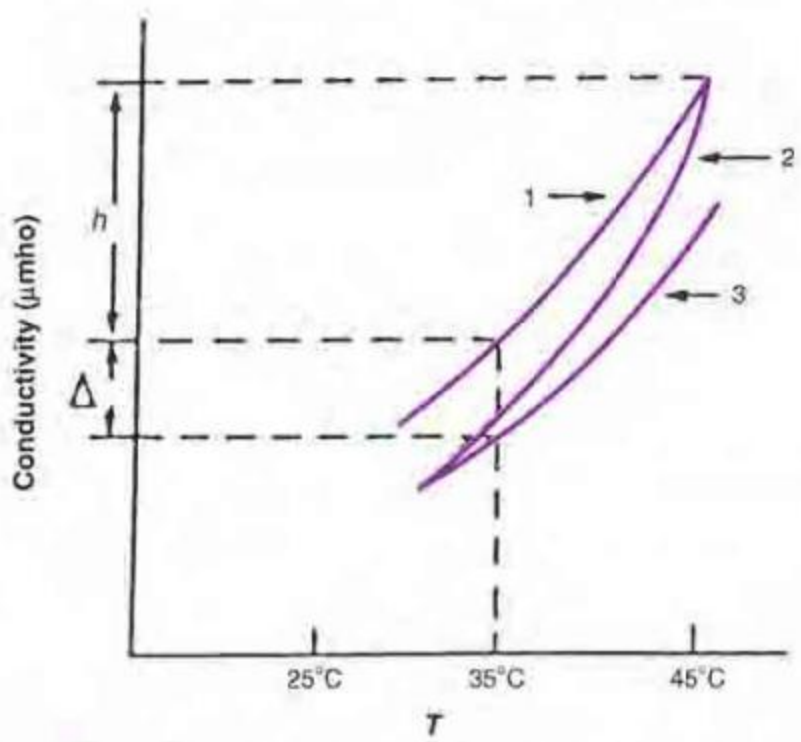


Fig. 17–12. A conductivity versus temperature plot involving successively (*a*) heating, (*b*) cooling, and (*c*) heating. (From N. Garti and S. Magdassi, Drug Dev. Ind. Pharm. **8**, 475, 1982. With permission.)

concentrations. The authors reviewed earlier work on electric conductivity of emulsions as related to stability.

### Phase Inversion

When controlled properly during the preparation of an emulsion, phase inversion often results in a finer product, but when it gets out of hand during manufacturing or is brought about by other factors after the emulsion is formed, it can cause considerable trouble.

An o/w emulsion stabilized with sodium stearate can be inverted to the w/o type by adding calcium chloride to form calcium stearate. Inversion can also be produced by alterations in phase-volume ratio. In the manufacture of an emulsion, one can mix an o/w emulsifier with oil and then add a small amount of water. Because the volume of the water is small compared with that of the oil, the water is dispersed by agitation in the oil even though the emulsifier preferentially forms an oil-in-water system. As more water is slowly added, the inversion point is gradually reached and the water and emulsifier envelope the oil as small globules to form the desired o/w emulsion. This procedure is sometimes used in the preparation of commercial emulsions, and it is the principle of the *continental method* used in compounding practice. The preparation of emulsions is discussed in books on general pharmacy and on compounding and dispensing.

## PRESERVATION OF EMULSIONS

Although it is not always necessary to achieve sterile conditions in an emulsion, even if the product is for topical or oral use, certain undesirable changes in the properties of the emulsion can be brought about by the growth of microorganisms. These include physical separation of the phases, discoloration, gas and odor formation, and changes in rheologic properties.[49] Emulsions for parenteral use obviously must be sterile.

The propagation of microorganisms in emulsified products is supported by one or more of the components present in the formulation. Thus, bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and vegetable gums present as thickeners, with a consequent deterioration of the emulsion. As a result, it is essential that emulsions be formulated to resist microbial attack by including an adequate concentration of preservative in the formulation. Given that the preservative has inherent activity against the type of contamination encountered, the main problem is obtaining an *adequate* concentration of preservative in the product. Some of the factors that must be considered to achieve this end are presented here.

Emulsions are heterogeneous systems in which partitioning of the preservative will occur between the oil and water phases. In the main, bacteria grow in the aqueous phase of emulsified systems, with the result that a preservative that is partitioned strongly in favor of the oil phase may be virtually useless at normal concentration levels because of the low concentration remaining in the aqueous phase. The phase–volume ratio of the emulsion is significant in this regard. In addition, the preservative must be in an un-ionized state to penetrate the bacterial membrane. Therefore, the activity of weak acid preservatives decreases as the pH of the aqueous phase rises. Finally, the preservative molecules must not be "bound" to other components of the emulsion, because the complexes are ineffective as preservatives. Only the concentration of free, or unbound, preservative is effective. These points have been discussed in some detail in earlier sections. In addition to partitioning, ionization, and binding, the efficacy of a particular preservative is also influenced by emulsion type, nutritive value of the product, degree of aeration, and type of container used. These factors are discussed by Wedderburn.[49]

## RHEOLOGIC PROPERTIES OF EMULSIONS

Emulsified products may undergo a wide variety of shear stresses during either preparation or use. In many of these processes, the flow properties of the product will be vital for the proper performance of the emulsion under the conditions of use or preparation. Thus, spreadability of dermatologic and cosmetic products must be controlled to achieve a satisfactory preparation. The flow of a parenteral emulsion through a hypodermic needle, the removal of an emulsion from a bottle or a tube, and the behavior of an emulsion in the various milling operations employed in the large-scale manufacture of these products all indicate the need for correct flow characteristics. Accordingly, it is important for the pharmacist to appreciate how formulation can influence the rheologic properties of emulsions.

The fundamentals of rheology are discussed in Chapter 19. Most emulsions, except dilute ones, exhibit non-Newtonian flow, which complicates interpretation of data and quantitative comparisons among different systems and formulations. In a comprehensive review, Sherman[50] discussed the principal factors that influence the flow properties of emulsions. The material of this section outlines some of the viscosity-related properties of the dispersed phase, the continuous phase, and the emulsifying agent. For a more complete discussion of these and other factors that can modify the flow properties of emulsions, the reader is referred to the original article by Sherman[50] and Sherman's book.[51]

The factors related to the dispersed phase include the phase–volume ratio, the particle-size distribution, and the viscosity of the internal phase itself. Thus, when volume concentration of the dispersed phase is low (less than 0.05), the system is Newtonian. As the volume concentration is increased, the system becomes more resistant to flow and exhibits pseudoplastic flow characteristics. At sufficiently high concentrations, plastic flow occurs. When the volume concentration approaches 0.74, inversion may occur, with a marked change in viscosity; reduction in mean particle size increases the viscosity; and the wider the particle size distribution, the

lower is the viscosity when compared with a system having a similar mean particle size but a narrower particle-size distribution.

The major property of the continuous phase that affects the flow properties of an emulsion is not, surprisingly, its own viscosity. The effect of the viscosity of the continuous phase may be greater, however, than that predicted by determining the bulk viscosity of the continuous phase alone. There are indications that the viscosity of a thin liquid film, of say 100 to 200 Å, is several times the viscosity of the bulk liquid. Higher viscosities may therefore exist in concentrated emulsions when the thickness of the continuous phase between adjacent droplets approaches these dimensions. Sherman pointed out that the reduction in viscosity with increasing shear may be due in part to a decrease in the viscosity of the continuous phase as the distance of separation between globules is increased.

Another component that may influence the viscosity of an emulsion is the emulsifying agent. The type of agent will affect particle flocculation and interparticle attractions, and these in turn will modify flow. In addition, for any one system, the greater the concentration of emulsifying agent, the higher will be the viscosity of the product. The physical properties of the film and its electric properties are also significant factors.

## MICROEMULSIONS

The term *microemulsion* may be a misnomer because microemulsions consist of large or "swollen" micelles containing the internal phase, much like that found in a solubilized solution. Unlike the common macroemulsions, they appear as clear, transparent solutions, but unlike micellar solubilized systems, microemulsions may not be thermodynamically stable. They appear to represent a state intermediate between thermodynamically stable solubilized solutions and ordinary emulsions, which are relatively unstable. Microemulsions contain droplets of oil in a water phase (o/w) or droplets of water in oil (w/o) with diameters of about 10 to 200 nm, and the volume fraction of the dispersed phase varies from 0.2 to 0.8.

As often recommended in the formation of ordinary emulsions or macroemulsions, an emulsifying adjunct or cosurfactant is used in the preparation of microemulsions. An anionic surfactant, sodium lauryl sulfate or potassium oleate, can be dispersed in an organic liquid such as benzene, a small measured amount of water is added, and the microemulsion is formed by the gradual addition of pentanol, a lipophilic cosurfactant, to form a clear solution at 30°C. The addition of pentanol temporarily reduces the surface tension to approximately zero, allowing spontaneous emulsification. The surfactant and cosurfactant molecules form an adsorbed film on the microemulsion particles to prevent coalescence.

Shinoda and Kunieda[52] showed that by choosing a surfactant and cosurfactant that have similar HLB values, one can increase the solubilization of an organic liquid in water and enlarge the microemulsion droplet size without affecting stability. With ionic surfactants at normal temperatures, one expects o/w microemulsions to be formed when the phase volume ratio favors water, analogous to the rule for macroemulsions.

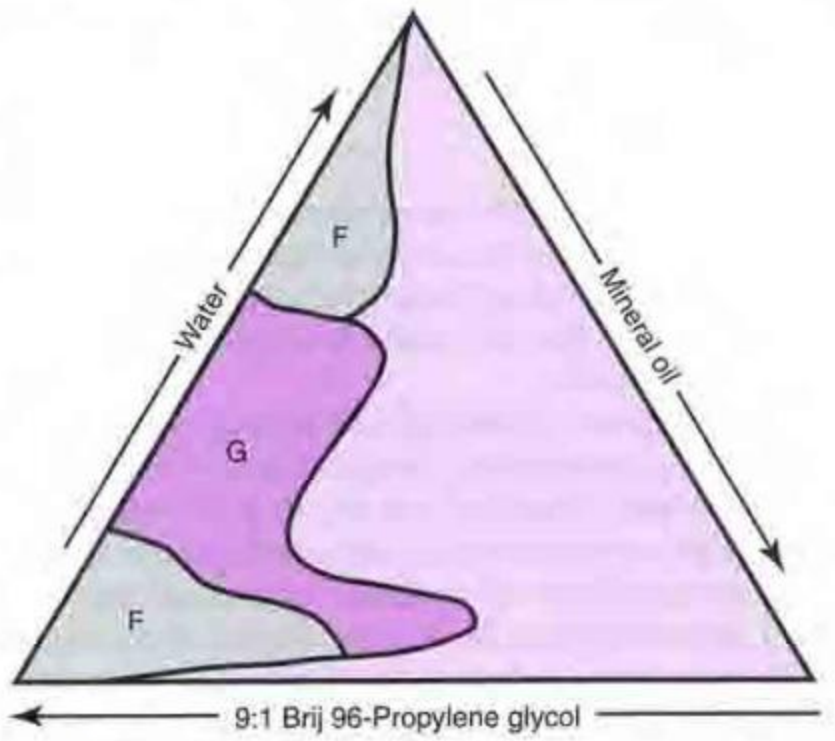


**Fig. 17–13.** A ternary-phase diagram of water, mineral oil, and a mixture of surfactants showing the boundary of the microemulsion region. The zones within the microemulsion region are labeled F for fluid and G for gel. (From N. J. Kate and L. V. Allen, Jr., Int. J. Pharm. **57**, 87, 1989. With permission.)

The microemulsion region is usually characterized by constructing ternary-phase diagrams, as shown in **Figure 17–13**, the axes representing water, mineral oil, and a mixture of surfactant and cosurfactant at different ratios.[53] The phase diagrams allow one to determine the ratios oil:water: surfactant–cosurfactant at the boundary of the microemulsion region. The microemulsion appears by visual observation as an isotropic, optically clear liquid system. Kale and Allen[53] studied water-in-oil microemulsions consisting of the system Brij 96-cosurfactant–mineral oil–water. Brij 96 [polyoxyethylene(10) oleyl ether] is a nonionic surfactant commonly used in the preparation of macro- and microemulsions. The cosurfactants studied were ethylene glycol, propylene glycol, and glycerin. **Figure 17–13** shows the phase diagram for the system upon varying the ratio Brij 96:propylene glycol. Within the microemulsion region, zones of different viscosity, labeled as fluid (F) or gel (G), can be observed. The microemulsion region becomes smaller as the cosurfactant concentration increases. According to the researchers, the transition from fluid microemulsion to gel-like microemulsion may be due to the change in the nature and shape of the internal oil phase. Thus, at low water content the internal phase consists of spherical structures, whereas at higher water concentration the interfacial film expands to form gel-like cylindrical and laminar structures. As the water content is further increased, aqueous continuous systems of low viscosity with internal phases of spherical structures (droplets) are again formed.

The droplet average molecular weight of a microemulsion can be measured by light-scattering techniques. Because the internal phase is not usually very dilute, the droplets interact with one another, resulting in a decrease in the turbidity. Thus, the effective diameter obtained is smaller than the actual droplet diameter. The latter can be obtained from a plot of the effective diameter (obtained at various dilutions of the microemulsion) against the concentration of the internal phase. Extrapolation to zero concentration gives the actual diameter.[53] Attwood and Ktistis[54] showed that the extrapolation procedure often cannot be applied because many microemulsions exhibit phase separation on dilution. They described a procedure for overcoming these difficulties and obtaining true particle diameter using light scattering.

Microemulsions have been studied as drug delivery systems. They can be used to increase the bioavailability of drugs poorly soluble in water by incorporation of the drug into the internal phase. Halbert et al.[55] studied the incorporation of both etoposide and a methotrexate diester derivative in water-in-oil microemulsions as potential carriers for cancer chemotherapy. Etoposide was rapidly lost from the microemulsion particles, whereas 60% of the methotrexate diester remained incorporated in the internal phase of the microemulsion. The methotrexate diester microemulsions showed an in vitro cytotoxic effect against mouse leukemia cells. Microemulsions have also been considered as topical drug delivery systems. Osborne et al.[56] studied the transdermal permeation of water from water-in-oil microemulsions formed from water, octanol, and dioctyl sodium sulfosuccinate, the latter functioning as the surfactant. These kinds of microemulsions can be used to incorporate polar drugs in the aqueous internal phase. The skin used in the experiments was fully hydrated so as to maximize the water permeability. The delivery of the internal phase was found to be highly dependent on the microemulsion water content: The diffusion of water from the internal phase increased tenfold as the water amount in the microemulsion increased from 15% to 58% by weight. Linn et al.[57] compared delivery through hairless mouse skin of cetyl alcohol and octyl dimethyl para-aminobenzoic acid (PABA) from water-in-oil microemulsions and macroemulsions. The delivery of these compounds from microemulsions was faster and showed deeper penetration into the skin than delivery from the macroemulsions. The authors reviewed a number of studies on the delivery of drugs from the microemulsions. These reports, including several patents, dealt with the incorporation of fluorocarbons as blood substitutes and for the topical delivery of antihypertensive and anti-inflammatory drugs. Microemulsions are used in cosmetic science,[58] foods, and dry cleaning and wax-polishing products.[59]

## SEMISOLIDS

### Gels

A gel is a solid or a semisolid system of at least two constituents, consisting of a condensed mass enclosing and interpenetrated by a liquid. When the coherent matrix is rich in liquid, the product is often called a *jelly*. Examples are ephedrine sulfate jelly and the common table jellies. When the liquid is removed and only the framework remains, the gel is known as a *xerogel*. Examples are gelatin sheets, tragacanth ribbons, and acacia tears.

Hydrogels retain significant amounts of water but remain water-insoluble and, because of these properties, are often used in topical drug design. The diffusion rate of a drug depends on the physical structure of the polymer network and its chemical nature. If the gel is highly hydrated, diffusion occurs through the pores. In gels of lower hydration, the drug dissolves in the polymer and is transported between the chains.[60] Cross-linking increases the hydrophobicity of a gel and diminishes the diffusion rate of the drug. The fractional release, $F$, of a drug from a gel at time $t$ can be expressed in general as

$$F = \frac{M_t}{M_0} = kt^n \qquad (17\text{–}9)$$

where $M_t$ is the amount released at time $t$, $M_0$ is the initial amount of drug, $k$ is the rate constant, and $n$ is a constant

### KEY CONCEPT CLASSIFICATION OF GELS

Gels can be classified as two-phase or single-phase systems. The gel mass may consist of floccules of small particles rather than large molecules, as found in aluminum hydroxide gel, bentonite magma, and magnesia magma, and the gel structure in these two-phase systems is not always stable (Fig. 17–14a and b). Such gels may be thixotropic, forming semisolids on standing and becoming liquids on agitation.

On the other hand, a gel may consist of macromolecules existing as twisted, matted strands (Fig. 17–14c). The units are often bound together by stronger types of van der Waals forces so as to form crystalline and amorphous regions throughout the entire system, as shown in Figure 17–14d. Examples of such gels are tragacanth and carboxymethylcellulose. These gels are considered to be one-phase systems because no definite boundaries exist between the dispersed macromolecules and the liquid.

Gels can be classified as *inorganic* and *organic*. Most inorganic gels can be characterized as two-phase systems, whereas organic gels belong to the single-phase class because the condensed matrix is dissolved in the liquid medium to form a homogeneous gelatinous mixture. Gels may contain water, and these are called *hydrogels*, or they may contain an organic liquid, in which case they are called *organogels*. Gelatin gel belongs to the former class, whereas petrolatum falls in the latter group.

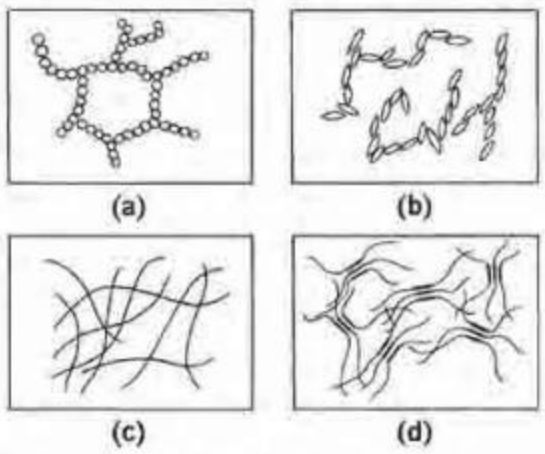


Fig. 17–14. Representations of gel structures. (*a*) Flocculated particles in a two-phase gel structure. (*b*) Network of elongated particles or rods forming a gel structure. (*c*) Matted fibers as found in soap gels. (*d*) Crystalline and amorphous regions in a gel of carboxymethylcellulose. (From H. R. Kruyt, *Colloid Science*, Vol. II, Elsevier, New York, 1949.)

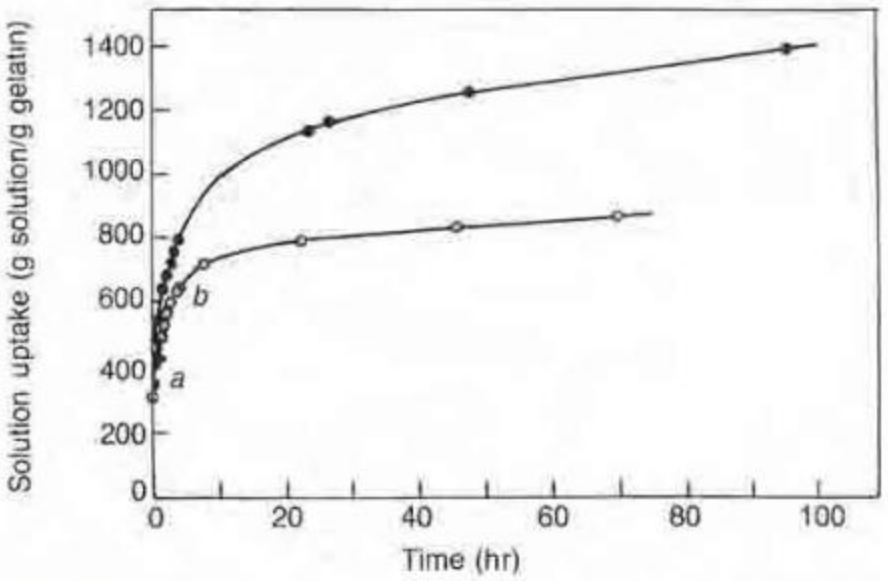


Fig. 17–15. Swelling isotherms of gelatin at (•) 25°C and (○) at 20°C. Swelling is measured as the increase in weight of gelatin strips in buffer solution at various times. The points *a* and *b* are discussed in the text. (From C. M. Ofner III and H. Schott, J. Pharm. Sci. **75**, 790, 1986. With permission.)

called the *diffusional exponent*. When $n = 0$, $t^n = 1$ and the release $F$ is of zero order; if $n = 0.5$, Fick's law holds and the release is represented by a square root equation. Values of $n$ greater than 0.5 indicate anomalous diffusion due generally to the swelling of the system in the solvent before the release takes place.[61] Morimoto et al.[62] prepared a polyvinyl alcohol hydrogel for rectal administration that has a porous, tridimensional network structure with high water content. The release of indomethacin from the gel followed Fickian diffusion over a period of 10 hr.

**EXAMPLE 17–6**

**Diffusional Component**

**The release fraction, $F$, of indomethacin is 0.49 at $t = 240$ min. Compute the diffusional exponent, $n$, knowing that $k = 3.155\%$ $\text{min}^{-n}$.**

**Because the rate constant $k$ is expressed as percentage, the fractional release, $F$, is also expressed in percentage units in equation (17–9), that is, 49%. Taking the ln on both sides of equation (17–9), we obtain**

$$\ln F = \ln k + n \ln t$$

$$n = \frac{\ln F - \ln k}{\ln t} = \frac{\ln 49 - \ln 3.155}{\ln 240}$$

$$n = \frac{3.892 - 1.149}{5.481} = 0.5$$

**Therefore, with the exponent of $t$ equal to 0.5, equation (17–9) becomes $F = kt^{1/2}$, which is a Fickian diffusion.**

## Syneresis and Swelling

When a gel stands for some time, it often shrinks naturally, and some of its liquid is pressed out. This phenomenon, known as *syneresis*, is thought to be due to the continued coarsening of the matrix or fibrous structure of the gel with a consequent squeezing-out effect. Syneresis is observed in table jellies and gelatin desserts. The "bleeding" in connection with the liberation of oil or water from ointment bases usually results from a deficient gel structure rather than from the contraction involved in syneresis.

The opposite of syneresis is the taking up of liquid by a gel with an increase in volume. This phenomenon is known as *swelling*. Gels may also take up a certain amount of liquid without a measurable increase in volume, and this is called *imbibition*. Only those liquids that solvate a gel can bring about swelling. The swelling of protein gels is influenced by pH and the presence of electrolytes.

Ofner and Schott[63] studied the kinetics of swelling of gelatin by measuring the increase in weight of short rectangular strips of gelatin films after immersion in buffer solutions as a function of time, $t$. A plot of the weight, $W$, in grams of aqueous buffer absorbed per gram of dry gelatin against $t$ in hours gives the swelling isotherms (**Fig. 17–15**). The horizontal portions of the two isotherms correspond to equilibrium swelling. To obtain a linear expression, $t/W$ is plotted against $t$ (the plot is not shown here) according to the equation

$$\frac{t}{W} = A + Bt \qquad \textbf{(17–10)}$$

Rearranging and differentiating equation **(17–10)**, we obtain

$$\frac{dW}{dt} = \frac{A}{(A + Bt)^2} \qquad \textbf{(17–11)}$$

As $t \to 0$, equation **(17–11)** gives the *initial swelling rate*, $dW/dt = 1/A$, which is the reciprocal of the intercept of equation **(17–10)**. The reciprocal of the slope, $1/B = W_\infty$, is the *equilibrium swelling*, that is, the theoretical maximum uptake of buffer solution at $t_\infty$.

**EXAMPLE 17–7**

**Initial Swelling Rate**

The increase in weight of 330 mg for a 15% gelatin sample 0.27 mm thick was measured in 0.15 M ammonium acetate buffer at 25°C. The $t/W$ values at several time periods are as follows:*

| $t$ (hr) | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| $t/W$ $\frac{\text{hr}}{\text{g(buffer)/g(gelatin)}}$ | 0.147 | 0.200 | 0.252 | 0.305 | 0.410 | 0.515 |

Compute the initial swelling rate and the equilibrium swelling.

A regression of $t/W$ against $t$ gives

$$\frac{t}{W} = 0.0946 + 0.1051\,t$$

The initial swelling rate, $1/A$, is the reciprocal of the intercept,

$$\frac{1}{A} = \frac{1}{0.0946} = 10.57 \text{ g(buffer solution)/hr g(gelatin)}$$

The equilibrium swelling is

$$W_\infty = \frac{1}{B} = \frac{1}{0.1051} = 9.513 \frac{\text{g(buffer solution)}}{\text{g(gelatin)}}$$

Equation (17–10) represents a second-order process. When the constants $A$ and $B$ are used to backcalculate the swelling, $W$, at several times and are compared with the experimental data, the higher deviations are found in the region of maximum curvature of the isotherms (**Fig. 17–15**). Ofner and Schott[63] attributed the deviations to the partially crystalline structure of gelatin. Thus, the first part of curve *a* in **Figure 17–15** corresponds to the swelling of the amorphous region, which is probably complete at times corresponding to maximum curvature, namely 6 to 10 hr at 20°C. The penetration of the solvent into the crystalline region is slower and less extensive because this region is more tightly ordered and has a higher density (part *b* of the curve in **Fig. 17–15**).

Gelatin is probably the most widely employed natural polymer in pharmaceutical products; it is used in the preparation of soft and hard gelatin capsules, tablet granulations and coatings, emulsions, and suppositories. Gelatin may interact with gelatin-encapsulated drugs or excipients by absorbing significant amounts of them, and some compounds may change the dissolution rate of soft gelatin capsules. Ofner and Schott[64] studied the effect of six cationic, anionic, and nonionic drugs or excipients on the initial swelling rate and equilibrium swelling in gelatin. The cationic compounds reduced the equilibrium swelling, $W_\infty$, substantially, whereas the nonionic and anionic compounds increased it. The researchers suggested that the cationic additives such as quaternary ammonium compounds may cause disintegration and dissolution problems with both hard and soft gelatin capsules.

Cross-linked hydrogels with ionizable side chains swell extensively in aqueous media. The swelling depends on the nature of the side groups and the pH of the medium. This property is important because diffusion of drugs in hydrogels depends on the water content in the hydrogel. Kou et al.[65] used phenylpropanolamine as a model compound to study its diffusion in copolymers of 2-hydroxyethyl methacrylate and methacrylic acid cross-linked with tetraethylene glycol dimethacrylate. The drug diffusivity, $D$, in the gel matrix is related to the matrix hydration by the relation

$$\ln D = \ln D_0 - K_f\left(\frac{1}{\mathbf{H}} - 1\right) \qquad (17\text{–}12)$$

where $D_0$ is the diffusivity of the solute in water and $K_f$ is a constant characteristic of the system. The term **H** represents the matrix hydration and is defined as

$$\mathbf{H} = \frac{\text{Equilibrium swollen gel weight} - \text{Dry gel weight}}{\text{Equilibrium swollen gel weight}}$$

According to equation (17–12), a plot of ln $D$ against $1/(\mathbf{H} - 1)$ should be linear with slope $K_f$ and intercept ln $D_0$.

**EXAMPLE 17–8**

**Diffusion Coefficients**

Compute the diffusion coefficients of phenylpropanolamine in a gel for two gel hydrations, H = 0.4 and H = 0.9. The diffusion coefficient of the solute in water is $D_0 = 1.82 \times 10^{-6}$ cm²/sec, and $K_f$, the constant of equation (17–12), is 2.354.

For H = 0.4,

$$\ln D = \ln(1.82 \times 10^{-6}) - 2.354\left(\frac{1}{0.4} - 1\right) = -16.748$$

$$D = 5.33 \times 10^{-8} \text{ cm}^2/\text{sec}$$

For H = 0.9,

$$\ln D = \ln(1.82 \times 10^{-6}) - 2.354\left(\frac{1}{0.9} - 1\right) = -13.479$$

$$D = 1.4 \times 10^{-6} \text{ cm}^2/\text{sec}$$

The swelling (hydration) of the gel favors drug release because it enhances the diffusivity of the drug, as shown in the example.

## Classification of Pharmaceutical Semisolids

Semisolid preparations, with special reference to those used as bases for jellies, ointments, and suppositories, can be classified as shown in **Table 17–2**. The arrangement is arbitrary and suffers from certain difficulties, as do all classifications.

Some confusion of terminology has resulted in recent years, partly as a result of the rapid development of the newer types of bases. Terms such as "emulsion-type," "water-washable," "water-soluble," "water-absorbing," "absorption base," "hydrophilic," "greaseless," and others have appeared in the literature as well as on the labels of commercial bases where the meaning is obscure and sometimes misleading. The title "greaseless" has been applied both to water-dispersible bases that contain no grease and to o/w bases because they feel greaseless to the touch and are easily removed from the skin and clothing. The terms "cream" and "paste" are also often used ambiguously. Pectin paste is a jelly, whereas zinc oxide paste is a semisolid suspension. And what does the term

*The data are calculated from the slope and intercept given in Table III in Ofner and Schott.[64]

**TABLE 17–2**
**A CLASSIFICATION OF SEMISOLID BASES**

| | Examples |
|---|---|
| I. Organogels | |
| A. Hydrocarbon type | Petrolatum, mineral oil–polyethylene gel* |
| B. Animal and vegetable fats | Lard, hydrogenated vegetable oils, Theobroma oil |
| C. Soap base greases | Aluminum stearate, mineral oil gel |
| D. Hydrophilic organogels | Carbowax bases, polyethylene glycol ointment |
| II. Hydrogels | |
| A. Organic hydrogels | Pectin paste, tragacanth jelly |
| B. Inorganic hydrogels | Bentonite gel, colloidal magnesium aluminum silicate gels |
| III. Emulsion-type semisolids | |
| A. Emulsifiable bases | |
| 1. Water-in-oil (absorption) | Hydrophilic petrolatum, wool fat |
| 2. Oil-in-water | Anhydrous Tween base† |
| B. Emulsified bases | |
| 1. Water-in-oil | Hydrous wool fat, rose water ointment |
| 2. Oil-in-water | Hydrophilic ointment, vanishing cream |

*Plastibase (E. R. Squibb). J. Am. Pharm. Assoc. Sci. Ed. **45**, 104, 1956.
†White petrolatum, stearyl alcohol, glycerin, Tween 60 (Atlas-ICI).

"absorption base" mean? Does it imply that the base is readily absorbed into the skin, that drugs incorporated in such a base are easily released and absorbed percutaneously, or that the base is capable of absorbing large quantities of water? These few examples point out the difficulties that arise when different titles are used for the same product or when different definitions are given to the same term.

### Organogels

Petrolatum is a semisolid gel consisting of a liquid component together with a "protosubstance" and a crystalline waxy fraction. The crystalline fraction provides rigidity to the gel structure, whereas the protosubstance or gel former stabilizes the system and thickens the gel. Polar organogels include the polyethylene glycols of high molecular weight known as Carbowaxes (Union Carbide Corp., New York). The Carbowaxes are soluble to about 75% in water and therefore are completely washable, although their gels look and feel like petrolatum.

### Hydrogels

Bases of this class include organic and inorganic ingredients that are colloidally dispersible or soluble in water. Organic hydrogels include the natural and synthetic gums such as tragacanth, pectin, sodium alginate, methylcellulose, and sodium carboxymethylcellulose. Bentonite mucilage is an inorganic hydrogel that has been used as an ointment base in about 10% to 25% concentration.

### Emulsion-Type Bases

Emulsion bases, as might be expected, have much greater affinity for water than do the oleaginous products.

The o/w bases have an advantage over the w/o bases in that the o/w products are easily removed from the skin and do not stain clothing. These bases are sometimes called *water washable*. They have the disadvantage of water loss by evaporation and of possible mold and bacterial growth, thus requiring preservation. Two classes of emulsion bases are discussed: emulsifiable and emulsified.

(*a*) *Emulsifiable bases*. We choose to call these bases *emulsifiable* because they initially contain no water but are capable of taking it up to yield w/o and o/w emulsions. The w/o types are commonly known as *absorption bases* because of their capacity to absorb appreciable quantities of water or aqueous solutions without marked changes in consistency.

(*b*) *Emulsified bases*. Water-in-oil bases in which water is incorporated during manufacture are referred to in this book as *emulsified* w/o *bases* to differentiate them from the emulsifiable w/o bases (absorption bases), which contain no water. The emulsified *oil-in-water bases* are formulated as is any emulsion with an aqueous phase, an oil phase, and an emulsifying agent. The components of emulsified ointments, however, differ in some ways from the ingredients of liquid emulsions.

The oil phase of the ointment may contain petrolatum, natural waxes, fatty acids or alcohols, solid esters, and similar substances that increase the consistency of the base and provide certain desirable application properties.

### Comparison of Emulsion Bases

The absorption bases have the advantage over oleaginous products in absorption of large amounts of aqueous solution. Furthermore, they are compatible with most drugs and are stable over long periods. When compared with o/w bases, the w/o preparations are superior in that they do not lose water readily by evaporation because water is the internal phase. Although emulsified o/w or washable bases do have the

undesirable property of drying out when not stored properly and of losing some water during compounding operations, they are more acceptable than the nonwashable absorption bases because they are easily removed with water from the skin and clothing.

## Hydrophilic Properties of Semisolids

Petrolatum is hydrophilic to a limited degree, taking up about 10% to 15% by weight of water through simple incorporation.

The water-absorbing capacity of oleaginous and water-in-oil bases can be expressed in terms of the *water number*, first defined in 1935 by Casparis and Meyer[66] as the maximum quantity of water that is held (partly emulsified) by 100 g of a base at 20°C. The test consists in adding increments of water to the melted base and triturating until the mixture has cooled. When no more water is absorbed, the product is placed in a refrigerator for several hours, removed, and allowed to come to room temperature. The material is then rubbed on a slab until water no longer exudes, and, finally, the amount of water remaining in the base is determined. Casparis and Meyer found the water number of petrolatum to be about 9 to 15; the value for wool fat is about 185.

## Rheologic Properties of Semisolids

Manufacturers of pharmaceutical ointments and cosmetic creams have recognized the desirability of controlling the consistency of non-Newtonian materials.

Probably the best instrument for determining the rheologic properties of pharmaceutical semisolids is some form of a rotational viscometer. The cone–plate viscometer is particularly well adapted for the analysis of semisolid emulsions and suspensions. The Stormer viscometer, consisting of a stationary cup and rotating bob, is also satisfactory for semisolids when modified, as suggested by Kostenbauder and Martin.[67]

Consistency curves for the emulsifiable bases hydrophilic petrolatum and hydrophilic petrolatum in which water has been incorporated are shown in **Figure 17–16**. It will be observed that the addition of water to hydrophilic petrolatum has lowered the yield point (the intersection of the extrapolated downcurve and the load axis) from 520 to 340 g. The plastic viscosity (reciprocal of the slope of the downcurve) and the thixotropy (area of the hysteresis loop) are increased by the addition of water to hydrophilic petrolatum.

The effect of temperature on the consistency of an ointment base can be analyzed by use of a properly designed rotational viscometer. **Figures 17–17** and **17–18** show the changes of plastic viscosity and thixotropy, respectively, of petrolatum and Plastibase as a function of temperature.[68] The modified Stormer viscometer was used to obtain these curves. As observed in **Figure 17–17**, both bases show about the same temperature coefficient of plastic viscosity. These results account for the fact that the bases have about the same degree of "softness" when rubbed between the fingers. Curves of yield value versus temperature follow approxi-

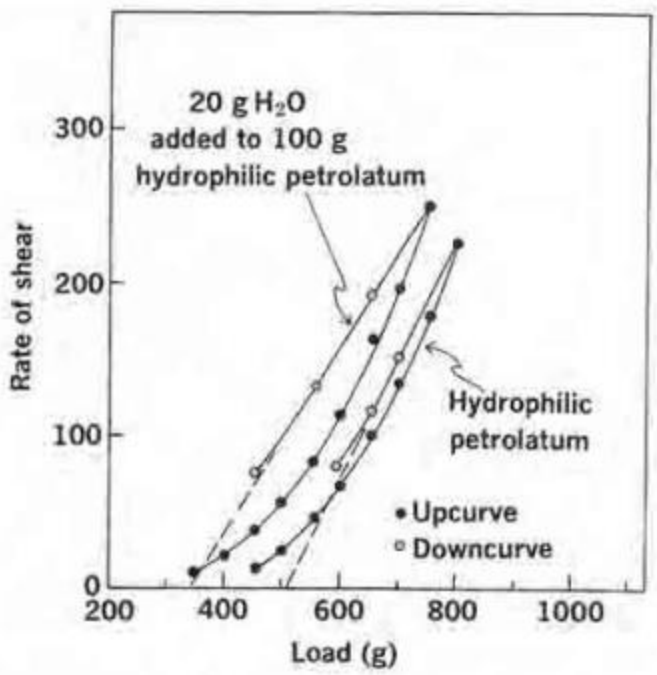


Fig. 17–16. Flow curves for hydrophilic petrolatum and hydrophilic petrolatum containing water. (After H. B. Kostenbauder and A. Martin, J. Am. Pharm. Assoc. Sci. Ed. **43**, 401, 1954.)

mately the same relationship. The curves of **Figure 17–18** suggest strongly that it is the alternation of thixotropy with temperature that differentiates the two bases. Because thixotropy is a consequence of gel structure, **Figure 17–18** shows that the waxy matrix of petrolatum is probably broken down considerably as the temperature is raised, whereas the resinous structure of Plastibase withstands temperature changes over the ranges ordinarily encountered in its use.

Based on data and curves such as these, the pharmacist in the development laboratory can formulate ointments with more desirable consistency characteristics, the worker in the

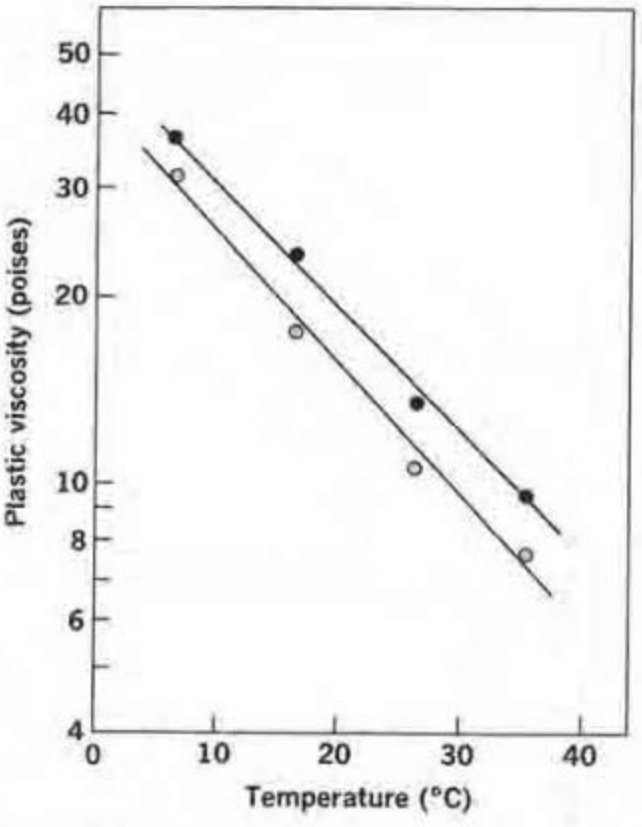


Fig. 17–17. The temperature coefficient of plastic viscosity of (•) Plastibase (E. R. Squibb and Sons, New Brunswick, NJ) and (○) petrolatum. (From A. H. C. Chun, M. S. Thesis, Purdue University, Purdue, Ind., June 1956.)

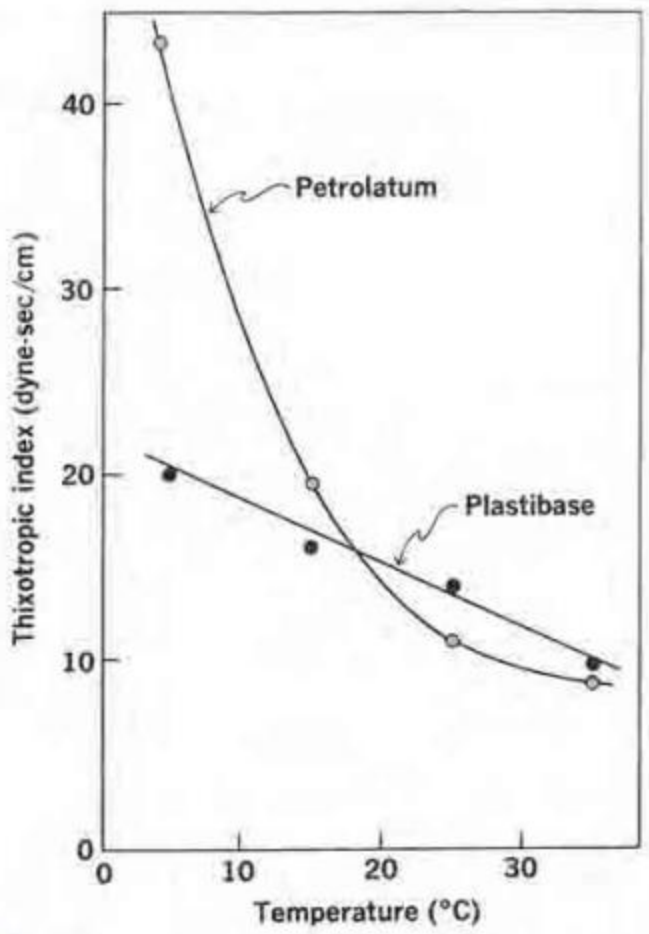


Fig. 17–18. The temperature coefficient of thixotropy of Plastibase (E. R. Squibb and Sons) and petrolatum. (After A. H. C. Chun, M. S. Thesis, Purdue University, Purdue, Ind., June 1956.)

production plant can better control the uniformity of the finished product, and the dermatologist and the patient can be assured of a base that spreads evenly and smoothly in various climates, yet adheres well to the affected area and is not tacky or difficult to remove.

Rigidity and viscosity are two separate parameters used to characterize the mechanical properties of gels. Ling[69] studied the effect of temperature on rigidity and viscosity of gelatin. He used a *rigidity index, f*, which is defined as the force required to depress the gelatin surface a fixed distance. To measure rigidity, a sample of gelatin solution or gel mass is subjected to penetrative compression by a flat-ended cylindrical plunger that operates at a constant speed. In this method, the strain rate (rate of deformation of the gel) is constant and independent of stress (force applied). Ling found that thermal degradation with respect to rigidity followed second-order kinetics,

$$-df/dt = k_f f^2 \qquad (17\text{–}13)$$

The integrated form of equation (17–13) is

$$\frac{1}{f} - \frac{1}{f_0} = k_f t \qquad (17\text{–}14)$$

where $f$ is the *rigidity index* of the gelatin solution or gelatin gel at time $t$, $f_0$ is the rigidity index at time zero, $k_f$ is the rate constant ($g^{-1}$ $hr^{-1}$), and $t$ is the heating time in hours. The quantities $f_0$ and $k_f$ can be computed from the intercept and the slope of equation (17–14) at a given temperature.

**EXAMPLE 17–9**

**Rigidity Index**

The rigidity degradation of a 6% pharmaceutical-grade gelatin USP was studied[69] at 65°C. The rigidity index values at several times are as follows:

| $t$ (hr) | 10 | 20 | 30 | 40 | 50 |
|---|---|---|---|---|---|
| $\frac{1}{f}(g^{-1})$ | 0.0182 | 0.0197 | 0.0212 | 0.0227 | 0.0242 |

Compute the rigidity index, $f_0$, at time zero and the rate constant, $k_f$, at 65°C.

The regression of $1/f$ versus $t$ gives the equation

$$\frac{1}{f} = 1.5 \times 10^{-4}\, t + 0.0167$$

At $t = 0$ we have intercept $1/f_0 = 0.0167\ g^{-1}$; $f_0 = 59.9$ g. The slope is $k_f = 1.5 \times 10^{-4}\ g^{-1}\ hr^{-1}$. Using the regression equation, we can compute the rigidity index, $f$, at time $t$, say 60 hr:

$$\frac{1}{f} = (1.5 \times 10^{-4} \times 60) + 0.0167 = 0.0257\ g^{-1}$$

$$f = \frac{1}{0.0257} = 38.9\ g$$

The force needed to depress the gelatin surface has decreased from its original value, $f_0 = 59.9$ g. Therefore, gelatin lost rigidity after heating for 60 hr.

The effect of temperature on the rate constant, $k_f$, can be expressed using the Arrhenius equation,

$$k_f = Ae^{-E_a/RT} \qquad (17\text{–}15)$$

Thus, a plot of $\ln k_f$ against $1/T$ gives the Arrhenius constant, $A$, and the energy of activation, $E_a$.

Fassihi and Parker[70] measured the change in the rigidity index, $f$, of 15% to 40% gelatin gel, USP type B, before and after gamma irradiation (which is used to sterilize the gelatin). They found that the rigidity index diminished with irradiation and that the kinetics of rigidity degradation is complex. For gels containing more than 20% gelatin, the rigidity index follows a sigmoidal curve at increasing radiation doses, as shown in **Figure 17–19**. Gelatin is widely used in tablet manufacturing as a binder to convert fine powders into granules. The loss of rigidity index reduced the binding properties of gelatin and decreased the hardness of lactose granules prepared with irradiated gelatin. These workers suggested that doses of gamma radiation should be held to less than 2 megarad (Mrad) to obtain gelatins of acceptable quality for pharmaceutical applications.

## Universe of Topical Medications

Katz[71] devised a "universe of topical medications" (**Fig. 17–20**) by which one can consider the various topical medications such as pastes, absorption bases, emulsified products, lotions, and suspensions. The basic components of most dermatologic preparations are powder, water, oil, and emulsifier. Beginning at *A* on the "universal wheel" of **Figure 17–20**, one is confronted with the simple powder medication, used

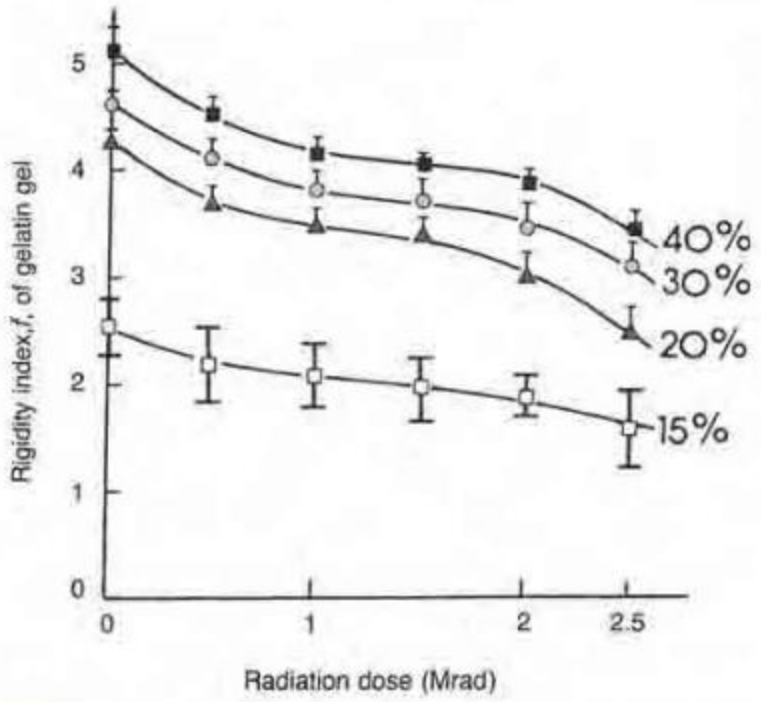


Fig. 17–19. Rigidity index of gelatin gel as a function of gamma irradiation at various concentrations (15%–40%) of the gel. (From A. R. Fassihi and M. S. Parker, J. Pharm. Sci. **77**, 876, 1988. With permission.)

as a protective, drying agent and lubricant and as a carrier for locally applied drugs. Passing counterclockwise around the wheel, we arrive at the paste, *B*, which is a combination of powder from segment *A* and an oleaginous material such as mineral oil or petrolatum. An oleaginous ointment for lubrication and emolliency and devoid of powder is shown in segment *C*.

The next section, *D*, is a waterless absorption base, consisting of oil phase and w/o emulsifier and capable of absorbing aqueous solutions of drugs. At the next region of the wheel, *E*, water begins to appear along with oil and emulsifier, and a w/o emulsion results. The proportion of water is increased at *F* to change the ointment into a w/o cream. At *G*, the base is predominantly water, and an o/w emulsifier is used to form the opposite type of emulsion, that is, an o/w cream. Still more water and less oil converts the product into an o/w lotion at *H*. At point *I* on the universal wheel, only water remains, both oil and surfactant being eliminated, and this segment of the wheel represents an aqueous liquid preparation, a soak, or a compress.

Finally, at section *J*, the powder from *A* is incorporated, and the aqueous product becomes a shake preparation, as represented by calamine lotion. Accordingly, this ingenious wheel classifies nearly all types of topical preparations from solid pastes and ointments, through w/o and o/w emulsions, to liquid applications and shake lotions. It serves as a convenient way to discuss the various classes of dermatologic and toiletry products that are prepared by the manufacturer or practicing pharmacist and applied topically by the patient.

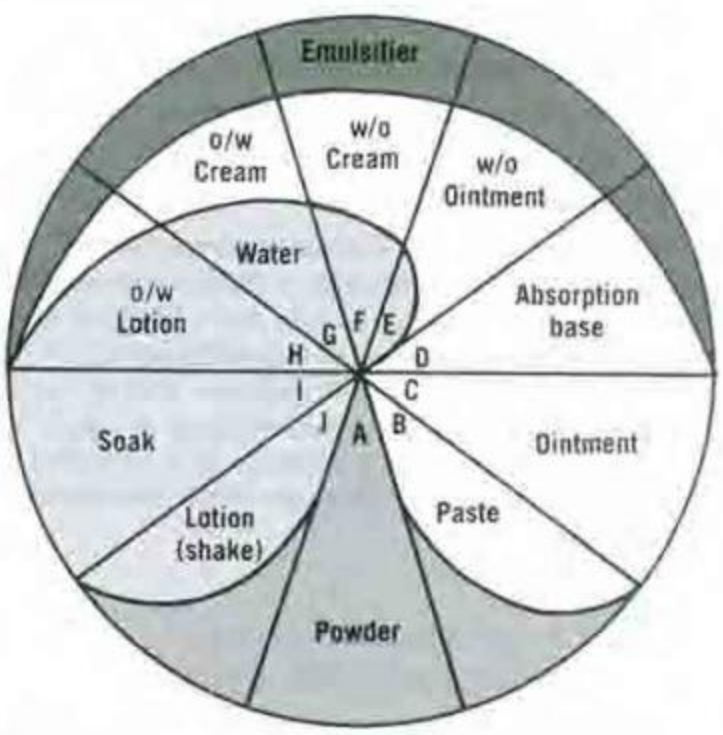


Fig. 17–20. Universe of topical medication. (From M. Katz, in E. J. Ariens (Ed.), *Drug Design*, Academic Press, New York, 1973. With permission.)

## DRUG KINETICS IN COARSE DISPERSE SYSTEMS

The kinetics of degradation of drugs in suspension[72] can be described as a pseudo–zero-order process (see Chapter 14),

$$M = M_0 - k_1 V C_s t \qquad (17\text{–}16)$$

where $k_1$ is the first-order constant of the dissolved drug, $V$ is the volume of the suspension, and $C_s$ is the solubility of the drug. If the solubility is very low, the kinetics can be described as found in the section on solid-state kinetics (see Chapter 14). For very viscous dispersed systems, the kinetics of degradation can be partially controlled by the dissolution rate as given by the Noyes–Whitney equation,

$$dc/dt = KS(C_s - C) \qquad (17\text{–}17)$$

where $C_s$ is the solubility of the drug, $C$ is the concentration of solute at time $t$, $S$ is the surface area of the expanded solid, and $K$ is the dissolution rate constant. It is assumed that as a molecule degrades in the liquid phase it is replaced by another molecule dissolving. The overall decrease in concentration in the liquid phase can be written as

$$dc/dt = -kC + KS(C_s - C) \qquad (17\text{–}18)$$

where $-kC$ expresses the rate of disappearance at time $t$ due to degradation, and $KS(C_s - C)$ is the rate of appearance of the drug in the liquid phase due to dissolution of the particles. The solution of this differential equation is

$$C = [C_s KS/(k_1 + KS)]e^{-(k_1 + SK)t} \qquad (17\text{–}19)$$

At large $t$ values, $C$ becomes

$$C = C_s KS/(k_1 + KS) \qquad (17\text{–}20)$$

and the amount of drug remaining in suspension at large values of $t$ is

$$M = M_0 - [k_1 SKC_s V/(k_1 + KS)]t \qquad (17\text{–}21)$$

where $M_0$ is the initial amount of drug in suspension. Equation (17–21) is an expression for a zero-order process, as is equation (17–16), but the slopes of the two equations are different. Because the dissolution rate constant, $K$, in equation (17–21) is proportional to the diffusion coefficient, $D$, $K$ is inversely proportional to the viscosity of the medium; therefore, the more viscous the preparation, the greater is the stability.

**EXAMPLE 17–10**

**Particles and Decomposition**

The first-order decomposition rate of a drug in aqueous solution is $5.78 \times 10^{-4}$ sec$^{-1}$ and the dissolution rate constant, $K$, is $3.35 \times 10^{-6}$ cm$^{-2}$ sec$^{-1}$. What is the amount of drug remaining in 25 cm$^3$ of a 5% w/v suspension after 3 days? Assume spherical particles of mean volume diameter, $d_{vn}$, $2 \times 10^{-4}$ cm. The density of the powder is 3 g/cm$^3$ and the solubility of the drug is $2.8 \times 10^{-4}$ g/cm$^3$.

The initial amount of drug is

$$\frac{5}{100} = \frac{M_0}{25}, \; M_0 = 1.25 \text{ g}/25 \text{ cm}^3$$

The number of particles, $N$, in 25 cm$^3$ can be computed from equation (18–4):

$$N = \frac{6}{\pi(d_{vn})^3 \rho} = \frac{6}{3.1416 \times (2 \times 10^{-4})^3 \times 3}$$

$$= 7.96 \times 10^{10} \frac{\text{particles}}{\text{gram}}$$

The number of particles in 1.25 g is $N = 7.96 \times 10^{10} \times 1.25 = 9.95 \times 10^{10}$ particles.

The total surface area is

$$S = N\pi d^2 = 9.95 \times 10^{10} \times 3.1416 \times (2 \times 10^{-4})^2$$
$$= 1.25 \times 10^4 \text{ cm}^2$$

From equation (17–21),

$$M = 1.25 - \frac{5.78 \times 10^{-4} \times 1.25 \times 10^4 \times 3.35 \times 10^{-6} \times 2.8 \times 10^{-4} \times 25}{5.78 \times 10^{-4} + (3.35 \times 10^{-6} \times 1.25 \times 10^4)} \times (2.6 \times 10^5 \text{ sec})$$

$$= 1.25 - [(3.99 \times 10^{-6})(2.6 \times 10^5)] = 1.25 - 1.0374 = 0.213 \text{ g}$$

Kenley et al.[73] studied the kinetics of degradation of fluocinolone acetonide incorporated into an oil-in-water cream base. The degradation followed a pseudo–first-order constant at pH values from 2 to 6 and at several temperatures. The observed rate constants increased with increasing temperature, and acid catalysis at low pH values and basic catalysis at pH above 4 were observed. The observed rate constant for the degradation process can be written as

$$k = k_o + k_H[H^+] + k_{OH}[OH^-] \qquad (17\text{–}22)$$

Figure 17–21 compares the degradation of fluocinolone acetonide from oil-in-water creams with that of triamcinolone acetonide, a related steroid, in aqueous solution. From the figure, both creams and solution share a similar log(Rate)–pH profile over the pH range of 2 to 6, with a minimum rate near pH 4. This may indicate that the degradation in oil-in-water creams is confined to an aqueous environment, the nonaqueous components of the cream having little influence.[73]

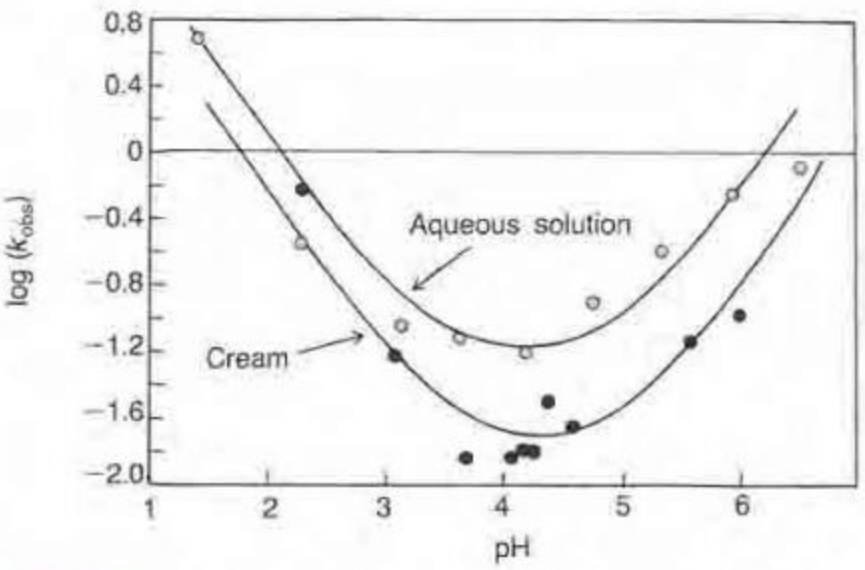


Fig. 17–21. The pH–log($k_{obs}$) profile for degradation of fluocinolone acetonide and triamcinolone acetonide at 50°C. Key: ● = experimentally determined $k_{obs}$ (month$^{-1}$) for fluocinolone acetonide cream; ○ = triamcinolone acetonide solution. The solid lines were obtained from the calculated values of $k_{obs}$ using equation (17–22). (From A. Kenley, M. O. Lee, L. Sukumar, and M. Powell, Pharm. Res. **4**, 342, 1987. With permission.)

Because $\ln k = \ln A - E_a/RT$, where $A$ is the Arrhenius factor and $E_a$ is the energy of activation, equation (17–22) can be rewritten in terms of activation parameters, $A$ and $E_a$, for each of the catalytic coefficients, $k_o$, $k_H$, and $k_{OH}$:

$$k = \exp[\ln A_o - (E_{ao}/RT)] + \exp[\ln A_H - (E_{aH}/RT)][H^+] + \exp[\ln A_{OH} - (E_{aOH}/RT)][OH^-] \qquad (17\text{–}23)$$

Equation (17–23) allows one to compute the degradation rate constant $k$ at several temperatures and pH values.

**EXAMPLE 17–11**

**Degradation Rate Constant**

The natural logarithm of the Arrhenius parameters for neutral-, acid-, and base-catalyzed hydrolysis of fluocinolone acetonide in oil-in-water creams are $\ln A_o = 22.5$, $\ln A_H = 38.7$, and $\ln A_{OH} = 49.5$. The corresponding energies of activation are $E_{aO} = 17{,}200$, $E_{aH} = 22{,}200$, and $E_{aOH} = 21{,}100$ cal/mole. The $H^+$ and $OH^-$ concentrations in equation (17–23) are expressed, as usual, in moles per liter, and the first-order rate constant, $k$, is expressed in this example in month$^{-1}$. Compute the degradation rate constant, $k$, at 40°C and pH 4.

From equation (17–23),

$$k = \exp[22.5 - (17{,}200/1.9872 \times 313)] + \exp[38.7 - (22{,}200/1.9872 \times 313)] \times (1 \times 10^{-4}) + \exp[49.5 - (21{,}100/1.9872 \times 313)] \times (1 \times 10^{-10})$$
$$= (5.782 \times 10^{-3}) + (2.025 \times 10^{-3}) + (5.820 \times 10^{-4})$$
$$k = 8.39 \times 10^{-3} \text{ month}^{-1}$$

Teagarden et al.[74] determined the rate constant, $k$, for the degradation of prostaglandin $E_1$ ($PGE_1$) in an oil-in-water emulsion. At acidic pH values, the degradation of $PGE_1$ showed large rate constants. This fact was attributed to the greater effective concentration of hydrogen ions at the oil–water interface, where $PGE_1$ is mainly located at low pH values.

## DRUG DIFFUSION IN COARSE DISPERSE SYSTEMS

The release of drugs suspended in ointment bases can be calculated from the Higuchi equation:

$$Q = [D(2A - C_s)C_s t]^{1/2} \qquad \textbf{(17–24)}$$

where $Q$ is the amount of drug released at time $t$ per unit area of exposure, $C_s$ is the solubility of the drug in mass units per $cm^3$ in the ointment, and $A$ is the total concentration, both dissolved and undissolved, of the drug. $D$ is the diffusion coefficient of the drug in the ointment ($cm^2$/sec).

Iga et al.[75] studied the effect of ethyl myristate on the release rate of 4-hexylresorcinol from a petrolatum base at pH 7.4 and temperature 37°C. They found that the release rate was proportional to the square root of time, according to the Higuchi equation. Increasing concentrations of ethyl myristate enhanced the release rate of the drug owing to the increase of drug solubility, $C_s$, in the ointment [see equation **(17–24)**]. This behavior was attributed to formation of 1:1 and 1:2 complexes between hexylresorcinol and ethyl myristate.

**EXAMPLE 17–12**

**Calculate $Q$**

**The solubility of hexylresorcinol in petrolatum base is 0.680 mg/cm³. After addition of 10% ethyl myristate, the solubility, $C_s$, of the drug is 3.753 mg/cm³. Compute the amount, $Q$, of drug released after 10 hr. The diffusion coefficient, $D$, is $1.31 \times 10^{-8}$ cm²/sec and the initial concentration, $A$, is 15.748 mg/cm³.**

**We have**

$$Q = \{(1.31 \times 10^{-8}\text{cm}^2/\text{sec})[(2 \times 15.748\ \text{mg/cm}^3) - 0.68\ \text{mg/cm}^3)]\}^{\frac{1}{2}} \times [0.68\ \text{mg/cm}^3 \times (10 \times 3600)\ \text{sec}]^{\frac{1}{2}} = 0.099\ \text{mg/cm}^3$$

**After addition of 10% ethyl myristate, we find**

$$Q = \{(1.31 \times 10^{-8}\ \text{cm}^2/\text{sec})\,[(2 \times 15.748\ \text{mg/cm}^3) - 3.753\ \text{mg/cm}^3)]\}^{\frac{1}{2}} \times [3.753\ \text{mg/cm}^3 \times (10 \times 3600)\ \text{sec}]^{\frac{1}{2}} = 0.222\ \text{mg/cm}^2$$

The release of a solubilized drug from emulsion-type creams and ointments depends on the drug's initial concentration. It is also a function of the diffusion coefficient of the drug in the external phase, the partition coefficient between the internal and external phases, and the volume fraction of the internal phase. If the drug is completely solubilized in a minimum amount of solvent, the release from the vehicle is faster than it is from a suspension-type vehicle.

Ong and Manoukian[76] studied the delivery of lonapalene, a nonsteroidal antipsoriatic drug, from an ointment, varying the initial concentration of drug and the volume fraction of the internal phase. In the study, lonapalene was completely solubilized in the ointment systems. Most of the drug was dissolved in the internal phase, consisting of propylene carbonate–propylene glycol, but a fraction was also solubilized in the external phase of a petrolatum base consisting of glyceryl monostearate, white wax, and white petrolatum. The data were treated by the approximation of Higuchi,[77]

$$Q = 2C_0\sqrt{\frac{D_e t}{\pi}} \qquad \textbf{(17–25)}$$

where $Q$ is the amount of drug released per unit area of application, $C_0$ is the initial concentration in the ointment, $D_e$ is the effective diffusion coefficient of the drug in the ointment, and $t$ is the time after application. For a small volume of the internal phase,

$$D_e = \frac{D_1}{\phi_1 + K\phi_2}\left[1 + 3\phi_2\left(\frac{KD_2 - D_1}{KD_2 + 2D_1}\right)\right] \qquad \textbf{(17–26)}$$

where the subscripts 1 and 2 refer to the external and internal phases, respectively, and $K$ is the partition coefficient between the two phases. When $D_2$ is much greater than $D_1$,

$$D_e = \frac{D_1(1 + 3\phi_2)}{\phi_1 + K\phi_2} \qquad \textbf{(17–27)}$$

$D_e$, the effective diffusion coefficient, is obtained from the release studies [equation **(17–25)**], and $D_1$ can be computed from equation **(17–27)** if one knows the volume fraction of the external and internal phases, $\phi_1$ and $\phi_2$, respectively. The drug is released according to two separate rates: an initial nonlinear and a linear, diffusion-controlled rate (**Fig. 17–22**). The initial rates extending over a period of 30 min are higher than the diffusion-controlled rates owing to the larger transference of drug directly to the skin from the surface globules. The high initial rates provide immediate availability of the drug for

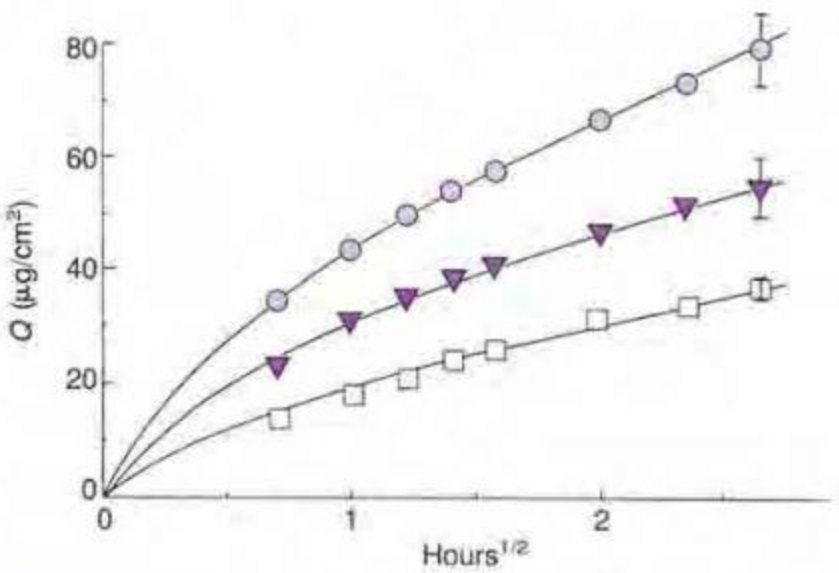


Fig. 17–22. Amount per unit area, $Q$, of lonapalene at time $t$ from an emulsion-type ointment. Key: □ = 0.5%; ▼ = 1.0%; and ● = 2.0% drug. (From J. T. H. Ong and E. Manoukian, Pharm. Res. **5**, 16, 1988. With permission.)

absorption. In addition, the release of drug from the external phase contributes to the initial rates. Equation (17–25) is applicable only to the linear portion of the graph, where the process becomes diffusion controlled (**Fig. 17–22**).

**EXAMPLE 17–13**

**Amount Released**

Compute the amount of lonapalene released per $cm^2$ after $t$ = 24 hr from a 0.5% *w/v* emulsified ointment. The internal phase of the ointment consists of the drug solubilized in a propylene carbonate–propylene glycol mixture and the external phase is a white petrolatum–glyceryl monostearate–white wax mixture. The volume fraction of the internal phase, $\phi_2$, is 0.028, the diffusion coefficient of the drug in the external phase, $D_1$, is $2.60 \times 10^{-9}$ $cm^2$/sec, and the partition coefficient, $K$, between the internal and external phases is 69.

From equation (17–27), the effective diffusion coefficient is

$$D_e = \frac{(2.60 \times 10^{-9}\ \text{cm}^2/\text{sec})[1 + (3 \times 0.028)]}{(1 - 0.028) + (69 \times 0.028)}$$

$$= 0.97 \times 10^{-9}\ \text{cm}^2/\text{sec}$$

Note that the sum of the volume fractions of internal and of external phases is equal to 1; therefore, knowing the external volume fraction to be $\phi_2 = 0.028$, one simply has the internal volume fraction, $\phi_1 = 1 - 0.028$. The initial concentration of drug is 0.5 g per 100 $cm^3$, that is, 5 mg/mL. From equation (17–25), the amount of lonapalene released after 24 hr is

$$Q = 2 \times (5\ \text{mg/cm}^3)\sqrt{\frac{(0.97 \times 10^{-9}\text{cm}^2/\text{sec}) \times (24 \times 3600)\ \text{sec}}{3.1416}}$$

$$= 0.05\ \text{mg/cm}^2$$

The rate of release also depends on the solubility of the drug as influenced by the type of emulsion. Rahman et al.[78] studied the in vitro release and in vivo percutaneous absorption of naproxen from anhydrous ointments and oil-in-water and water-in-oil creams. The results fitted equation (17–25), the largest release rates being obtained when the drug was incorporated into the water phase of the creams by using the soluble sodium derivative of naproxen. After application of the formulations to rabbit skin, the absorption of the drug followed first-order kinetics, showing a good correlation with the in vitro release.

Chiang et al.[79] studied the permeation of minoxidil, an antialopecia (antibaldness) agent, through the skin from anhydrous, oil-in-water, and water-in-oil ointments. The rate of permeation was higher from water-in-oil creams.

Drug release from fatty suppositories can be characterized by the presence of an interface between the molten base and the surrounding liquid. The first step is drug diffusion into the lipid–water interface, which is influenced by the rheologic properties of the suppository. In a second step, the drug dissolves at the interface and is then transported away from the interface.[80] Because the dissolution of poorly water-soluble drugs on the aqueous side of the lipid–water interface is the rate-limiting step, the release is increased by the formation of a water-soluble complex. Arima et al.[80] found that the release of ethyl 4-biphenyl acetate, an anti-inflammatory drug, from a lipid suppository base was enhanced by complexation of the drug with a hydrosoluble derivative of $\beta$-cyclodextrin. The increase in solubility and wettability as well as the decrease in crystallinity due to an inclusion-type complexation may be the cause of the enhanced release. On the other hand, complexation of flurbiprofen with methylated cyclodextrins, which are oil soluble and surface active, enhances the release from hydrophilic suppository bases. This is due to the decreased interaction between the drug complex and the hydrophilic base.[81] Coprecipitation of indomethacin with PVP also enhances the release from lipid suppository bases because it improves wetting, which avoids the formation of a cake at the oil–aqueous suppository interface.[82]

Nyqvist-Mayer et al.[83] studied the delivery of a eutectic mixture of lidocaine and prilocaine (two local anesthetics) from emulsions and gels. Lidocaine and prilocaine form eutectic mixtures at approximately a 1:1 ratio. The eutectic mixture has a eutectic temperature of 18°C, meaning that it is a liquid above 18°C and can therefore be emulsified at room temperature. The mechanism of release from this emulsion and transport through the skin is complex owing to the presence of freely dissolved species, surfactant-solubilized species, and emulsified species of the local anesthetic mixture. The passage of these materials across the skin membrane is depicted in **Figure 17–23**. The solute lost due to transport across the membrane is replenished by dissolution of droplets as long as a substantial number of droplets are present. Micelles of surfactant with a fraction of the solubilized drug may act as carriers across the aqueous diffusion layer, diminishing the diffusion layer resistance. Droplets from the bulk are also transported to the boundary layer and supply solute, which diffuses through the membrane, thus decreasing the limiting effect of the aqueous layer to diffusion of solute. Because the oil phase of this emulsion is formed by the eutectic mixture itself, there is no transport of drug between the inert oil and water, as occurs in a conventional emulsion and which would result in a decreased thermodynamic activity, $a$, or "escaping tendency." The system actually resembles a suspension that theoretically has high thermodynamic activity owing to the saturation of the drug in the external phase. In a suspension, the dissolution rate of the particles could be a limiting factor. In contrast, the fluid state of the eutectic mixture lidocaine–prilocaine

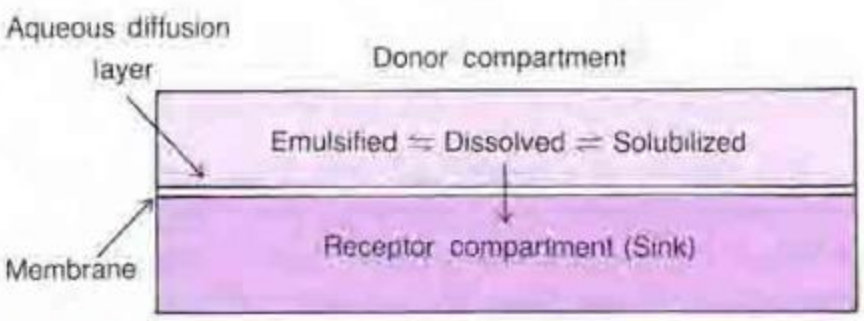


**Fig. 17–23.** Delivery of a eutectic mixture of lidocaine–prilocaine from an emulsion into a receptor compartment. (From A. A. Nyqvist-Mayer, A. F. Borodin, and S. G. Frank, J. Pharm. Sci. **75**, 365, 1986. With permission.)

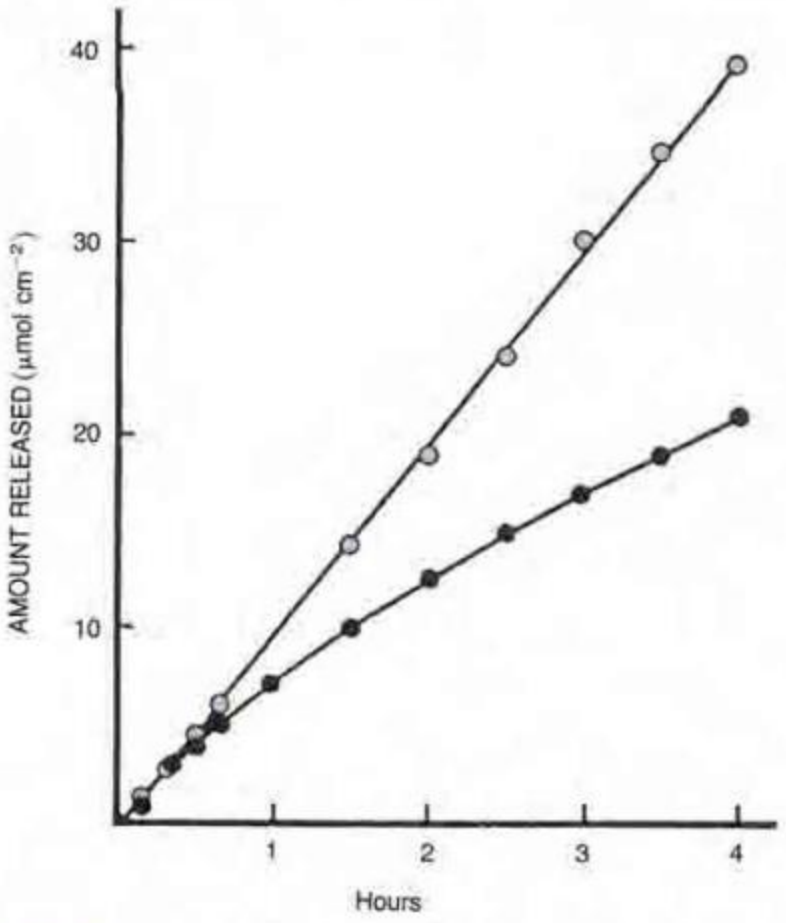


Fig. 17–24. Release of lidocaine–prilocaine from an emulsion (○) and from a gel (●). (From A. A. Nyqvist-Mayer, A. F. Borodin, and S. G. Frank, J. Pharm. Sci. **75**, 365, 1986. With permission.)

may promote a higher dissolution rate. The total resistance, $R_T$, to the skin permeation of the free dissolved fraction of prilocaine is given by the sum of the resistances of the aqueous layer, $R_a$, and the resistance of the membrane, $R_m$:

$$R_T = R_a + R_m \tag{17–28}$$

or

$$R_T = \frac{1}{P} = \frac{h_m}{D_m K} + \frac{h_a}{D_a} \tag{17–29}$$

where $D$ is the diffusion coefficient of the drug, $h_a$ is the thickness of the aqueous layer, $h_m$ is the thickness of the membrane, and $P$ is the permeability coefficient associated with the membrane and the aqueous layer; $K$ is the partition coefficient between the membrane and the aqueous layer. The subscripts a and m stand for aqueous layer and membrane, respectively. Equation **(17–29)** is analogous to equation **(11–30)**, except that the constant 2 in the denominator has been eliminated in this case because we consider only one aqueous layer (**Fig. 17–24**).

**EXAMPLE 17–14**

**Compute the total permeability, $P$, of a 1:1.3 ratio of lidocaine–prilocaine in the form of a eutectic mixture. The thicknesses of the aqueous and membrane layers are 200 and 127 $\mu$m, respectively. The diffusion coefficient and the partition coefficient of the drugs at the membrane–aqueous layers are as follows: lidocaine, $D_a = 8.96 \times 10^{-6}$ cm²/sec, $D_m = 2.6 = 10^{-7}$ cm²/sec, and $K = 9.1$; prilocaine, $D_a = 9.14 \times 10^{-6}$ cm²/sec, $D_m = 3 \times 10^{-7}$ cm²/sec, and $K = 4.4$.**

For lidocaine, according to equation (17–29),

$$\frac{1}{P} = \frac{127 \times 10^{-4}\text{ cm}}{(2.6 \times 10^{-7}\text{ cm}^2/\text{sec}) \times 9.1} + \frac{200 \times 10^{-4}\text{ cm}}{8.96 \times 10^{-6}\text{ cm}^2/\text{sec}}$$

$$= 7599.8\text{ sec/cm}$$

$$P = 1/7599.8 = 1.32 \times 10^{-4}\text{ cm/sec}$$

For prilocaine,

$$\frac{1}{P} = \frac{127 \times 10^{-4}\text{ cm}}{(3 \times 10^{-7}\text{ cm}^2/\text{sec}) \times 4.4} + \frac{200 \times 10^{-4}\text{ cm}}{9.14 \times 10^{-6}\text{ cm}^2/\text{sec}}$$

$$= 11809.2\text{ sec/cm}$$

$$P = 1/11809.2 = 8.47 \times 10^{-5}\text{ cm/sec}$$

The permeability of the mixture $P_T$ can be calculated from the proportion of each component.[83] Because the proportion of lidocaine is 1 and that of prilocaine 1.3, the total amount is $1 + 1.3 = 2.3$. Therefore, the permeability of the mixture is

$$P_T = \frac{(1 \times 1.32 \times 10^{-4}) + (1.3 \times 8.47 \times 10^{-5})}{2.3}$$

$$= 1.05 \times 10^{-4}\text{ cm/sec}$$

The total amount released from the emulsion consists of an initial steady-state portion, from which the release rate can be computed. When the formulation is thickened with carbomer 934P (carbopol), a gel results. The release rates from the gel and the emulsion are compared in **Figure 17–24**. In the gel, the release rate continuously decreases owing to the formation of a depletion zone in the gel. The thickness of the stagnant diffusion layer next to the membrane increases to such a degree that the release process becomes *vehicle controlled*. After 1 hr, the amount delivered is a function of the square root of time, and the apparent diffusion coefficient in the gel can be computed from the Higuchi equation **(17–24)**. The release process is both membrane layer and aqueous layer controlled for nongelled systems (emulsions). For gelled systems the initial release is also membrane layer and aqueous layer controlled, but later, at $t > 1$ hr, the release becomes formulation or vehicle controlled, that is, the slowest or rate-determining step in the diffusion of the drug is passage through the vehicle.

## CHAPTER SUMMARY

Particulate systems have been classified on the basis of size into molecular dispersions, colloidal systems, and coarse dispersions. This chapter attempts to provide the pharmacist with an insight into the role of physics and chemistry in the research and development of the several classes of coarse dispersions. The theory and technology of these important pharmaceutical classes are based on interfacial and colloidal principles, micromeritics, and rheology (Chapters 15, 16, 18 and 19, respectively). Pharmaceutical suspensions were introduced and the roles they play in the pharmaceutical sciences were described. In addition, the desirable qualities of pharmaceutical suspensions and the factors that affect the stability of suspensions were also discussed. The concepts

of flocculation, settling and sedimentation theory were introduced and the student was shown how to calculate sedimentation rates. Two useful sedimentation parameters, sedimentation volume and degree of flocculation were discussed. The student should be aware of the approaches commonly used in the preparation of physically stable suspensions. Pharmaceutical emulsions and emulsifying agents were introduced and the main types of emulsions discussed. The student should be able to classify pharmaceutical semisolids as well as understand thixotropic properties, syneresis, and swelling. Finally, examples of coarse dispersions were given.

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

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### CHAPTER LEGACY

**Fifth Edition:** published as Chapter 18 (Coarse Dispersions). Updated by Patrick Sinko.

**Sixth Edition:** published as Chapter 17 (Coarse Dispersions). Updated by Patrick Sinko.

CHAPTER

# 2 Micromeritics

*Micromeritics* is the science and technology of small particles and includes the study of the fundamental and derived properties of individual as well as a collection of particles. The micromeritic properties of a drug can be related in a significant way to the physical, chemical and pharmacological properties of a drug. Clinically, the particle properties can affect its release from dosage forms that are administered orally, parenterally, topically and rectally. The product quality of tablets, capsules, suspensions and emulsions from the viewpoint of both uniformity and stability depends on the micromeritic properties such as particle size, shape, surface morphology, density and flowability. The study of the fundamental and derived properties of particles has a number of applications in the field of pharmacy, including the following:

**Dissolution:** The surface area per unit weight, which is known as the *specific surface*, is increased by reduction in the particle size. The increase in surface area by particle size reduction increases the rate of drug dissolution.

**Appearance:** Feel, texture and colour of certain excipients or drugs depend on the particle size. For example, the difference in colour of red and yellow mercuric oxide is due to the differences in their particle size. Particle size may also affect the texture, taste and rheology of oral suspensions. Elegance of emulsions and suspensions often depends on the particle size of the dispersed phase.

**Flowability:** The flow properties of powders depend on the particle size, size distribution and the particle shape. Asymmetric and small particles have poor flow characteristics; therefore, granulation techniques are used to convert powders into granules of uniform size having good flow properties.

**Compressibility:** Physical properties of powders such as compressibility, porosity and bulk density depend on particle size and size distribution. For example, the difference in bulk density of light and heavy magnesium carbonate is due to the difference in their particle size.

**Rheology:** Maintaining a constant mass of particles in a suspension while reducing the particle size leads to increased number of particles. A higher number of smaller particles results in more particle–particle interactions and an increased resistance to flow.

**Weight uniformity:** Weight uniformity of solid oral formulations depends on particle properties. Symmetric, spherical particles with good flowability and compressibility result in uniform feed from hoppers to die cavity of tableting or capsule-filling equipment, allowing uniform particle packing and a constant volume-to-mass ratio, which maintains dose uniformity.

**Drug release:** The release characteristics of drugs from creams, ointments and suppositories are dependent on the particle size of the dispersed drug.

**Stability:** The stability of biphasic formulations including suspensions and emulsions depends on the particle size, and an increase in the particle size decreases the stability of these systems.

**Adsorption:** The adsorption capacity of a material also increases by a decrease in its particle size.

**Mixing:** The mixing of several solid ingredients is easier and more uniform if the ingredients are of approximately the same size. This provides a greater uniformity of dose. Solid pharmaceuticals that are artificially coloured are often milled to distribute the colouring agent to ensure that the mixture is not mottled.

**Drying:** The drying of wet masses may be facilitated by size reduction, which increases the surface area and reduces the distance that the moisture must travel within the particle to reach the outer surface. During tablet production by wet granulation process, the sieving of the wet mass is performed to ensure more rapid and uniform drying.

**Extraction:** The particle size reduction during extraction process results in increased surface area and increased area of contact between the solvent and the solid, thus resulting in complete extraction.

# FUNDAMENTAL PROPERTIES OF PARTICLES

The following are the five fundamental properties of powders from which other properties can be derived:

1. Particle size and size distribution
2. Particle volume
3. Particle number
4. Particle shape
5. Particle surface area

## Particle Size and Size Distribution

### *Spherical or symmetrical particle*

The size of a spherical particle can be expressed in terms of its diameter. The surface area is proportional to the square of the diameter, and the volume is proportional to the cube of the diameter. Thus, for a perfect sphere, the surface area is given by

$$S = \pi d^2 \tag{2.1}$$

And the volume is given by

$$V = \frac{\pi d^3}{6} \tag{2.2}$$

As the volume of a sphere is $\pi d^3/6$, the diameter of a spherical particle with a volume $V$ is given by

$$d = \sqrt[3]{\frac{6V}{\pi}} \tag{2.3}$$

### Nonspherical or asymmetrical particle

In naturally occurring particulate solids and milled solids, the shape of particles is irregular with different numbers of faces. An asymmetric particle has a definite surface area and volume, but its length varies with its orientation. As the degree of asymmetry increases, so does the difficulty of expressing size in terms of meaningful diameter. Hence, an asymmetric or a nonspherical particle is often considered to be approximate to a sphere that can then be characterized by determining its diameter. Because measurement is then based on a hypothetical sphere, which represents only an approximation to the true shape of the particle, the dimension is referred to as the *equivalent spherical diameter* of the particle. The size of the particle is expressed in terms of equivalent spherical diameters by using some measurable properties such as surface area, volume, diameter or density. Thus,

1. Surface diameter, $d_s$, is the diameter of a sphere having the same surface area as that of the asymmetric particle in question.
2. Volume diameter, $d_v$, is the diameter of a sphere having the same volume as the asymmetric particle in question.
3. Projected diameter, $d_p$, is the diameter of a sphere having the same observed area as the asymmetric particle in question when viewed normal to its most stable plain. This diameter is usually determined by the microscopic technique.
4. Stokes' diameter, $d_{st}$, is the diameter of a sphere with the same density as the asymmetric particle in question and which undergoes sedimentation as the same rate as the asymmetric particle in a given fluid within the range of Stokes' law. This diameter is usually measured by the sedimentation method.

Unless the particles are unsymmetrical in three dimensions, these diameters will be independent of particle orientation. The other two diameters, the values of which are dependent on both the orientation and the shape of the particles, are Feret's diameter and Martin's diameter (see Fig. 2.1).

1. Feret's diameter is the mean distance between two tangents on the opposite sides of the particle parallel to some fixed direction.
2. Martin's diameter is the length of the line that bisects the particle. The line may be drawn in any direction but must be in the same direction for all the particles measured.

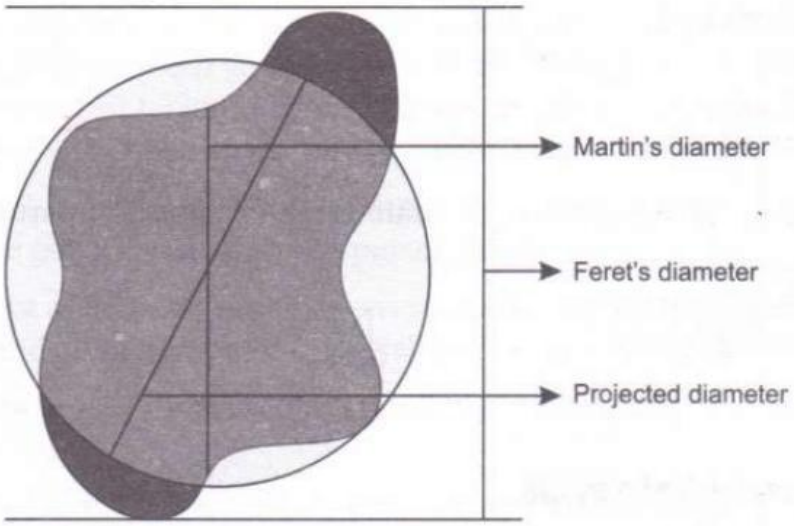



**Figure 2.1** Equivalent diameters of asymmetric particle.

## *Particle size distribution*

A particle population that consists of spheres or equivalent spheres with uniform dimensions is monosized and its characteristics can be described by a single diameter or an equivalent diameter. However, most pharmaceutical powders are polydisperse (i.e. consists of a mixture of particles of varying sizes and shapes). Therefore, it is necessary to know not only the size of particle in the sample but also the number of particles of each size present in the sample. This is called the *particle size distribution*. Thus, the size range present and the number of particles in each particle size should be estimated and from which the average particle size of the collection of particles can be derived (see Table 2.1).

**Table 2.1** Particle size distribution data obtained by particle size analysis

| Particle size range (μm) | Mean particle diameter, $d$ (μm) | Frequency, $n$ (no. of particles in each diameter) | Frequency (%) | $nd$ |
|---|---|---|---|---|
| 10–30 | 20 | 100 | 4.5 | 2000 |
| 30–50 | 40 | 200 | 9.1 | 8000 |
| 50–70 | 60 | 400 | 18.2 | 24,000 |
| 70–90 | 80 | 800 | 36.4 | 64,000 |
| 90–110 | 100 | 400 | 18.2 | 40,000 |
| 110–130 | 120 | 200 | 9.1 | 24,000 |
| 130–150 | 140 | 100 | 4.5 | 14,000 |
| | | $\Sigma n = 2200$ | | $\Sigma nd = 17,600$ |

### Average particle size

**HIGHLIGHTS**

Average particle size $= \Sigma nd/\Sigma n$

Suppose that the particle size of a powder is analysed and the number of particles in each size range is determined, from the data, the average particle size of the powder may be calculated as

$$D_{avs} = \frac{n_1 d_2 + n_2 d_2 + n_n d_n}{n_1 + n_2 + n_n} = \frac{\Sigma(nd)}{\Sigma n} \tag{2.4}$$
$$= \frac{17{,}600}{2200} = 80\ \mu m$$

In the above calculation, only the total number and mean size of the particles have been considered for expressing the average particle size. The calculation can be modified to take into account the surface and volume of the particle also. Such a modified equation for calculation of the average particle size is derived by Edmundson:

$$d = \left(\frac{\Sigma n d^{p+f}}{\Sigma n d^{f}}\right)^{1/p} \tag{2.5}$$

where $n$ is the number of particles in each size range, $d$ the diameter of particles in a given size range (usually the midvalue), $p$ an index related to the size of an individual particle and $f$ the frequency index. Some of the significant mean diameters are shown in Table 2.2.

**Table 2.2** Some significant mean diameters

| Diameter | Representation | Equation |
|---|---|---|
| Geometric mean | $d_{geo}$ | $d_{geo} = \frac{\Sigma(n \log d)}{\Sigma n}$ |
| Arithmetic mean | $d_{ave}$ | $d_{ave} = \frac{\Sigma(nd)}{\Sigma n}$ |
| Mean surface | $d_s$ | $d_s = \sqrt{\frac{\Sigma nd^2}{\Sigma n}}$ |
| Mean volume | $d_v$ | $d_v = \sqrt[3]{\frac{\Sigma nd^3}{\Sigma n}}$ |
| Length–number mean | $d_{ln}$ | $d_{ln} = \frac{\Sigma(nd)}{\Sigma n}$ |
| Volume–surface mean | $d_{vs}$ | $d_{vs} = \frac{\Sigma nd^3}{\Sigma nd^2}$ |
| Mean weight | $d_w$ | $d_w = \frac{\Sigma nd^4}{\Sigma nd^3}$ |

Value of $p = 1$ indicates particle length
$p = 2$ indicates particle surface
$p = 3$ indicates particle volume

Value of $p = 0$ indicates geometric mean
$p = +$ indicates arithmetic mean
$p = *$ indicates harmonic mean

For a collection of particles, the frequency with which a particle in a certain size range occurs is expressed as $nd^f$.

Value of $f = 0$ expresses size distribution in total number
$f = 1$ expresses size distribution in length
$f = 2$ expresses size distribution in surface
$f = 3$ expresses size distribution in volume

### Frequency distribution curve

When the number (or weight) of particles lying within a certain size range is plotted against the mean particle size, a frequency distribution curve is obtained. A histogram plotted from the data in Table 2.1 is shown in Figure 2.2. Such histograms can give a visual representation of the distribution, which an average diameter cannot achieve. Two powder samples may have the same average diameter but may not have the same frequency distribution. From the frequency distribution curve, one can readily obtain the particle size that occurs most frequently and is referred to as mode. When the number of particles is plotted against the mean particle size, the curve is known as the *number frequency distribution curve* and when the weight of particles is plotted against the mean particle size, the curve is known as the *weight distribution frequency curve*.

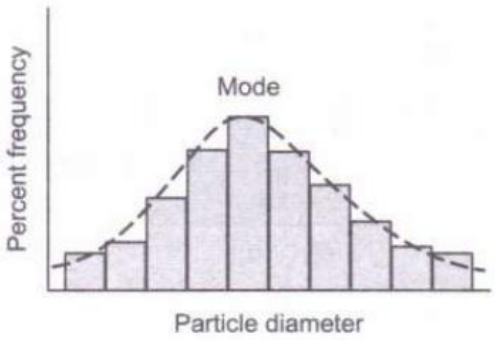



**Figure 2.2** Symmetrical frequency distribution curve.

When size distributions are not symmetrical, the frequency distribution curve of such populations exhibit skewness (see Fig. 2.3). If the distribution is skewed, it can be frequently made symmetric if the sizes are replaced by the logarithms of the sizes.

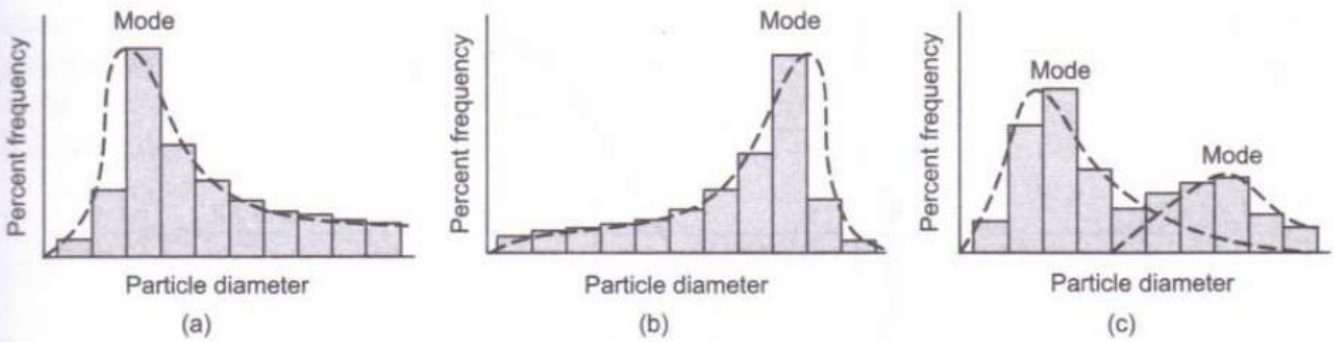



**Figure 2.3** Frequency curves: (a) positively skewed, (b) negatively skewed and (c) bimodal distribution.

1. **Positively skewed:** Frequency curve with an elongated tail towards higher size ranges.
2. **Negatively skewed:** Frequency curve with an elongated tail towards lower size ranges.
3. **Bimodal distribution:** Frequency curve with more than one mode.

### *Cumulative frequency distribution curve*

An alternative to the histogram representation of a particle size distribution is obtained by sequentially adding the percentage frequency values to produce a cumulative percentage frequency distribution (see Table 2.3). This gives a sigmoidal curve with the mode being the particle size of the greatest slope (see Fig. 2.4). If the addition sequence begins with the coarsest particles, the values obtained will be cumulative percentage frequency undersize; the reverse case produces a cumulative percentage oversize.

**Table 2.3** Particle size distribution data obtained by particle size analysis

| Particle size range (μm) | Mean particle diameter, $d$ (μm) | Frequency, $n$ (no. of particles in each diameter) | Frequency (%) | Cumulative frequency (%) |
|---|---|---|---|---|
| 10–30 | 20 | 100 | 4.5 | 4.5 |
| 30–50 | 40 | 200 | 9.1 | 13.6 |
| 50–70 | 60 | 400 | 18.2 | 31.8 |
| 70–90 | 80 | 800 | 36.4 | 68.2 |
| 90–110 | 100 | 400 | 18.2 | 86.4 |
| 110–130 | 120 | 200 | 9.1 | 95.5 |
| 130–150 | 140 | 100 | 4.5 | 100.00 |
| | | $\Sigma n = 2200$ | | |

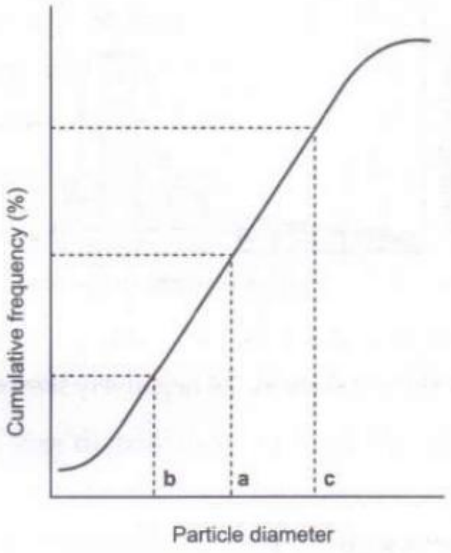



**Figure 2.4** Cumulative frequency distribution curves. Point a is the median diameter, point b the lower quartile point and point c the upper quartile point.

## *Log–probability curve*

When the log of the particle size is plotted against the cumulative percentage frequency on a probability scale, a linear relationship is observed. This is known as the *log–probability plot* (see Fig. 2.5). The log–probability curve has a distinct advantage in that the log–normal distribution

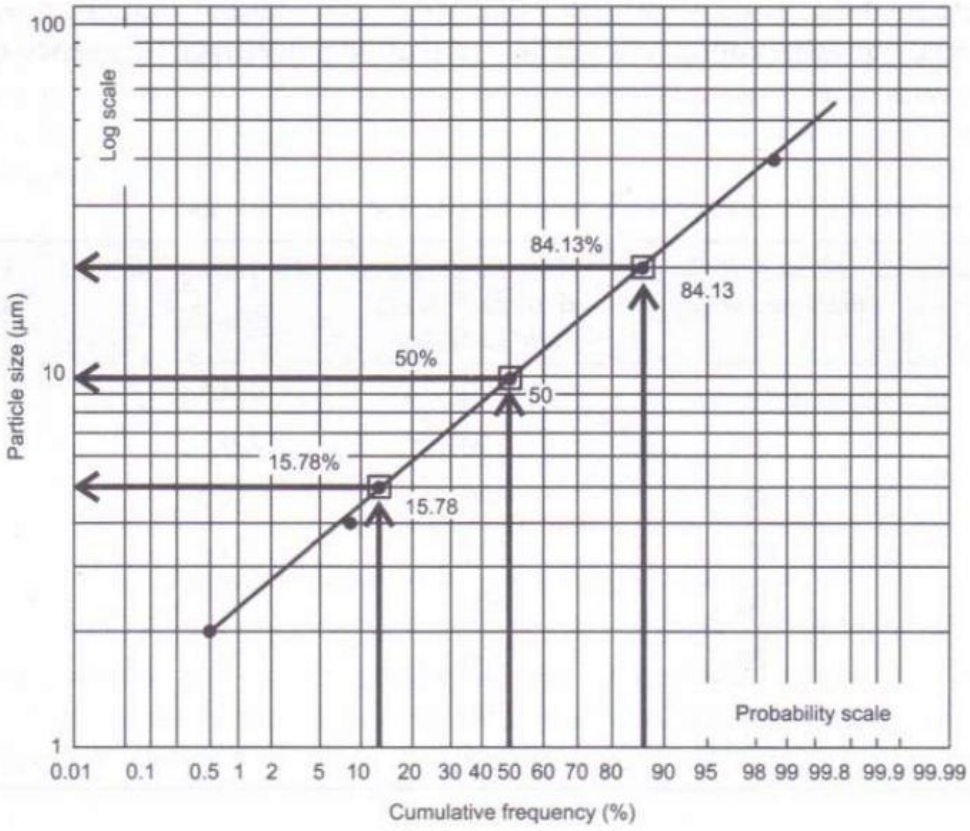



**Figure 2.5** Representation of the log–probability curve.

curve can be characterized by two parameters, the slope of the line and a reference point. The reference point used is the logarithm of the particle size equivalent to 50% on the probability scale (i.e. the 50% size). This is known as the *geometric mean diameter*, $d_g$. The geometric standard deviation $\sigma_g$ is given by the slope of the line, which is

$$\sigma_g = \frac{84\% \text{ Undersize of } 16\% \text{ oversize}}{50\% \text{ Size}} = \frac{50\% \text{ Size}}{16\% \text{ Undersize or } 84\% \text{ oversize}} \quad (2.6)$$

## PARTICLE SIZE DETERMINATION METHODS

The particle size distribution can be quantified by the following:

1. **Determining the number of particles:** *Optical microscopy,* electron microscopy (SEM, TEM)
2. **Determining the weight of particles:** *Sieving technique, sedimentation,* centrifugation
3. **Determining light scattering by particles:** Photon correlation spectroscopy
4. **Determining volume of particles:** *Coulter counter method*

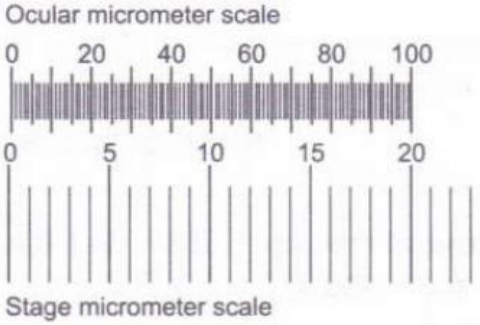
A summary of the different methods is presented below with few commonly used techniques (in italics) described in detail.

### Optical Microscopy

**Equivalent diameter:** It is used to determine projected area diameter, Feret's diameter and Martin's diameter.

**Range of analysis:** 1 μm to about 100 μm.

**Methodology:** The size determination of the particles is carried out through an optical microscope equipped with an ocular micrometer and a stage micrometer. The ocular meter serves as a scale to estimate the planar dimension of the particle. It is a disc of glass upon which equally spaced divisions are etched. The ocular micrometer is calibrated against a fixed




*Observation at 100x magnification,*

Total ocular divisions = 100
Each stage micrometer division = 0.1 mm or 100 μm

*Now suppose,*

100 ocular division = 20 stage micrometer divisions
100 ocular division = 20 × 100 μm
1 ocular division = 20 μm (at 100x magnification)

**Figure 2.6** Calibration of ocular and stage micrometers.

and known ruler, the stage micrometer, which is a microscope slide with a finely divided scale marked on the surface. Most common stage micrometers are 2 mm long and subdivided into 0.01 mm (10 μm) lengths. It helps convert the apparent size of a particle, as seen through the ocular meter scale, into real dimension. To use, the ocular meter is placed below the eye piece of the microscope and the stage micrometer on the microscope stage. They are then positioned in such a way that the scale of the ocular micrometer superimposes on the scale of the stage micrometer and their zero values correspond. With the zero values aligned, the number of ocular divisions equivalent to one stage division is calculated (see Fig. 2.6).

To determine particle size of a powder, a dilute suspension of the powder particles is prepared in a liquid vehicle in which it is insoluble. A drop of the suspension is mounted on a fresh slide and observed through a calibrated ocular micrometer. The zero value of the ocular micrometer scale is kept at one edge of a particle and the number of divisions covered by the length of the particle is recorded. All the particles are measured along an arbitrary fixed line. This procedure is repeated until the entire size range is covered. An arbitrary data is shown in Table 2.4 and may be further represented as a log–probability curve. From the data, the geometric mean diameter and standard deviation are determined.

**Table 2.4** Representation of number distribution values obtained by the microscopic method

| Ocular divisions | Particle size range (μm) | Mean particle size (μm) | Frequency (no. of particles in each diameter) | Frequency (%) | Cumulative frequency (%) | Log particle size |
|---|---|---|---|---|---|---|
| 0–1 | 0–20 | 10 | As counted | – | – | 1.00 |
| 1–2 | 20–40 | 30 | As counted | – | – | 1.47 |

*Note:* After obtaining complete experimental data, log particle size is plotted against cumulative frequency (%) on a probability scale (linear relation) to determine the geometric mean diameter and standard deviation.

### Advantage

1. Agglomerates can be detected.

### Disadvantages

1. This method is tedious and slow as at least 300–500 particles must be counted to obtain a good size distribution analysis.
2. The measured diameter of the particles represents two dimensions only (i.e. the length and the breadth) and an estimate of the depth is not obtained.

### Alternative techniques

To measure very small particle size, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) may be used. SEM is particularly appropriate when a three-dimensional particle image is required.

## Sieving Technique

**Equivalent diameter:** Sieve diameter—the particle dimension that passes through a square aperture (see Fig. 2.7).

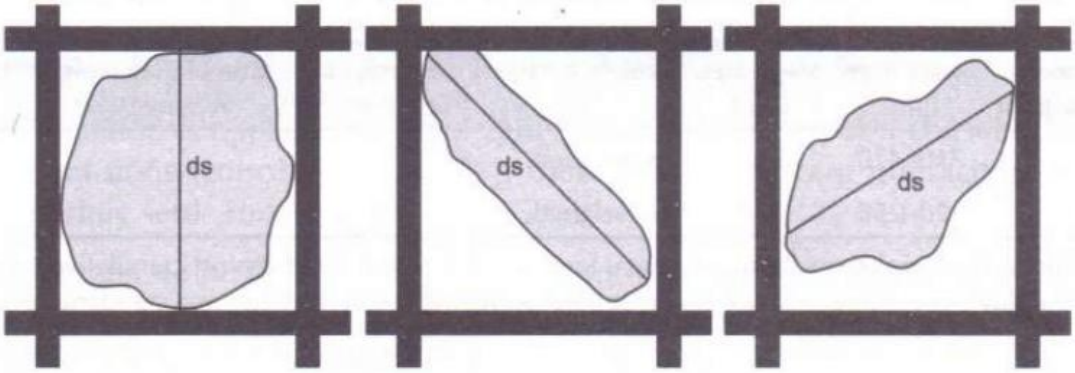
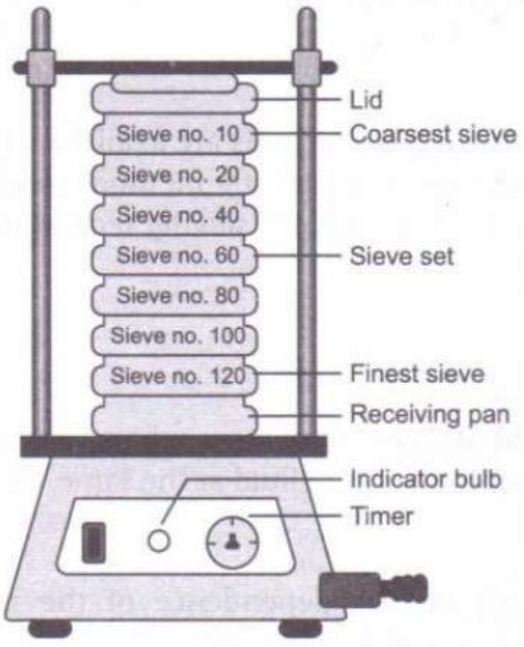



**Figure 2.7** Sieve diameter for various shaped particles.

**Range of analysis:** 5 μm to about 1000 μm.

**Methodology:** Sieves are constructed from a woven wire mesh, which is assumed to give nearly square apertures of known diameters. Sieve analysis is usually carried out using dry powders. In this method, the standard sieves are stacked on top of one another, with the sieve of the largest aperture on top followed by sieves of gradually decreasing pore sizes (see Fig. 2.8). A sieve stack usually comprises 6–8 sieves. The powder whose particle size is to be determined is placed on the top sieve and the nest of sieves is subjected to a standardized period of mechanical vibration. The weight of material retained on each sieve is accurately




| US sieve no. | Aperture size |
|---|---|
| 10 | 2.00 mm |
| 14 | 1.40 mm |
| 18 | 1.00 mm |
| 20 | 840 μm |
| 25 | 710 μm |
| 40 | 420 μm |
| 60 | 258 μm |
| 80 | 180 μm |
| 100 | 149 μm |
| 120 | 125 μm |
| 200 | 74 μm |
| 400 | 37 μm |

**Figure 2.8** Arrangements of sieves during sieving and sizes of standard sieves.

determined. The size of the particles retained is taken as the arithmetic mean of the two sieves (a powder passing a 40-mesh sieve and retained on a 60-mesh sieve is assigned an arithmetic mean diameter of (420 + 258)/2, or 339 μm). An arbitrary data is shown in Table 2.5.

**Table 2.5** Representation of weight distribution values obtained by the sieving method

| Sieve numbers (passed/retained) | Size range (μm) | Mean size (μm) | Weight retained (g) | Weight retained (%) | Cumulative weight retained (%) | Log particle size |
|---|---|---|---|---|---|---|
| 25/40 | 710–420 | 565 | As weighed | – | – | 2.75 |
| 40/60 | 420–258 | 339 | As weighed | – | – | 2.53 |

*Note:* After obtaining complete experimental data, log particle size is plotted against cumulative weight retained (%) on a probability scale (linear relation) to determine geometric mean diameter and standard deviation.

### *Advantages*

1. This method is inexpensive, simple and rapid, with little variation between operators.
2. Micromesh sieves are available for extending the lower limit to 10 μm.

### *Disadvantages*

1. Appreciable amount of sample (normally at least 25 g) is needed.
2. Measurement of particle below size of 50 μm is difficult.
3. Sieving of cohesive powders is difficult as they tend to clog the sieve openings.
4. It gives two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length.
5. Aggregation of particles may occur during sieving because of the generation of electrostatic charge and thus, the actual particle size may not be obtained.
6. Attrition of particles during sieving may lead to size reduction.

### *Alternative techniques*

Sieving equipments based on size determination by moving air currents are available. The air jet sieve method uses a single sieve at a time, whereas the sonic sifting method uses a nest of sieves. Both these methods may be useful when the standard dry sieving techniques are incapable of giving a meaningful analysis.

## Sedimentation Technique

**Equivalent diameter:** Stokes' diameter; frictional drag diameter—a sphere having an equivalent drag force to a particle of the same diameter in the same fluid at the same velocity.

**Range of analysis:** 1 μm to about 200 μm.

**Methodology:** The sedimentation method is based on the dependence of the rate of sedimentation of the particles on their size as expressed by Stokes' equation:

$$d_{\text{Stokes}} = \sqrt{\frac{18\eta}{(\rho - \rho_o)g}\frac{x}{t}} \tag{2.7}$$

where $d_{\text{Stokes}}$ is the effective or Stokes' diameter, $\eta$ the viscosity of the dispersion fluid, $x/t$ the rate of sedimentation or distance of fall $x$ in time $t$, $g$ the gravitational constant and $\rho$ and $\rho_0$ are the densities of the particle and the medium, respectively.

Stokes' equation is applicable to free spheres that are falling at a constant rate. In case of dilute suspensions (concentration <2%), there is no significant interaction between the particles, and they settle independent of one another.

Andreasen pipette is the most popular method to determine particle size distribution by the sedimentation technique (see Fig. 2.9). The Andreasen fixed-position pipette consists of a 20 cm graduated cylinder of about 5.5 cm internal diameter, which can hold about 550 mL of suspension fluid. A pipette is located centrally in the cylinder and is held in position by a ground-glass stopper so that its tip coincides with the zero level. The stem of the pipette is made up of narrow bore tubing to minimize the volume retained in the stem after each sampling. A three-way tap allows fluid to be drawn into a 10-mL reservoir, which can then be emptied into a china dish.

For analysis of the particle size distribution, a dilute (1–2%) suspension of the powder in a suitable liquid medium, containing a suitable deflocculating agent to break powder aggregates, is introduced into the vessel. The vessel is stoppered, shaken to distribute the particle uniformly and is kept undisturbed in a constant temperature bath. At designated time intervals, 10 mL of samples are withdrawn from a specified depth without disturbing the suspension, which can then be emptied into a previously weighed china dish. The samples are dried and weighed and necessary correction is made for the deflocculating agent added.

Using Stokes' equation, the particle diameter corresponding to each interval of time is calculated, with $x$ being the height of the liquid above the lower end of the pipette at

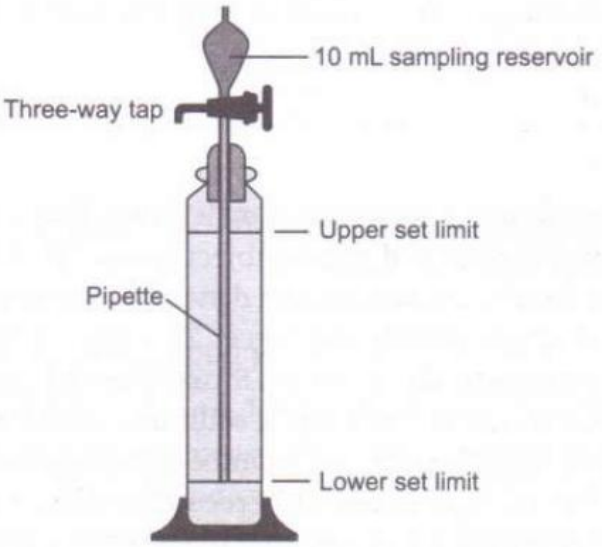



**Figure 2.9** Andreasen pipette apparatus for size determination by sedimentation.

time $t$ when each sample is withdrawn. The residue of dried sample obtained at a particular time is the weight fraction having particles of size obtained by Stokes' law calculation. The larger particles settle at a faster rate than the smaller particles and thus each sample drawn contains particles of smaller diameter than the previous sample. The weight of each sample residue is therefore called the *weight undersize* and the sum of the successive weight is known as the *cumulative weight undersize*. The cumulative weight undersize is then plotted on the probability scale against the particle diameter on the log scale using a log–probability graph paper. Various statistical diameters are then obtained from the plot. Typical data obtained by using the Andreasen pipette are given in Table 2.6.

**Table 2.6** Representation of weight distribution values obtained by the sedimentation method

| Time (s) | Height (cm) | Particle diameter calculated by Stokes' equation (μm) | Weight of residue (g) | Weight of residue (%) | Cumulative weight of residue (%) | Log particle size |
|---|---|---|---|---|---|---|
| 120 | 20.0 | 44.5 | As weighed | – | – | 1.65 |
| 240 | 19.6 | 30.5 | As weighed | – | – | 1.5 |

*Note:* After obtaining the complete experimental data, log particle size is plotted against cumulative weight of residue (%) on a probability scale (linear relation) to determine the geometric mean diameter and standard deviation.

### Advantages

1. The apparatus is inexpensive and the technique is simple.
2. The results obtained are precise, provided the technique is adequately standardized.

### Disadvantages

1. The method is laborious as separate analyses are required for each experimental point on the distribution curve.
2. Very small particles subjected to Brownian motion cannot be determined accurately due to prolonged settling rates.

### Alternative techniques

One of the limitations of gravitational sedimentation is that below a diameter of approximately 5 μm, particle settling becomes prolonged and is subject to interference from Brownian motion. These effects can be minimized by increasing the driving force of sedimentation by replacing gravitational forces with a larger centrifugal force. The second type of sedimentation size analysis, using retention zone methods, also uses Stokes' law to quantify particle size. One of the most common retention zone methods uses a sedimentation balance. In this method, the amount of sedimented particles falling on to a balance pan suspended in the fluid is recorded. The continual increase in weight of sediment is recorded with respect to time. Centrifugal methods are sometimes used to accelerate the rate of sedimentation and minimize the above effects.

### *Example 2.1 (Diameter determination)*

The following data were obtained by means of an optical microscope:

| Diameter (μm) | 10 | 20 | 30 | 40 |
|---|---|---|---|---|
| Number of particles ($n$) | 4 | 7 | 3 | 2 |

Determine the arithmetic (length-number) mean particle diameter and mean volume surface diameter.

#### *Solution*

Length number mean diameter ($d_{ln}$) $= \dfrac{\Sigma nd}{\Sigma n}$

$= \dfrac{305}{16} = 21.87\ \mu m$

Volume surface mean diameter ($d_{vs}$) $= \dfrac{\Sigma nd^3}{\Sigma nd^2}$

$= \dfrac{269{,}000}{9{,}100} = 29.56\ \mu m$

### *Example 2.2 (Stokes' diameter)*

A sample of powdered drug, density 5.60 g/cm$^3$, is allowed to settle under the acceleration of gravity, 981 cm/s$^2$, at 25°C. The rate of settling, $v$, is $7.30 \times 10^{-3}$ cm/s. The density of the medium is 1.01 g/cm$^3$, and its viscosity is 0.01 g/cm s. Calculate the Stokes' diameter of the drug powder.

#### *Solution*

According to Eq. (2.7)

$$d_{strokes} = \sqrt{\frac{(18 \times 0.01\ \text{g/cm s}) \times (7.30 \times 10^{-3}\ \text{cm/s})}{(5.60 - 1.01\ \text{g/cm}^3) \times (981\ \text{cm/s}^2)}}$$

$= 5.4 \times 10^{-4}$ or 5.4 μm

## Coulter Counter Method (Particle Volume Measurement)

**Equivalent diameter:** Volume diameter.

**Range of analysis:** 0.1 μm to about 1000 μm.

**Methodology:** Coulter counter is a popular instrument to determine particle volume and particle size based on the conductivity measurement. It operates on the principle that when a particle suspended in a conducting liquid passes through a small orifice (opening), on either side of which are electrodes, a change in electric resistance occurs. The change in electric resistance is proportional to the volume of the particle.

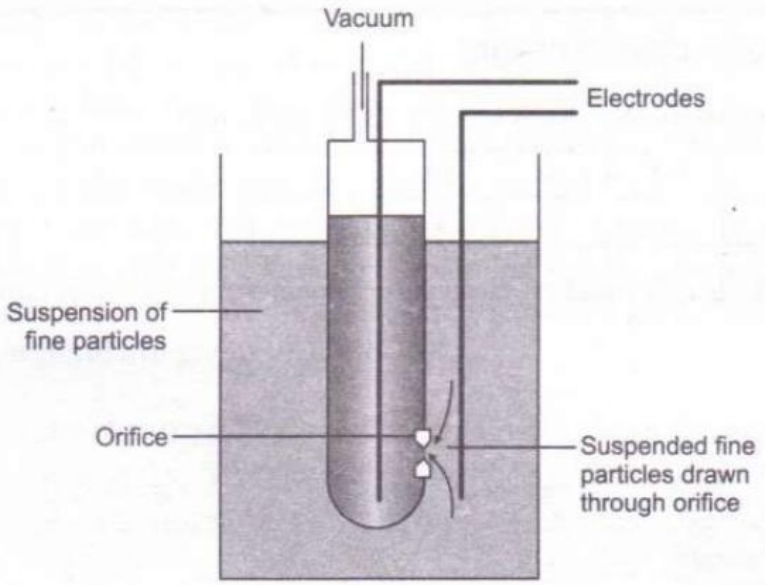



**Figure 2.10** Representation of Coulter counter apparatus.

Figure 2.10 shows the mechanical parts of the instrument. It consists of two electrodes: one is dipped into a beaker containing the particle suspension in an electrolyte (such as 0.9% NaCl) and the other is dipped into the electrolyte solution contained in a glass tube, which in turn is immersed into the beaker containing the particle suspension in the electrolyte. The glass tube has a very small aperture at its lower end through which the particles are sucked into the inner glass tube. For the experiment, powder samples are suspended in the electrolyte to form a very dilute suspension. The particle concentration is arranged so that only one particle travels through the aperture. A constant voltage is applied across the electrodes so as to produce a current. As the particle passes through the aperture, it displaces its own volume of electrolyte and changes the resistance between the electrodes, which causes a pulse in the voltage. The magnitude of pulse will be proportional to the volume of the particle. The changes in voltage are amplified and impulses above a predetermined threshold value are counted, so that the recorder provides a count of the number of particles over a certain size.

### *Advantages*

1. Results are expressed as particle volume, and hence the diameter of the sphere of equivalent volume can be easily calculated.
2. Process is rapid with a single count taking less than 30 s.
3. Results are reliable since large numbers of particles are counted.
4. Operational simplicity reduces operator variables, enabling reproducible results.

### *Disadvantages*

1. The material has to be suspended in an electrolyte liquid before measurement.
2. Aggregation of particles can give false results.

### *Hatch–Choate equation*

Hatch derived equations relating various types of diameters using the standard deviation and mean. These statistical parameters are a function of the size and numeric frequency of the particles for a given size. To calculate their values, the size distribution data must be expressed in terms of a number frequency. In microscopy, this requirement is met directly. However, in sieving and sedimentation methods, the data obtained provide a weight distribution. However, it is possible to convert the weight distribution to number distribution using Hatch–Choate equations (Table 2.7).

**Table 2.7** Hatch–Choate equations for conversion of weight to number distribution and vice versa

| Diameter | Number distribution | Weight distribution |
|---|---|---|
| Geometric mean | | $\log d_{geo} = \log d_{geo}' - 6.908 \log^2 \sigma_{geo}'$ |
| Arithmetic mean | $\log d_{ave} = \log d_{geo} + 1.151 \log^2 \sigma_{geo}$ | $\log d_{ave} = \log d_{geo}' - 5.757 \log^2 \sigma_{geo}'$ |
| Mean surface | $\log d_s = \log d_{geo} + 2.303 \log^2 \sigma_{geo}$ | $\log d_s = \log d_{geo}' - 4.605 \log^2 \sigma_{geo}'$ |
| Mean volume | $\log d_v = \log d_{geo} + 3.454 \log^2 \sigma_{geo}$ | $\log d_v = \log d_{geo}' - 3.454 \log^2 \sigma_{geo}'$ |
| Mean volume–surface | $\log d_{vs} = \log d_{geo} + 5.757 \log^2 \sigma_{geo}$ | $\log d_{vs} = \log d_{geo}' - 1.151 \log^2 \sigma_{geo}'$ |

Thus,
$$\log d_{ln} = \log d_g + 1.151 \log^2 \sigma_g \text{ (number distribution)} \quad (2.8)$$
$$\log d_{ln} = \log d'_g - 5.757 \log^2 \sigma_g \text{ (weight distribution)} \quad (2.9)$$

## Particle Number

Particle number, $N$, is defined as the number of particles per unit weight of a powder and can be obtained in the following manner. Assuming that the particles of the powder are spherical, the volume of a single particle is $\pi d_{vn}^3 p/6$ and the mass (volume × density) is $\pi d_{vn}^3 p/6$ g per particle, where $d_{vn}$ is the mean diameter based on volume and number and $p$ is density of the particle.

The number of particles per gram can then be obtained from the following expression:

$$N = \frac{1 \text{ g of the powder}}{\text{Mass of one particle}}$$

or
$$N = \frac{1}{\pi d_{vd}^3 p/6} \quad (2.10)$$

or
$$N = \frac{6}{\pi d_{vd}^3 p} \quad (2.11)$$

### *Example 2.3 (Number of particles)*

The mean volume number diameter of a sample of powder is 3.62 mm. If the density of the powder is 3.0 g/cm$^3$, what is the number of particles per gram?

### *Solution*

Volume number mean diameter ($d_{vn}$) = 3.62 mm

$= 3.62 \times 10^{-10}$ cm

(**Note:** Since density of the powder is given in g/cm$^3$, the diameter should also be expressed in cm). Density of the powder ($\rho$) = 3.0 g/cm$^3$.

The following formula should be used:

Number of particles per gram,

$$N = \frac{6}{\pi d_{vn}{}^3 \rho}$$

$$= \frac{6}{3.14 \times (3.62 \times 10^{-4}) \times 3.0}$$

$$= 1.34 \times 10^{10}$$

## Particle Shape

Particle sizes combined with particle shape affect the packing properties and flow of the powder, and they also influence the surface area. It is generally accepted that the flowability of powders decreases as the shapes of particles become more irregular.

### *Shape factors*

#### *Surface–volume shape coefficient*

A sphere is characterized by its diameter ($d$). The surface area and volume of a spherical particle are proportional to the square of the diameter and cube of the diameter, respectively.

An asymmetric particle is more difficult to characterize in terms of surface diameter. Hence, the asymmetric particle's surface diameter is measured in terms of some equivalent spherical diameter. Suppose, the particle size is determined in terms of the projected diameter, $d_p$. Then,

$$\text{Surface area} = \alpha_s d_p^2 = \pi d_s^2 \tag{2.12}$$

where $\alpha_s$ is the surface area factor and $d_s$ the equivalent surface diameter.

$$\text{Volume} = \alpha_v d_p^3 = \frac{\pi d_v^3}{6} \tag{2.13}$$

where $\alpha_v$ is the volume factor and $d_v$ the equivalent volume diameter.

The ratio $\alpha_s/\alpha_v$ is also used to characterize a particle shape.

For a sphere,

$$d_p = d_s = d_v$$

and, therefore

$$\alpha_s = \frac{\pi d_p^2}{d_p^2} = \pi \text{ and } \alpha_v = \frac{\pi d_p^3}{6\, d_p^3} = \frac{\pi}{6}$$

$$\frac{\alpha_s}{\alpha_v} = 6 \text{ (when the particle is spherical)}$$

If this ratio exceeds the minimum value of 6, the particles deviate from being spherical. This ratio exceeds the minimum value of 6, more asymmetric are the particles.

### *Sphericity*

Sphericity is a measure of the roundness of a shape and is independent of particle size. The sphericity, $\Psi$, of a particle is the ratio of the surface area of a sphere (with the same volume as of test particle) to the surface area of the particle.

$$\Psi = \frac{\text{Surface area of sphere}}{\text{Surface area of particle}}$$

where the sphere has the same volume as that of the particle.

Sphericity is a ratio and therefore a dimensionless number and is calculated for any three-dimensional object if its surface area and volume are known.

For a nonspherical particle:

$$\Psi = \frac{6\, V_p}{D_p S_p} \tag{2.14}$$

For a spherical particle of diameter $D_p$,

$$\Psi = 1$$

where $D_p$ is equivalent diameter of particle, $S_p$ the surface area of one particle and $V_p$ the volume of one particle. Sphericity values of some common shapes are shown in Table 2.8.

**Table 2.8** Sphericity values of some common shapes

| Shape | Sphericity | Shape | Sphericity |
|---|---|---|---|
|  Tetrahedron | 0.671 |  Cone | 0.724 |
|  Cube | 0.806 |  Cylinder | 0.874 |
|  Octahedron | 0.846 |  Sphere | 1.0 |

### *Elongation*

Elongation provides an indication of the length:width ratio of the particle and is calculated as 1–(width/length). Shapes symmetrical in all axes, such as circles or squares, will have an elongation close to 0, whereas needle-shaped particles will have values closer to 1.

### *Convexity*

Convexity is a measurement of the surface roughness of a particle and is calculated by dividing the particle area by a total area. An irregular or a spiky shape has a convexity closer to 0, whereas a smooth shape has a convexity of 1.

### *Circularity*

Circularity is a measurement of the ratio of the actual perimeter of a particle to the perimeter of a circle of the same area. An irregular or a spiky shape has a circularity closer to 0, whereas a perfect circle has a circularity of 1.

## Particle Surface Area

### *Specific surface*

The specific surface of a powder is defined as the surface area per unit volume ($S_v$) or per unit weight ($S_w$) and may be derived from equations given below.

Taking into account the surface area and volume correction factors for asymmetric particles, the specific surface area per unit volume is given by

$$S_v = \frac{\text{Surface area of particles}}{\text{Volume of particles}}$$

$$S_v = \frac{n\alpha_s d^2}{n\alpha_v d^3} = \frac{\alpha_s}{\alpha_v d} \tag{2.15}$$

where $n$ is the number of particles.

Estimation of surface area per unit weight ($S_w$): .

$$S_w = \frac{\text{Surface area}}{\text{Weight}} = \frac{\text{Surface area}}{\text{Volume} \times \text{Density}} \tag{2.16}$$

$$S_w = \frac{S_v}{\rho}$$

where $\rho$ is the true density of the particles.

Substituting for $S_v$

$$S_w = \frac{\alpha_s}{\rho d_{vs} \alpha_v} \tag{2.17}$$

in which the dimension is now defined as $d_{vs}$, the volume–surface diameter characteristic of a specific surface.

For spherical or nearly spherical particles,

$$S_w = \frac{6}{\rho d_{vs}} \tag{2.18}$$

(since $\alpha_s/\alpha_v = 6$ for a sphere).

---

### *Example 2.4 (Surface area)*

Determine the total surface of 5 g of an antibiotic powder in which particles have an average diameter $d_{vs}$ of 2 μm and a true density of 2.4 g/cm³. Assume that the particles are spheres.

### *Solution*

Volume surface mean diameter of the particles ($d_{vs}$)

$= 2\ \mu m$

$= 2 \times 10^{-4}$ cm

True density of the powder ($\rho$) = 2.4 g/cm³

Specific surface per unit weight

$$S_w = \frac{6}{\rho d_{vs}}$$

$$= \frac{5}{2.4 \times 2 \times 10^{-4}}$$

$$= 1.25 \times 10^4 \text{ cm}^2/\text{g}$$

Total surface of 1 g of powder $= 1.25 \times 10^4\ cm^2$

Total surface of 5 g of powder $= 5 \times 1.25 \times 10^4\ cm^2$

$= 6.25 \times 10^4\ cm^2$

### *Example 2.5 (Specific surface area)*

Determine the specific surface, $S_w$ and $S_v$ of a sample of spray-dried lactose having spherical particles of diameter ($d_{vs}$) 3.0 µm and true density of 1.54 g/cm³.

### *Solution*

Volume surface mean diameter ($d_{vs}$) = 3.0 µm = $3 \times 10^{-4}$ cm

True density ($\rho$) = 1.54 g/cm³

Specific surface per unit weight

$$S_w = \frac{6}{\rho d_{vs}}$$

$$= \frac{6\ cm^2/g}{1.54 \times 3 \times 10^{-4}}$$

$$= 1.29 \times 10^4\ cm^2/g$$

Specific surface per unit volume

$$S_v = 6/d$$

$$= 6/3 \times 10^{-4}\ cm^2/cm^3$$

$$= 2 \times 10^4\ cm^2/cm^3$$

## SURFACE AREA DETERMINATION METHODS

The above-mentioned method of estimation is based on particle size distribution and particle volume. This method can accurately estimate the specific surface of nonporous particles. However, porous particles have an irregular surface and contain pores or crevices and the above-mentioned method cannot account for these pores. Therefore, it is necessary to directly determine the surface area of powder. The surface area can be determined directly by one of the following two methods:

1. Adsorption method
2. Air permeability method

## Adsorption Method

Particles with a small particle size (large specific surface) are good adsorbents for the adsorption of gases and of solutes from the solution. The amount of gas or solute adsorbed on the sample of powder to form a monolayer calculated, and from this data, the surface area of the powder is determined.

### *Solute adsorption method*

**Principle:** Adsorption of a solute from its solution onto the surface of the adsorbent powder whose area is to be determined (Fig. 2.11). Here, *solute* refers to substance of known surface area, which gets adsorbed and forms a monolayer such as stearic acid and *adsorbent powder* refers to powder sample whose surface area is to be determined. It adsorbs the solute molecules.

**Method:** A solution of a known amount of solute (5.0 g) is first prepared in a medium in which the adsorbent powder is insoluble. A known amount of the adsorbent powder (0.5 g) is then added to the solution and the contents are stirred till equilibrium has been attained. The powder is then filtered and the amount of solute remaining in the solution (4.0 g) is determined by a suitable method. The difference between the quantity of solute added and that remaining in the solution gives the quantity of solute that has been adsorbed (1.0 g). From this value, the amount of solute adsorbed per gram of the powder is calculated.

0.5 g of powder adsorbs ~ 1.0 g of solute

Therefore, the amount of solute adsorbed per gram of the powder is 2.0 g.

Now, the number of molecules present in 1 g-mol of a material is given by Avogadro's number $6.0223 \times 10^{23}$. From this data, the number of molecules present in 2.0 g of solute can be calculated.

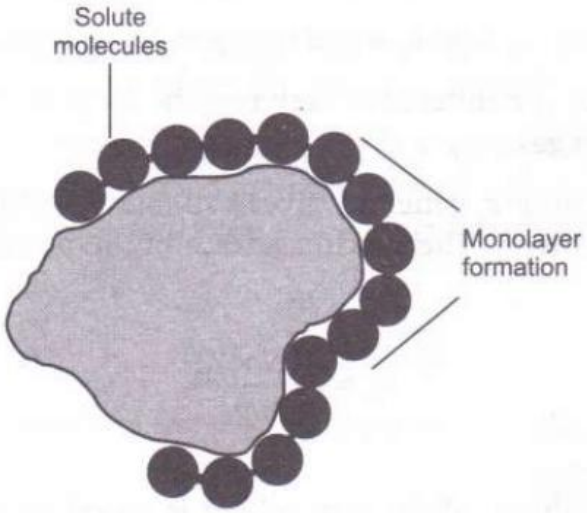



**Figure 2.11** Process of solute adsorption through monolayer formation.

Since the surface area of one molecule of solute is known, the specific surface area of the powder is calculated by the following equation:

$$\text{Specific surface area of the power} = \text{number of molecules adsorbed} \times \text{surface area of one molecule of solute}$$

The accurate determination of surface area by this method is difficult because the adsorbed solvent molecules on the powder prevent close packing of the adsorbed solute in the formation of a monolayer. Methanolic solution of stearic acid has been used to determine the surface area of powders that are insoluble in methanol. Stearic acid being a linear molecule gets adsorbed on the powder surface as a monolayer.

### Gas adsorption method

Surface area determination by gas adsorption method is carried out using an instrument called *quantasorb*.

**Method:** The powders whose surface area is to be determined are introduced into a cell in the instrument and nitrogen (adsorbate gas) and helium (inert, nonadsorbing gas) are passed through the powder in the cell. A thermal conductivity detector measures the amount of nitrogen adsorbed at every equilibrium pressure and a bell-shaped curve is obtained on a strip-chart recorder. The signal height gives the rate of adsorption of nitrogen gas, and the area under the curve provides the amount of gas adsorbed on the powder sample. The volume of nitrogen gas $V_m$ in cubic centimetre adsorbed by 1 g of the powder when the monolayer is given by the BET equation:

$$\frac{P}{V(p_0 - p)} = \frac{1}{V_m b} + \frac{(b-1)p}{V_m b p_o} \tag{2.19}$$

where $V$ is the volume of gas in $cm^3$ adsorbed per gram of powder at pressure $p$.

$p_0$ is the saturated vapour pressure of liquefied nitrogen at the temperature of the experiment.

$b$ is a constant and it gives the difference between the heat of adsorption and the heat of liquefaction of the nitrogen gas.

A plot of $p/V(p_0 - p)$ versus $p/p_0$ generally gives a straight line. The slope and intercept yield the values $b$ and $V_m$, respectively. The specific surface of the powder is obtained by applying the following equation:

$$S_w = \frac{A_m N \times V_m}{m/p} \tag{2.20}$$

where $m/p$ is the molar volume of the gas, which is equal to 22,414 $cm^3$/mol at NTP. $N$ is Avogadro's number $6.02 \times 10^{23}$. $A_m$ is the area of a single close packed gas molecule absorbed as a monolayer on the surface of the powder particles. For nitrogen, the value is $16.2 \times 10^{-16} cm^2$.

## Air Permeability Method

**Principle:** This method is based on the principle that the resistance offered to the flow of a fluid, such as air, through a plug of compacted powder is proportional to the surface area of the powder. The greater the surface area per gram of the powder, the greater is the resistance to flow. Surface area determination by the air permeability method is generally carried out with an instrument called the *Fisher subsieve sizer* (Fig. 2.12).

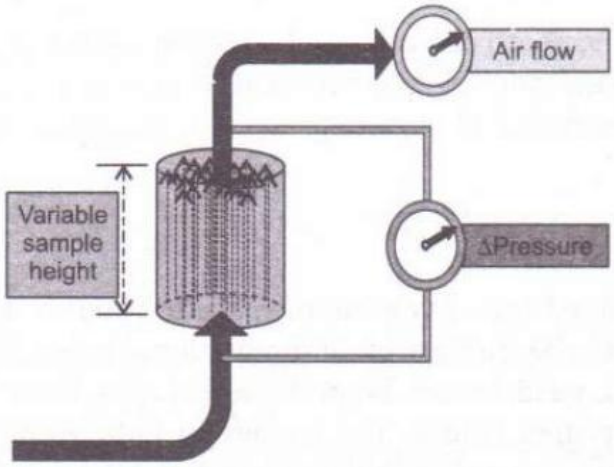



**Figure 2.12** Representation of Fisher subsieve sizer apparatus.

**Method:** A plug of powder can be considered as a series of capillaries whose diameter is related to average particle size. The internal surface of the capillaries is a function of the surface area of the particles. According to Poiseuille's equation:

$$V = \frac{\pi d^4 \Delta P t}{128\ l\eta} \tag{2.21}$$

where $V$ is the volume of air flowing through a capillary of internal diameter $d$ and length $l$ in $t$ seconds under a pressure difference of $\Delta P$. The viscosity of the fluid (air) is $\eta$ poise.

When the air is allowed to pass through the plug of a compacted powder, resistance to the flow of air occurs. This resistance is related to the surface area of the powder. According to the Kozeny–Carman equation derived from Poiseuille's equation:

$$V = \frac{A}{\eta S_w 2} \times \frac{\Delta P t}{Kl} \times \frac{E^3}{(1-E)^2} \tag{2.22}$$

where $A$ is the cross-sectional area of the plug, $K$ is a constant (usually $5.0 \pm 0.5$) and $E$ is the porosity.

From the above equation, the specific ($S_w$) can be calculated. This method is widely used to control batch-to-batch variations in specific surface of powders.

**HIGHLIGHTS**

As porosity of the powder decreases, surface area of the powders is also decreased.

# DERIVED PROPERTIES OF POWDERS

There are numerous derived properties that are based on fundamental properties. Those with particular relevance to pharmacy are discussed here. Important properties such as powder dissolution and dissolution rate are discussed in separate chapters.

1. Packing geometry
2. Porosity
3. Density
4. Bulkiness
5. Flow property

## Packing Geometry

A set of particles can be filled into a volume of space to produce a powder bed, which is in static equilibrium owing to the interaction of gravitational and adhesive/cohesive forces. By slight vibration of the bed, particles can be mobilized, and at static equilibrium, they occupy a different spatial volume than before. The change in bulk volume has been produced by rearranging the packing geometry of the particles. In general, such geometric rearrangements result in a transition from loosely packed particles to more tightly packed ones. A set of uniform-sized spherical particles can be arranged in many different geometric configurations; however, the two extreme packing arrangements are as follows:

- Cubic arrangement—particles are most loosely packed and have a porosity of 48% (Fig. 2.13a).
- Rhombohedral arrangement—particles are most densely packed and have a porosity of only 26% (Fig. 2.13b).

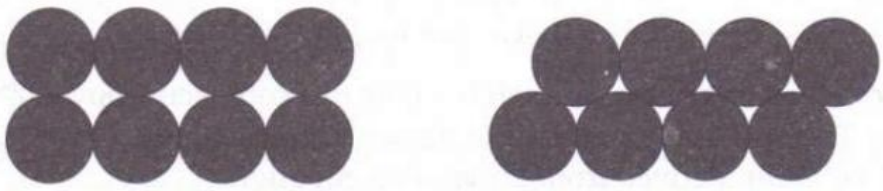



**Figure 2.13** Schematic representation of particles arranged in (a) cubic arrangement and (b) rhombohedral arrangement.

- It is to be expected that the particles of ordinary powders may have any porosity intermediate between the two extreme packing arrangements, 26–48%.
- Porosities below the theoretical minimum of 26% are possible in a powder bed with wide size range particles wherein the void spaces between coarse particles may become filled with finer particles.
- Porosities above the theoretical maximum of 48% are possible, if the particles are irregularly shaped and highly textured. Such particles arch or bridge within the powder bed through interlocking.
- Tightly packed particles require a higher driving force to produce powder flow than loosely packed particles of the same powder due to increase in cohesion between the particles.
- The porosity used to characterize packing geometry is linked to the bulk density of the powder.

## Porosity (*E*)

Porosity is a measure of the air spaces or voids in a material. In a powder bed, three types of air spaces or voids can be distinguished (Fig. 2.14):

1. **Open intraparticulate voids:** Those within a single particle but open to the external environment.
2. **Closed intraparticulate voids:** Those within a single particle but closed to the external environment.
3. **Interparticulate voids:** The air spaces between individual particles.

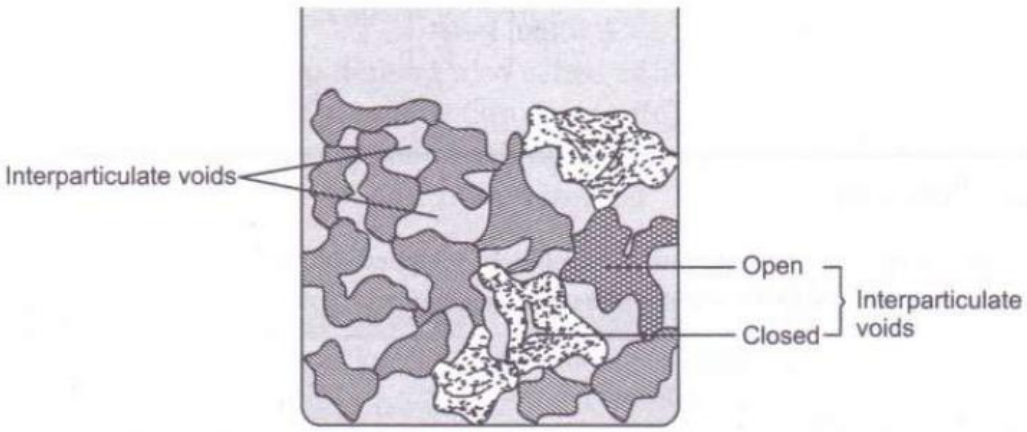



**Figure 2.14** Representation of various voids in a bed of powder.

Based on the types of voids, three interpretations of powder volume are proposed as shown below:

| Volume | Definition | Formula | Interpretation |
|---|---|---|---|
| Bulk ($V_b$) | Total volume occupied by the entire powder mass (including voids) | $V_b = M/\rho_b$ | $V_b$ = Total volume |
| Granular ($V_g$) | Volume of the solid particles excluding interparticulate (but not intraparticulate) void | $V_g = M/\rho_g$ | $V_g = V_b$ – interparticulate space |
| True ($V_t$) | Volume of the solid particles excluding both inter- and intraparticulate voids | $V_t = M/\rho_t$ | $V_t = V_b$ – (inter- and intraparticulate space) |

*Note:* $M$ is the mass and $\rho_b$, $\rho_g$ and $\rho_t$ are bulk, granular and true density, respectively.

The ratio of the total volume of void spaces ($V_v$) to the bulk volume of the material is often selected to monitor the progress of compression. This ratio $V_v/V_b$ is referred to as the *porosity* of the material:

$$V_v = V_b - V_t \tag{2.23}$$

**HIGHLIGHTS**

The use of porosity as a means of characterizing packing geometries can sometimes be misleading.

Therefore, porosity is

$$E = \frac{V_b - V_t}{V_b} = 1 - \frac{V_t}{V_b} \tag{2.24}$$

Porosity is frequently expressed as a percentage:

$$E = 100\left[1 - \frac{V_t}{V_b}\right] \tag{2.25}$$

## Example 2.6 (Porosity)

A cylindrical tablet of 10 mm diameter and 4 mm height weighed 480 mg and was made from the material of true density of 1.6 g $cm^{-3}$. Calculate porosity.

### Solution

The bulk volume $V_b$ is given by

$$V_b = \pi \left(\frac{10}{10 \times 2}\right)^2 \times \frac{4}{10} \text{ cm}^3 \tag{2.26}$$

(Volume of a cylinder is $\pi r^2 h$)

$= (0.5)^2 \times 0.4 = 0.3142 \text{ cm}^3$

The true volume of the solid is the true density divided by the mass, that is

$$V_t = \frac{480}{1000} \div 1.6 = \frac{0.48}{1.6} = 0.3 \text{ cm}^3$$

Therefore, the porosity is

$$E = 100 \times \left(1 - \frac{0.3}{0.3142}\right) = 100(1 - 0.9548) = 4.5\% \ (\textit{approximately})$$

## Density ($\rho$)

Density is defined as weight per unit volume. Based on the types of volume defined, the corresponding 'density' may be proposed. The *bulk density* of a powder is obtained by dividing its mass by the bulk volume it occupies. The bulk volume is the volume of the powder as poured or as passively filled into a measuring vessel and includes both inter- and intraparticulate spaces between and of the particles. The bulk density is often very difficult to measure since the slightest disturbance of the powder bed may result in a new bulk density. The density corresponding to granular volume is termed as *granular density*. The *true density* of a material is the density of the actual solid material. Unlike true density, bulk density of a powder is not a definite number but an indirect measurement of a number of factors, including particle size and size distribution, particle shape and the method of measurement. The bulk density of a powder is always less than the true density of its component particles because of the presence of pores or voids. This statement reveals that although a powder can only possess a single true density, it can have many different bulk densities, depending on the way in which the particles are packed and the bed porosity.

Another density term, i.e. tap density, also called as *compressed bulk density*, is the limiting density of a powder attained after compaction by tapping or vibration following a specified procedure. The sample is usually tapped or vibrated until an equilibrium volume is obtained and at that point the final tap density is determined. The various types of densities are summarized below:

| Density | Definition | Formula | Determination | Comment |
|---|---|---|---|---|
| Bulk ($\rho_b$) | Mass divided by bulk volume | $\rho_b = M/V_b$ | Bulk density apparatus, pycnometer | It is characteristic of the powder. Dependent on particle packing as the powder consolidates |
| Granular ($\rho_g$) | Mass divided by granular volume | $\rho_g = M/V_g$ | Mercury displacement | |
| True ($\rho_t$) | Mass divided by true volume | $\rho_t = M/V_t$ | Helium densitometer | It is characteristic of the particle. |
| Tapped ($\rho_t$) | Mass divided by volume obtained by compacting bulk volume by tapping | | Mechanical tapping device Jolting volumeter | Use to characterize powder flow |

# DENSITY DETERMINATION METHODS

## Bulk Density

Bulk density is determined by measuring the volume of the known mass of powder that has been passed through a screen into a graduated cylinder (Method I) or through a volume measuring apparatus into a cup (Method II).

### *Method I—Graduated cylinder method*

Approximately 50 g of powder sample ($M$), previously passed through sieve no. 18 to break up agglomerates that may have formed during storage, is introduced into a 100-mL graduated cylinder without compacting. The apparent volume ($V_b$) is then read to the nearest graduated unit. The bulk density is calculated in g/cm$^3$ by the formula

$$\frac{M}{V_b} \tag{2.26}$$

### *Method II—Scott volumeter*

A known volume of a powder is allowed to flow through the apparatus (Fig. 2.15) into the sample receiving cup and the weight of the powder is determined. The bulk density is calculated in g/cm$^3$ as described above.

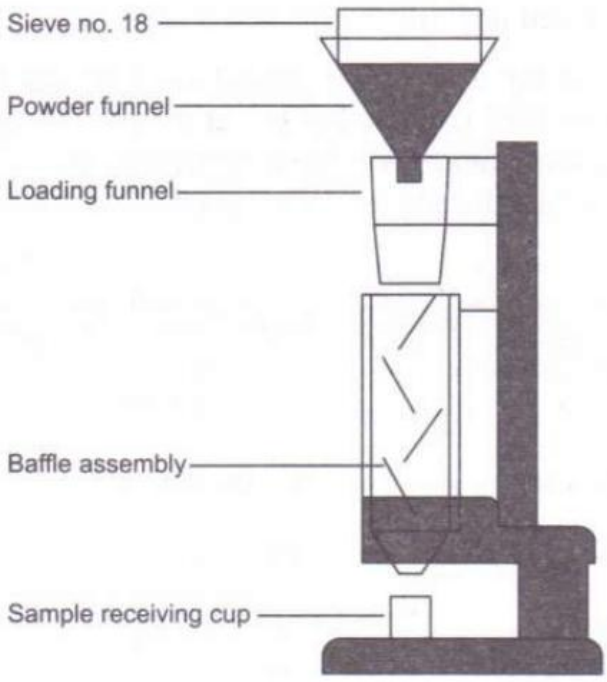



**Figure 2.15** Scott volumeter.

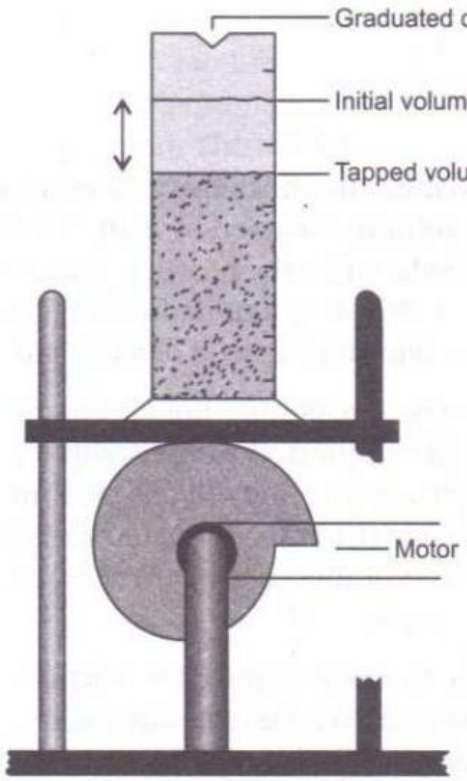





**Figure 2.16** Tapping device.

## Tapped Density

Tapped density is determined by mechanically tapping a graduated cylinder containing a powder sample. The mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight. Devices that rotate the cylinder during tapping may be preferred to minimize any possible separation of mass during tapping (Fig. 2.16).

### *Method I*

Approximately 50 g of powder sample ($M$), previously passed through sieve no. 18, is introduced into a 100-mL graduated cylinder without compacting. After observing the apparent volume ($V_b$), the cylinder is mechanically tapped by raising the cylinder and allowing it to drop under its own weight using a mechanical tapped density tester that provides a fixed drop of 142 mm at a nominal rate of 300 drops per minute. The cylinder is tapped 500 times initially and the tapped volume is measured ($V_x$). The tapping is repeated an additional 750 times and the tapped volume ($V_y$) is measured. If the difference between the two volumes is less than 2%, $V_y$ is the final tapped volume. If the difference between the two volumes is more than 2%, then an additional 1250 tappings in increments is recommended until the difference between successive measurements is less than 2%. The tapped density is calculated in g/cm$^3$ by the following formula:

$$\frac{M}{V_y}$$

## True Density

### *Gas pycnometer*

Gas pycnometer is a device used to measure the density, or more accurately the volume, of the powder. In a gas pycnometer, the volume occupied by a known mass of powder is determined by measuring the volume of gas displaced by the powder. A gas pycnometer is also sometimes referred to as a helium pycnometer. Helium is a nonadsorbing gas that penetrates the smallest pores and crevices and is useful in determining true density, particularly of porous solids.

The helium pycnometer consists of a sample holder chamber (A), which can be sealed after placing the sample; a valve (B) connected to the sample holder chamber, by means of which air from the sample chamber can be removed and helium gas can be admitted into the chamber; a pressure measuring device (C) and a movable variable volume piston (D) to read the pressure, which is related to the volume of the powder. The schematic representation of a helium pycnometer is shown in Figure 2.17.

In practice, the air in the sample holder is removed by vacuum and helium is passed into the chamber through the valve. The pressure is adjusted with the help of a movable piston and the reading on the scale at this stage denotes $U_1$. This represents the volume of the empty chamber.

In the next step, the pycnometer is calibrated by placing a standard sample, usually stainless steel spheres, of known true volume ($V_c$) in the sample holder chamber. The sample holder chamber is sealed, air is removed and the same amount of helium gas is introduced. The pressure is again adjusted to the preset value by moving the piston. The reading on the scale at this stage denotes $U_2$. The difference between $U_1$ and $U_2$ gives the volume occupied by the spheres.

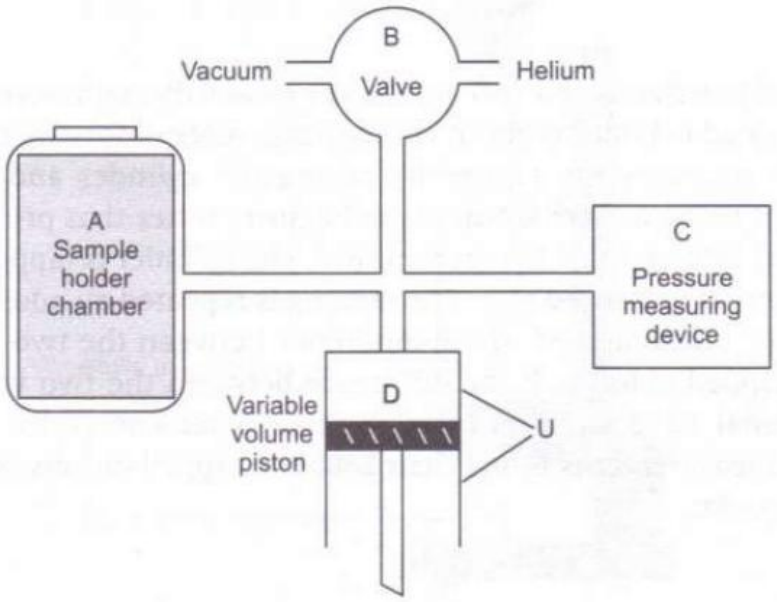



**Figure 2.17** Helium pycnometer to determine true density.

The last step involves determining the volume of the sample. Instead of stainless steel spheres, the chamber is now filled with sample powder. The sample holder chamber is sealed, air is removed and the same amount of helium gas is introduced. The pressure is again adjusted to the preset value by moving the piston. The reading on the scale at this stage denotes $U_s$. The difference between $U_1$ and $U_s$ gives the volume occupied by the powder sample. The working equation for a gas pycnometer is

$$V_t = V_c\left(\frac{U_1 - U_s}{U_1 - U_2}\right) \tag{2.27}$$

Although pycnometers are recognized as density-measuring devices, they are in fact devices for measuring volume only. Density is merely calculated as the ratio of mass to volume, mass being invariably measured on a discrete device, usually by weighing.

### Liquid displacement

The pycnometer can be used to determine the density of a solid object using liquid in which the solid does not dissolve. It uses a working liquid with well-known density, such as benzene, ethyl alcohol and water, for estimating true density of nonporous solid particles since these liquids cannot efficiently penetrate the smallest pores and crevices of a porous material. The powder pycnometer (Fig. 2.1) is a glass flask with a close-fitting ground glass stopper with a capillary hole through it. This fine hole releases a spare liquid after closing a pycnometer and allows for obtaining a given volume of working liquid with a high accuracy (Fig. 2.18).

First, the weight of empty pycnometer ($M_0$) is determined. The pycnometer is then filled with working liquid and the weight of liquid ($M_L$ = Total weight$-M_0$) determined. Now

**Figure 2.18** Pycnometer with glass body and capillary stopper.

the volume of the working liquid filling the pycnometer is determined using the following equation:

$$V_L = \frac{M_L}{\rho_L}$$

In the next step, about 1/3 of pycnometer volume is filled with powder sample ($M_s$) and the total weight ($M_0 + M_s$) is measured. The pycnometer is then filled with working liquid and weight determined ($M_T$).

Now, mass of liquid added is calculated as

$$M_{LA} = M_T - (M_0 + M_s)$$

The volume of liquid added can be obtained as

$$V_{LA} = \frac{M_{LA}}{\rho_L}$$

The volume of measured solid object ($V_s$) = $V_L - V_{LA}$.

Thus, the density of the measured solid object is calculated as

$$\rho_S = \frac{M_S}{V_S}$$

## Granular Density

### *Mercury displacement method or mercury porosimetry*

The volume of granules can be measured by the mercury displacement method. The method is similar to the liquid displacement method, but here instead of a working liquid, mercury is selected as a solvent. Mercury is suitable to determine granular density because it fills the interparticulate voids but fails to penetrate intraparticulate spaces due to its large size, which is of the order 10 μm.

Mercury porosimetry involves the intrusion of mercury, a nonwetting liquid, at high pressure into a material. The pore size can be determined based on the external pressure needed to force the liquid into a pore against the opposing force of the liquid's surface tension.

## Bulkiness

The reciprocal of bulk density is often called *bulk* or *bulkiness*. It is an important consideration in the packaging of the solid powders. For example, the bulk densities of calcium carbonate vary from 0.1 to 1.3, and the lightest or bulkiest type would require a container about 13 times larger than that needed for the heaviest type. A decrease in particle size increases the bulkiness.

## Flow Property

The preparation of essentially all dosage forms involves the handling of solid materials. The importance of solid-handling properties, especially flow properties, cannot be overemphasized since solid dosage forms are the most predominant in terms of volume and value. They are: (1) The flow properties of solids have great impact on the tableting processes since their manufacturing require the flow of powder from a storage container to tablet dies. (2) Weight and content uniformity are also dependent on flow of powders. (3) The flow properties of solids also greatly influence the mixing and demixing of powders. (4) The speed of tablet production is also greatly affected by the formulation's flow characteristics. (5) For the final product, weight, content uniformity, hardness, disintegration and dissolution are affected by formulation flow.

Powders are probably the least predictable of all materials in relation to flowability because many factors can change their rheological properties. Physical characteristics of the particles, such as size, shape, angularity, surface texture, porosity and hardness, will all affect flow properties. External factors such as humidity, conveying environment, vibration and, perhaps most importantly, aeration will compound the problem. Another characteristic of powders is that they are often inherently unstable in relation to their flow performance and even a free-flowing material could cease to flow. This transition may be initiated by the formation of a bridge, floccules, by adhesion to surfaces or by any event that may promote compaction of the powder. The tendency to switch in this way varies greatly from one powder to another, but can even be pronounced between batches of the same material.

The flow properties of a material result from forces that can act between solid particles including (1) frictional forces, (2) surface tension forces, (3) mechanical forces caused by interlocking of particles of irregular shape, (4) electrostatic forces and (5) cohesive or van der Waals forces. All of these forces can affect the flow properties of a solid. Most flow properties are significantly affected by changes in particle size, density, shape, electrostatic charge and adsorbed moisture, which may arise from processing or formulation.

In general, powders with large particles (>100 μm) will be noncohesive, permeable and will probably fluidize and will have low compressibility and relatively low shear strength.

Conversely, fine powders, say <10 μm, are likely to be cohesive, compressible, contain much entrained air and yet have poor aeration characteristics. Generally, they have high shear strength, high flow energy, low permeability and are very affected by being consolidated when entrained air is excluded. However, under forced flow conditions, fine powders can behave more like a fluid. They are able to extrude round corners or through holes, unlike coarse powders that are more likely to become solid-like as particles realign and lock together and become very resistant to flow.

**HIGHLIGHTS**

A small amount of aeration is sufficient to transform a consolidated powder into one with fluid-like rheology.

# CHARACTERIZATION OF POWDER FLOW

Commonly used methods for characterizing powder flow are as follows:

1. Compressibility index
2. Angle of repose
3. Flow rate through an orifice

## Compressibility Index

Carr reported that the more a material is compacted in a compaction or tap bulk density test, the poorer are its flow properties. A simple indication of the ease with which a material can be induced to flow is given by application of a *compressibility index* and *Hausner ratio* given by the following equation:

$$\text{Carr's compressibility index} = \frac{(\text{Tap density} - \text{Bulk density})}{\text{Tap density}} \times 100\%$$

$$\text{Hausner ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

Table 2.9 indicates the scale of flowability and Table 2.10 lists compressibility and flow property for some common pharmaceutical excipients.

**Table 2.9** Scale of flowability for compressibility index and Hausner ratio

| Flowability | Carr's index | Hausner ratio |
|---|---|---|
| Excellent | 5–15 | 1.05–1.18 |
| Good | 12–16 | 1.14–1.20 |
| Fair-passable | 18–21 | 1.22–1.26 |
| Poor | 23–35 | 1.30–1.54 |
| Very poor | 33–38 | 1.50–1.61 |
| Very, very poor | >40 | >1.67 |

**Table 2.10** Compressibility and flow property of some common pharmaceutical excipients

| Material | % Compressibility | Flowability |
|---|---|---|
| Celutab | 11 | Excellent |
| Emcompress | 15 | Excellent |
| Star X-1500 | 19 | Fair-passable |
| Lactose | 19 | Fair-passable |
| Maize starch | 26–27 | Poor |
| Magnesium stearate | 31 | Poor |
| Titanium dioxide | 34 | Very poor |
| Dicalcium phosphate | 41 | Very, very poor |
| Talc | 49 | Very, very poor |

### Angles of repose

If a powder is allowed to flow onto a flat surface, a pile or heap of powder is formed. A material that is not cohesive and flows well, spreads out, forming a low heap. More cohesive materials form higher heaps, which are less spread out. The angle of repose (θ) is defined as the angle of the free surface of a pile of powder to the horizontal plane and is represented by the following equation:

$$\tan \theta = \frac{h}{r} \tag{2.28}$$

where $h$ is the height of pile, $r$ the radius of pile and $\theta$ the angle of repose.

It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane, as shown in Figure 2.19. Such measurements give at least a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing, or in tablet die or capsule shell filling operations.

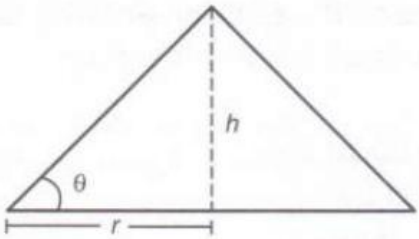



**Figure 2.19** Representation of pile of powder with measurement of angle of repose.

### Static angle of repose

The *fixed funnel method* uses a funnel that is secured with its tip at a given height, $h$, above the graph paper that is placed on a flat horizontal surface. Powder or granulation is carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius of the base of the conical pile is then determined to calculate the angle of repose (Fig. 2.20a).

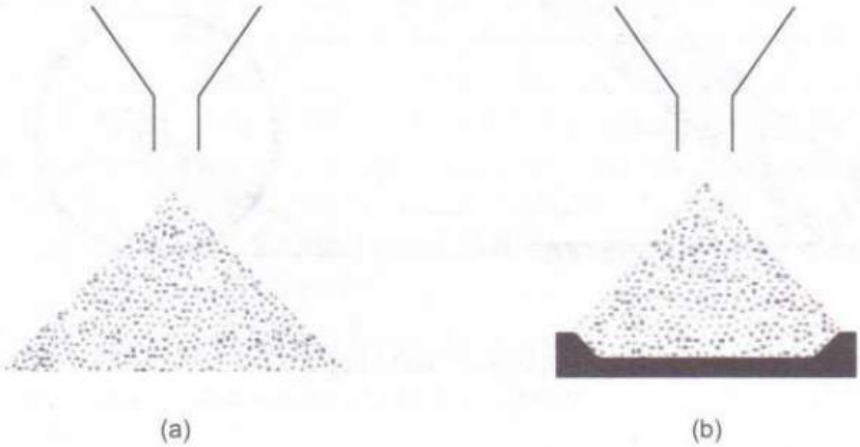



**Figure 2.20** Measurement of static angles of repose: (a) fixed funnel method and (b) fixed cone method.

The *fixed cone method* establishes the radius of the cone base, *r*, using a circular dish with sharp edges. Powder is poured onto the centre of the dish from a funnel that can be raised vertically until a maximum cone height, *h*, is obtained (Fig. 2.20b). The repose angle is calculated as before.

### Dynamic or kinetic angle of repose

Angle of repose methods, which result in a so-called *dynamic* angle, are preferred, since they most closely mimic the manufacturing situation, in which the powder is in motion.

**Tilting box method:** A sandpaper-lined rectangular box is filled with the powder and carefully tilted until the contents begin to slide, as shown in Figure 2.21a. The maximum angle that the plane of a powder makes with the horizontal surface on rotation is taken as the angle of repose.

**Rotating cylinder method:** A typical dynamic test involves a hollow cylinder half-filled with the test powder, with one end sealed by a transparent plate. The cylinder is rotated about its horizontal axis (Fig. 2.21b), until the powder surface cascades. The curved wall is lined with sandpaper to prevent preferential slip at this surface.

1. $\theta$ value < 20° exists rarely
2. $\theta$ value 25–30° indicates excellent flow
3. $\theta$ value 31–35° indicates good flow
4. $\theta$ value 36–40° indicates fair flow
5. $\theta$ value 41–45° indicates passable flow
6. $\theta$ value 46–55° indicates poor flow and such powder require agitation
7. $\theta$ value 56–65° indicates very poor flow
8. $\theta$ value ≥ 65° indicates very, very poor flow

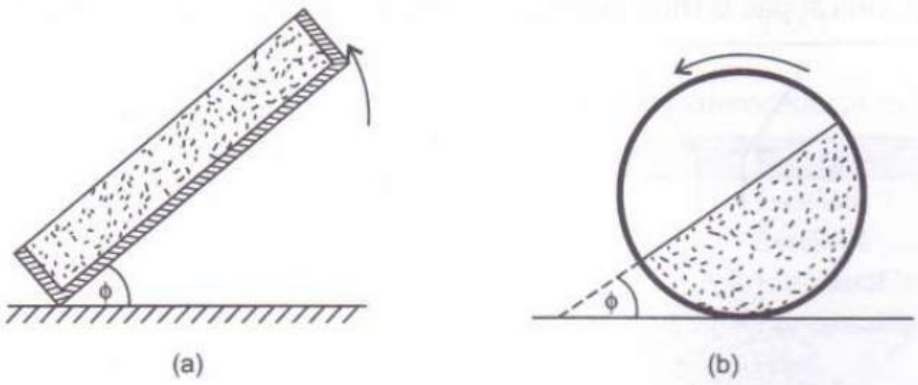



**Figure 2.21** Measurement of dynamic angles of repose: (a) tilting box method and (b) rotating cylinder method.

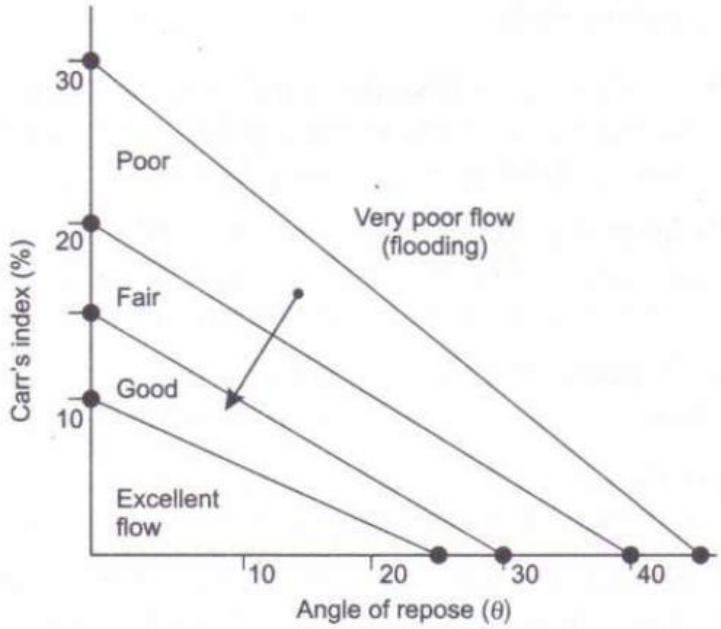



**Figure 2.22** Relationship between the angle of repose, Carr's index and the flow characteristics of a powder.

As mentioned previously, flow of coarse particles is also related to packing densities and mechanical arrangements of particles. Hence, a good auxiliary test to run in conjunction with the repose angle test is the compressibility test, as discussed previously (see Fig. 2.22). From the angle of repose and compressibility values, a reasonable indication of a material's inherent flow properties is possible.

## Flow Rate Through an Orifice

The simplest method of determining powder flowability directly is to measure the rate at which powder discharges from an orifice of the hopper. This method is not useful for cohesive materials and can be used only for materials that have some capacity to flow. Generally, cylindrical containers are used because this configuration results in the flow rate being determined by the movement of powder over powder rather than powder along the wall of the container. The orifice should be circular and the cylinder should be free of vibration. In practice, the shutter is placed over the orifice and the cylinder is filled with powder. The shutter is then removed and the time taken for the powder to discharge completely is recorded. By dividing the discharged powder mass by this time, a flow rate is obtained, which can be used for quantitative comparison of different powders. Cylinder or discharge tube outlets should be selected to provide a good model for a particular flow application. General guidelines for dimensions of the cylinder are as follows:

Diameter of opening > 6 times the diameter of the particle

Diameter of cylinder > 2 times the diameter of the opening

## Improvement of Flow Property

**Alteration of particle size and size distribution:** Because coarse particles are generally less cohesive than fine particles and an optimum size for free flow exists, there is a distinct disadvantage in using a finer grade of powder than is necessary.

**Alteration of particle shape:** In general, for a given particle size, spherical particles have better flow than irregular particles. The drug particles that are normally acicular can be made more spherical by spray drying, spheronization and temperature-cycling crystallization.

**Alteration of particle texture:** Particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth-surfaced particles.

**Alteration of surface forces:** Reduction of electrostatic charges can improve powder flowability. This can be achieved by altering process conditions to reduce frictional contacts.

**Control of moisture content:** The moisture content of particles is also important to powder flowability as adsorbed surface moisture films tend to increase bulk density and reduce porosity. In cases where moisture content is excessive, powders should be dried and, if hygroscopic, stored under low-humidity conditions.

**Temperature:** The cohesion of powder decreases as the temperature is decreased. This can be attributed to the reduction in plasticity and to the inability of asperities on the surface of neighbouring particles.

**Formulation additives—flow activators:** Flow activators are commonly called as *glidants*, although some also have lubricant or antiadherent properties. Flow activators improve the flowability of powders by reducing adhesion and cohesion. Some commonly used glidants include talc, magnesium stearate and maize starch, which may affect by reducing or altering electrostatic interactions. Colloidal silicon dioxide is a flow activator with an exceptionally high-specific surface area and thus acts by reducing the bulk density of tightly packed powders. To be effective, in general, the glidant particles should be very much smaller than those of the powder in order to coat them completely, smoothing out irregularities in their shape and reducing the frictional and adhesive forces that operate between them. In almost all systems, there is an optimum concentration above which the glidant ceases to be effective. If too much is added, powder flowability may decrease, and it is therefore necessary to control the addition carefully for best results. Where powder flowability is impaired through increased moisture content, a small proportion of very fine magnesium oxide, silicone-coated talc or sodium bicarbonate may be used as a flow activator. These agents appear to disrupt the continuous film of adsorbed water surrounding the moist particles. Glidant can improve the flow by any one or a combination of mechanisms described below:

1. Dispersion of static charge from the surface of particles
2. Adsorption of gases and vapours otherwise adsorbed onto the host particle
3. Physical separation of particles and reduction in van der Waals interactions
4. Adhere to the surfaces of host powders, smoothing out irregularities and reducing their tendency to interlock
5. Minimizing friction between particles by adhering to powder surface

## Questions

1. Give proper justification for the following:
   a. Addition of glidant at low concentration improves the flow properties of granules, but high concentration of glidant decreases the flow properties of granules.
   b. Mercury is used to determine granular density, but not true density.
   c. Andreasen pipette method is not suitable for size determination of colloidal particles.
   d. Bulk density of a powder is always less than its true density.
   e. Helium is the gas of choice used to determine true density using gas pycnometer.
2. Write short notes on the following:
   a. Equivalent spherical diameter
   b. Porosity
   c. Carr's compressibility index and its significance
   d. Quantasorb technique
   e. Coulter counter technique
3. Describe various parameters for the assessment of flow property of powders.
4. Describe any two techniques to determine weight distribution of particles.
5. Define different types of densities and methods used for their determination.

CHAPTER

# 12 Kinetics, Degradation and Stability

To ensure that the patient receives the correct dose of a drug, the rate of degradation must be known irrespective of the form it is carried in (solution, suspension, tablets and capsules). Degradative reactions in pharmaceutical formulations are chemical in nature and take place at definite rates. The experimental investigation of the possible breakdown of a new drug is not a simple matter. An effective and efficient study of these reactions requires the application of kinetic principles. Kinetics deals with the stability of drugs and the mode of action of their degradation through the examination of rate of reaction. Degradation kinetics can provide predictive information by predicting the intrinsic stability of a drug candidate to anticipate problems that may arise later in the development path. This chapter discusses the basic treatments of drug degradation studies including kinetics, factors affecting degradation rates and typical practices for assessing the stability of pharmaceutical drug products.

## RATE OF REACTION

In a chemical reaction, reactants yield products. When reaction starts, the concentrations of reactants and products change with time until the reaction reaches completion or equilibrium. The concentration of the reactants decreases, whereas that of the products increases over time. The velocity with which a reactant or product undergoes chemical change is called the *rate of a chemical reaction*. Therefore, the rate of a reaction is represented either by decrease in the concentration of a reactant or by increase in the concentration of a product with respect to time.

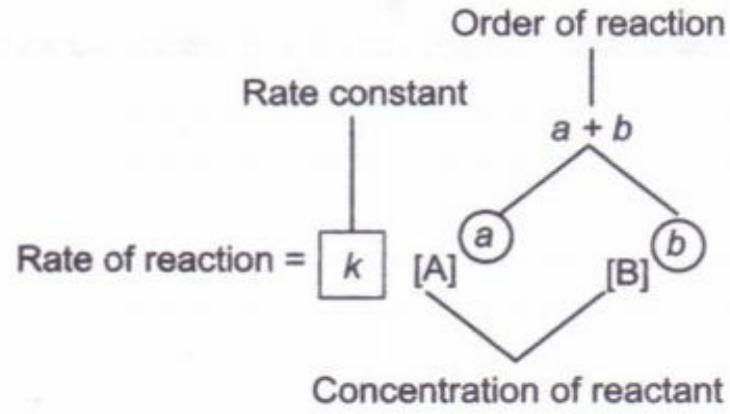
Consider the following reaction:

$$aA + bB \rightarrow cC + dD \tag{12.1}$$

Here $a$, $b$, $c$ and $d$ are the stoichiometric coefficients that represent the molar ratio of the reactants and the products of the reaction. The rate of change of concentration of each species can differ, depending on the stoichiometric coefficients.

$$\text{Rate of reaction} = -\frac{1}{a}\frac{d[A]}{dt} = -\frac{1}{b}\frac{d[B]}{dt} = \frac{1}{c}\frac{d[C]}{dt} = \frac{1}{d}\frac{d[D]}{dt} \qquad (12.2)$$

The *reaction rate law expression* relates the rate of a reaction to the concentrations of the reactants as indicated in Eq. (12.3).




(12.3)

Here $k$, the proportional constant, is called the *specific rate constant*, or the *rate constant*, and $a$ and $b$ are the *orders of reaction* with respect to A and B, respectively.

**HIGHLIGHTS**

In a rate equation, $k[A]^a[B]^b$, $a$ and $b$ are the reactant orders determined from the experiment and are not the stoichiometric coefficients.

Regardless of the order of the reaction, the rate of reaction has the units of concentration/time (i.e. mol/L.$s^{-1}$). The units of the rate constant depend on the overall order of the reaction:

$$k = (\text{concentration})^{1-n}\,(\text{time})^{-1}$$

## Elementary Reaction

When the rate equation corresponds stoichiometrically, the reaction is called an *elementary reaction*. When a reaction takes place via a single stoichiometric equation that has a single rate expression, it is called as the *single reaction* and when more than one stoichiometric equations are used to express the rate of reaction of all the constituents, it is called as *multiple reaction*. Consider the following reaction with the stoichiometric equation:

$$A + B \rightarrow P \qquad (12.4)$$

The above reaction is called an *elementary reaction* with the rate equation

$$\text{Rate} = k[A]\,[B] \qquad (12.5)$$

where $k$ is the rate constant and the square brackets indicate the concentrations of each reactant.

## Nonelementary Reaction

When the rate equation does not correspond stoichiometrically, the reaction is called a *nonelementary reaction* as exemplified by the thermal decomposition of nitrous oxide to nitrogen and oxygen: $N_2O \rightarrow N_2 + \frac{1}{2}O_2$,

which has the following rate equation:

$$\text{Rate} = \frac{k_1[N_2O]^2}{1 + k_2[N_2O]} \tag{12.6}$$

The overall reaction is the result of sequential elementary reactions but is expressed as a single reaction because the intermediates are very small, unnoticeable and difficult to isolate.

### Order of Reaction

The *order of reaction* is defined as the manner in which the rate of a reaction varies with the concentration of the reactants. According to Eq. (12.3), the overall order of the reaction is sum of the exponents ($a + b$) of the concentration terms A and B.

### Molecularity of Reaction

The *molecularity* of a single elementary reaction is the number of molecules engaged in the reaction. A simple elementary reaction is referred to as uni-, bi- or termolecular if one, two or three chemical species are involved in the chemical reaction, respectively:

Unimolecular: $A \rightarrow B + C$ (e.g. bromine decomposition; $Br_2 \rightarrow 2Br$)

Bimolecular: $A + B \rightarrow C + D$ (e.g. formation of hydroiodic acid; $H_2 + I_2 \rightarrow 2HI$)

Termolecular: $A + 2B \rightarrow C + D$ (rarely observed in pharmaceutical science)

Order and molecularity of a reaction are generally identical for elementary reactions; however, they may be different for complex reactions involving multiple steps.

## TYPES OF REACTION

For the most part, the degradation of pharmaceuticals can be treated as zero-order, first-order pseudo-zero-order, or pseudo-first-order reactions, even though many of the pharmaceutical compounds degrade by complicated mechanisms. Consequently, the higher-order reactions are briefly reviewed and the lower-order reaction types are discussed in detail.

### Zero-Order Reaction

A reaction is said to be zero-order if the reaction rate is independent of the concentration of the reacting substance or reaction rate depends on the zero power of the reactant.

**Example:** Degradation of solution

When solubility is the factor, only that amount of drug that is in solution undergoes degradation. As drug is consumed in the degradative reaction, more drug goes into the solution until all solid 'A' has reacted. Until this occurs, the degradative reaction does not depend on the total concentration of drug but only on the portion that is in solution, resulting in a zero-order reaction. This can be depicted as follows:

$$\text{A (solid)} \rightleftharpoons \text{A (sol)} \rightarrow \text{B}$$

**Equation:** In a zero-order reaction, the rate of an elementary unimolecular reaction can be described mathematically as follows:

$$r = -\frac{d[A]}{dt} = k_o \tag{12.7}$$

where $k_0$ is the zero-order rate constant and $t$ is the time. The rate of reaction is independent of the concentration of the reactants. Integrating Eq. (12.7) yields:

$$\int_{[A]_o}^{[A]} d[A] = -k_o \int_o^t dt \quad \text{or } [A] = [A]_o - k_o t \tag{12.8}$$

where $A_0$ is the initial drug concentration.

**Graphical representation:** A plot of the remaining drug concentration [$A$] versus $t$, as shown in Figure 12.1, gives a straight line with a slope equal to $-k_0$.

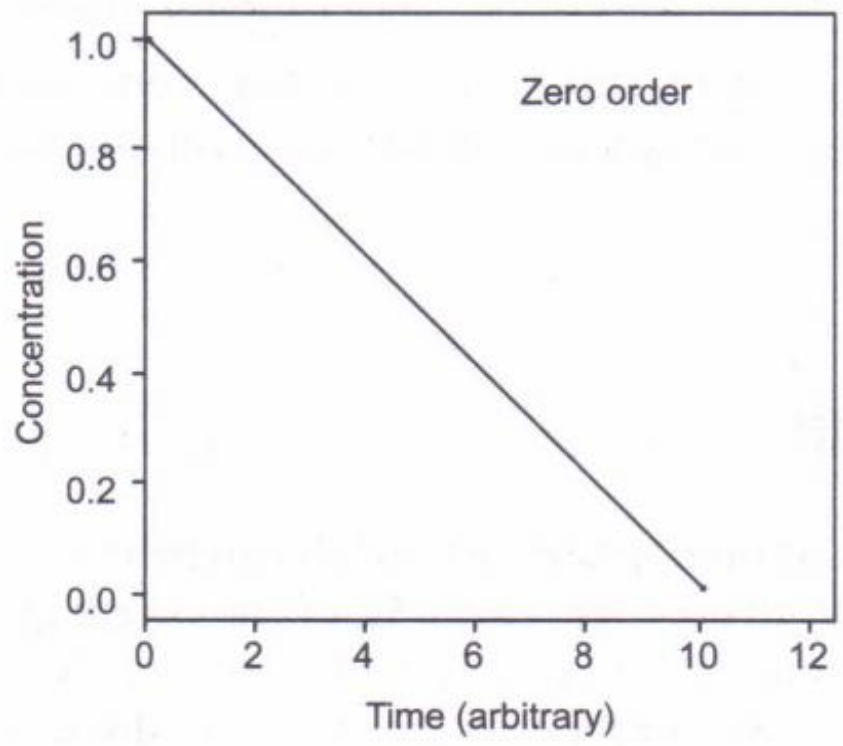



**Figure 12.1** A representative zero-order plot of the amount of drug reacting versus time.

**Units of rate constant:** mol/L·s$^{-1}$

**Half-life:**

$$t_{0.5} = \frac{0.5[A]_o}{k_o} \qquad (12.9)$$

**Shelf life:**

$$t_{0.9} = \frac{0.1[A]_o}{k_o} \qquad (12.10)$$

**HIGHLIGHTS**

The *half-life* ($t_{0.5}$) and *shelf life* ($t_{0.9}$) are defined as the times required for the concentration of the drug to decrease by 50% and 10%, respectively.

The half-life of a zero-order reaction is directly proportional to $[A]_0$. Unlike other reaction kinetics, it is possible to determine the time required for 100% of the drug in a formulation to completely decompose. It takes two half-lives for complete degradation for zero-order reactions.

### *Example*

- Loss of colour of a liquid multisulfa preparation at elevated temperatures
- Degradation of vitamin A acetate to anhydrovitamin A

## First-Order Reaction

A reaction is said to be first-order if the reaction rate depends on the first power of concentration of a single reactant.

**Equation:** In a first-order reaction, a substance decomposes directly into one or more products (A → products). The rate of reaction is directly proportional to the concentration of the reacting substance and can be expressed mathematically in the following form:

$$r = -\frac{d[A]}{dt} = k_1[A] \qquad (12.11)$$

where $k_1$ is the first-order rate constant. Integrating Eq. (12.11) yields

$$\int_{[A]_o}^{[A]} \frac{d[A]}{[A]} = -k_1 \int_o^t dt \quad \text{or} \quad \ln\left(\frac{[A]}{[A]_o}\right) = -k_1 t \qquad (12.12)$$

**Graphical representation:** A plot of the logarithm of the fraction remaining log[*A*] versus time, as shown in Figure 12.2, gives a straight line with a slope equal to $-k_1/2.303$. The higher the temperature, the greater is the *k* value, as evidenced by the steepness of the slopes.

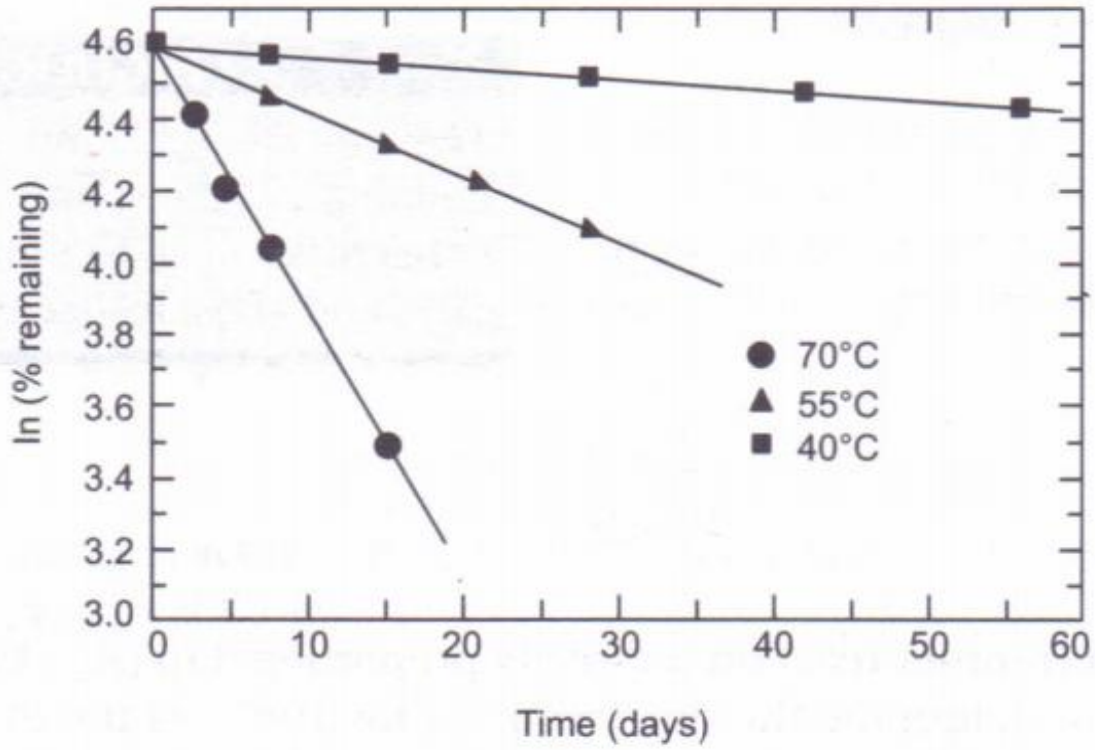



**Figure 12.2** Representative degradation curves for a material deteriorating according to first-order kinetics.

**Units of rate constant:** $s^{-1}$

**Half-life:**

$$t_{0.5} = \frac{-\ln 0.5}{k_1} = \frac{0.693}{k_1} \tag{12.13}$$

**Shelf life:**

$$t_{0.9} = \frac{-\ln 0.9}{k_1} = \frac{0.105}{k_1} \tag{12.14}$$

It is important to note here that the $t_{0.5}$ or $t_{0.9}$ is concentration independent. In other words, it takes the same time to reduce the concentration of drug from 0.1 to 0.05 mol as it would to go from 0.001 to 0.0005 mol.

***Example***

- Decomposition of $H_2O_2$ catalyzed by iodine ions

## Second-Order Reaction

A reaction is said to be second-order if the reaction rate depends on the concentration of two reactant species. Second-order reactions are of two types.

Type 1: $A + A \longrightarrow P$ (rate = $kC_aC_a$ or = $kC_a^2$),

Type 2: $A + B \longrightarrow P$ (rate = $kC_aC_b$).

**Equation:** When the initial concentrations of *A* and *B* are identical, the rate equation can be simplified as follows:

$$\frac{d[A]}{dt} = -k_2[A]^2 \tag{12.15}$$

where $k_2$ is the second-order rate constant. Integration of Eq. (12.15) yields

$$\int_{[A]_0}^{[A]} \frac{d[A]}{[A]^2} = -k_2 \int_0^t dt \quad \text{or} \quad \frac{1}{[A]} - \frac{1}{[A]_0} = -k_2 t \tag{12.16}$$

**Graphical representation:** For such reactions, the plot of $1/[A]$ versus $t$ gives a straight line with slope of $k_2$, as shown in Figure 12.3.

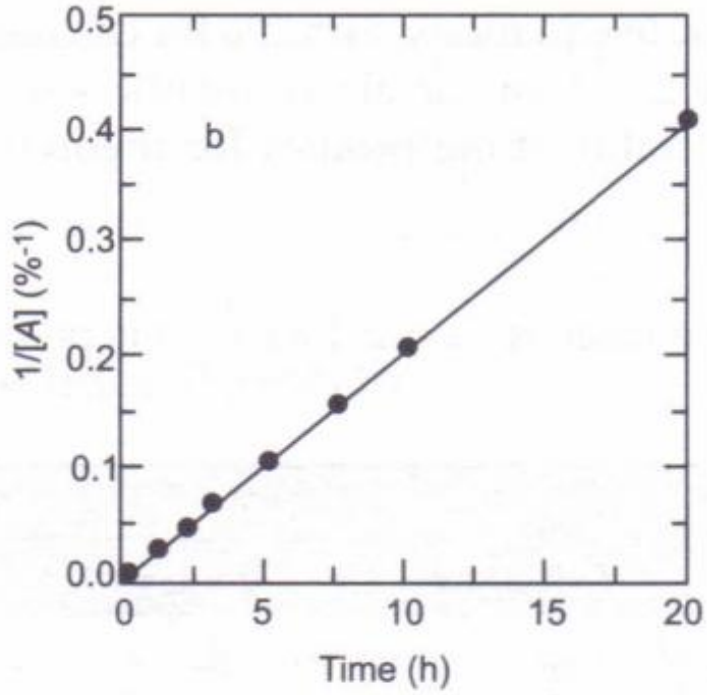



**Figure 12.3** Linear plot of kinetic data for second-order reaction.

**Units of rate constant:** mol/L•s$^{-1}$

**Half-life:**

$$t_{0.5} = \frac{1}{k_2[A]_0} = k_1[A] \tag{12.17}$$

**Shelf life:**

$$t_{0.9} = \frac{0.11}{k_2}[A]_0 \tag{12.18}$$

**Equation:** When initial concentrations of $A$ and $B$ are not identical, the rate can be expressed as follows:

$$\frac{d[A]}{dt} = k_2[A][B] \tag{12.19}$$

At time $t$, the amounts of A and B reacted are equal (i.e. stoichiometrically 1:1 ratio and $[A]_0 \cdot X_A = [B]_0 \cdot X_B$, where $X_A$ and $X_B$ are the fractional conversions of $A$ and $B$, respectively). Eq. (12.19) can then be written in terms of $X_A$ as follows:

$$[A]_o \frac{dX_A}{dt} = k_2[A]_0^2(1 - X_A)\ (M - X_A) \tag{12.20}$$

where $M = [B]_0/[A]_0$. Integrating Eq. (12.20), we obtain

$$\ln \frac{[B]\ [A]_o}{[A]\ [B]_o} = k_2([B]_o - [A]_o)t \tag{12.21}$$

### Example

- Saponification of ethyl acetate

Table 12.1 summarizes the rate equations, formula for calculating reactant concentration–time profiles, half-lives and shelf life for the above-mentioned simple order kinetics. Figure 12.4 plots the reactant concentration–time profiles for theoretical zero-, first- and second-order kinetics.

**Table 12.1** Summary of the rate equations, concentration–time profiles, half-lives and shelf life for simple-order kinetics

| | | | Second-order | |
|---|---|---|---|---|
| | **Zero-order** | **First-order** | $a = b = c_o$ | $a \neq b$ |
| Differential rate expression | $-\frac{dc}{dt} = k$ | $-\frac{dc}{dt} = kc$ | $-\frac{dc}{dt} = kc^2$ | $-\frac{dc}{dt} = kc_a c_b$ |
| Concentration time profile | $c = c_0 - kt$ | $c = c_0 \exp^{(-kt)}$ | $\frac{1}{c} - \frac{1}{c_o} = kt$ | $k = \frac{1}{t(a-b)} \ln \frac{b(a-b)}{a(b-x)}$ |
| Units of rate constant | moles/litre second | 1/second | litre/mole second | |
| Half-life ($t_{½}$) | $\frac{c_o}{2k}$ | $\frac{0.693}{k}$ | $\frac{1}{c_o k}$ | (i) When $x = 0.5a$ $\frac{1}{k(a-b)} \ln \frac{0.5ab}{a(b-0.5a)}$ (ii) When $x = 0.5b$ $\frac{1}{k\ (a-b)} \ln \frac{b(a-0.5\ b)}{0.5ab}$ |
| Shelf life ($t_{90\%}$) | $\frac{c_o}{10k}$ | $\frac{0.105}{k}$ | $\frac{0.11}{c_o k}$ | (i) When $x = 0.1a$ $\frac{1}{k(a-b)} \ln \frac{0.9ab}{a(b-0.1a)}$ (ii) When $x = 0.1b$ $\frac{1}{k\ (a-b)} \ln \frac{b(a-0.1\ b)}{0.9ab}$ |

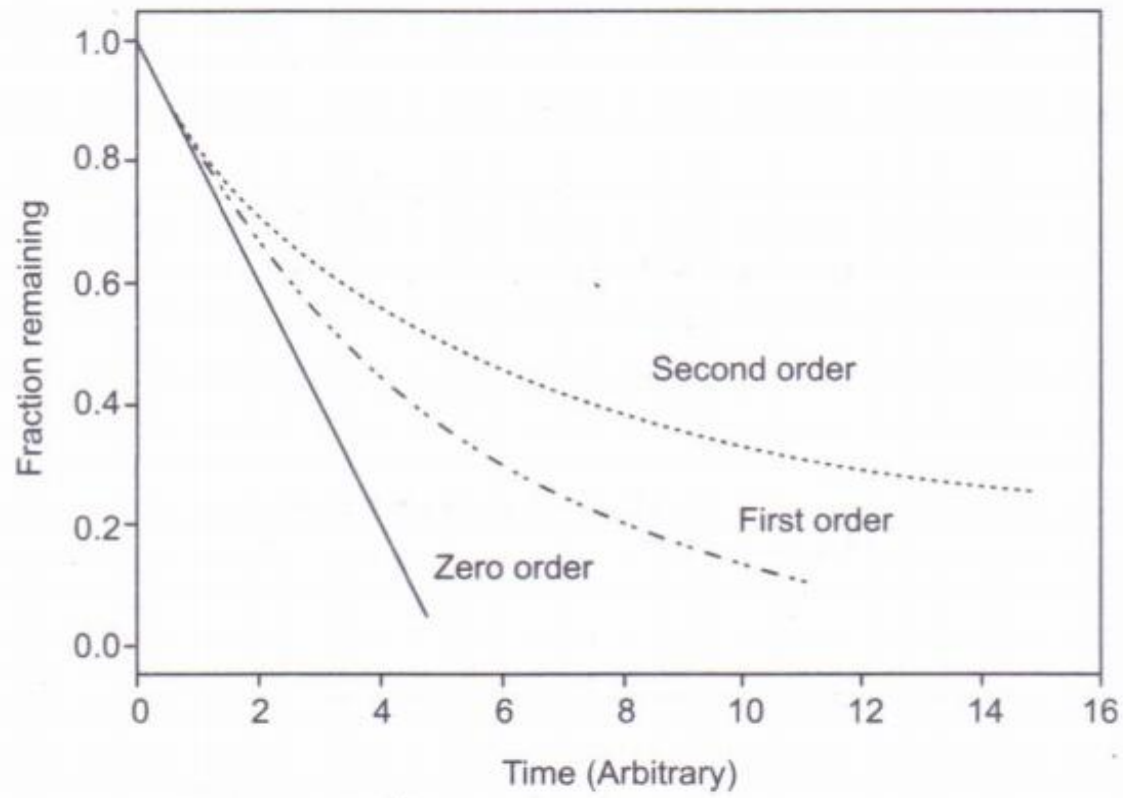



**Figure 12.4** Reactant concentration–time profiles for theoretical zero-, first- and second-order reactions.

## Apparent/Pseudo-Zero-Order Reaction

Some drugs in certain common dosage forms, such as suspensions, follow zero-order kinetics. Considering the phase where degradation takes place, first-order degradation kinetics is observed. However, the overall degradation kinetics in the entire dosage form is a zero-order rate. Many drugs, in the solid state, decompose according to pseudo-zero-order rates as reactions occur between the drug and moisture in the solid dosage form. The system behaves as a suspension, and because of the presence of excess solid drug, the first-order reaction rate becomes a pseudo-zero-order rate, and the drug loss rate is linear with time.

$$\frac{d[A]}{dt} = -k_1[A] \tag{12.22}$$

In suspension formulations, the concentration of the drug in the aqueous phase remains constant (i.e. saturated) until the suspended drug particles are completely exhausted:

$$k_1[A] = k_1[A]_s = k_o \tag{12.23}$$

where $[A]_s$ is the solubility of a drug. Substituting Eq. (12.23) into Eq. (12.22) yields

$$\frac{d[A]}{dt} = -k_o \tag{12.24}$$

---

*Example 12.1(Pseudo-zero-order kinetics)*

An aspirin suspension containing 6.0 g/ 100 ml of aspirin was prepared. The solubility of aspirin is 0.33 g/100 ml and the first-order rate constant for aspirin degradation in solution was found to be $4.5 \times 10^{-6}$ $s^{-1}$. Calculate zero-order rate constant and determine shelf life of the aspirin suspension.

### Solution

Based on Eq. (12.23), we get

$$k_0 = k \times [\text{aspirin in solution}]$$

$$k_0 = (4.5 \times 10^{-6}) \times (0.33 \text{ g}/100 \text{ ml})$$

$$k_0 = \frac{1.5 \times 10^{-6} \text{ g}}{100 \text{ ml s}^{-1}}$$

$$t_{90} = \frac{0.10 \text{ (aspirin in suspension)}}{k_0}$$

$$t_{90} = \frac{(0.10)\ (6.0 \text{ g}/100 \text{ ml})}{(1.5 \times 10^{-6})}$$

$$t_{90} = 4.0 \times 10^5 \text{ s} = 5.0 \text{ days (approximately)}$$

## Pseudo-First-Order Reaction

A pseudo-first-order reaction can be defined as a second-order or bimolecular reaction that is made to behave like a first-order reaction. This happens when one reacting material is present in great excess or is maintained at a constant concentration compared with the other substance. Under such circumstances, the reaction rate is determined by one reactant even though two are present, since the second reactant does not exhibit a significant change in concentration during the degradative reaction.

### *Example*

- An example of such a situation is the hydrolysis of an ester catalyzed by hydroxyl ion. If the hydroxyl ion concentration is high compared with the concentration of the ester, the reaction behaves as a first-order reaction and can easily be followed by assay for residual ester.
- An example of a drug that obeys pseudo-first-order kinetics is cefotaxime sodium.

# DETERMINATION OF ORDER OF REACTION

## Graphical Substitution Method

In this method a plot of data in form of graph is used to ascertain the order of reaction. A linear relation between concentration and time indicates zero-order reaction, whereas a linear relation between log concentration and time indicates first-order reaction. The reaction

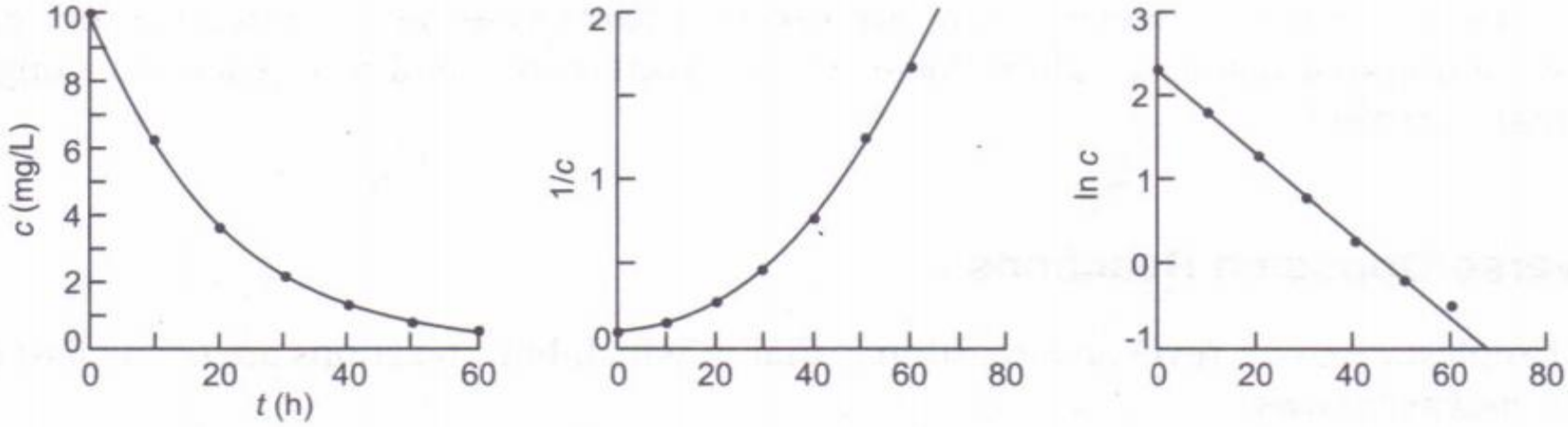



**Figure 12.5** (a) Plot of concentration against time, (b) plot of 1/concentration against time and (c) plot of ln (concentration) against time.

is second order if relation between 1/concentration and time is linear. As shown in Figure 12.5, the relation between concentration and time and between 1/concentration and time is non-linear. However, the relation between log concentration and time is linear indicating that the reaction is of first order.

### Half-Life Method

This involves the selection of a set of convenient initial concentrations and then determining the times taken to fall to half these values. In detail:

- The half-life of a zero-order reaction is proportional to the initial concentration.
- The half-life of a first-order reaction is independent of the initial concentration.
- The half-life of a second-order reaction is inversely proportional to the initial concentration.

In general:

$$t_{0.5} \alpha \frac{1}{a^{n-1}}$$

$$\frac{t_{0.5(1)}}{t_{0.5(2)}} = \frac{a_2^{n-1}}{a_1^{n-1}} = \left(\frac{a_2}{a_1}\right) n-1 \qquad (12.25)$$

## COMPLEX REACTIONS

Although most degradative reactions occurring in pharmaceutical systems can be treated by simple zero-order, first-order, pseudo-zero-order and pseudo-first-order kinetics, as

previously discussed. However, there are certain pharmaceutical formulations that exhibit more complicated reactions. These have reverse, consecutive and side reactions along with the main reaction.

## Reverse/Opposing Reactions

The simplest case of a reversible reaction is that in which both reactions are of the first order, illustrated as follows:

$$A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B \tag{12.26}$$

In the situation represented, $A$ decreases to form $B$ and some of the product of $B$ reverts back to $A$. According to this, the net rate at which $A$ decreases will be given by the rate at which $A$ decreases in the forward step less the rate at which $A$ increases in the reverse step:

$$-\frac{dA}{dt} = k_f A - k_r B \tag{12.27}$$

Under equilibrium condition and after integration, the rate law for such a reaction is as follows:

$$\log \frac{A_0 - A_{eq}}{A - A_{eq}} = t \frac{k_f + k_r}{2.303} \tag{12.28}$$

The equation corresponds to a straight line intersecting at zero and having a slope given by $k_f + k_r/2.303$. The equilibrium constant ($K$) of the reaction is given by:

$$k = \frac{k_f}{k_r} - \frac{B_{eq}}{A_{eq}} \tag{12.29}$$

Both the forward and reverse rate constants can be estimated once the slope of the line and equilibrium constant have been determined.

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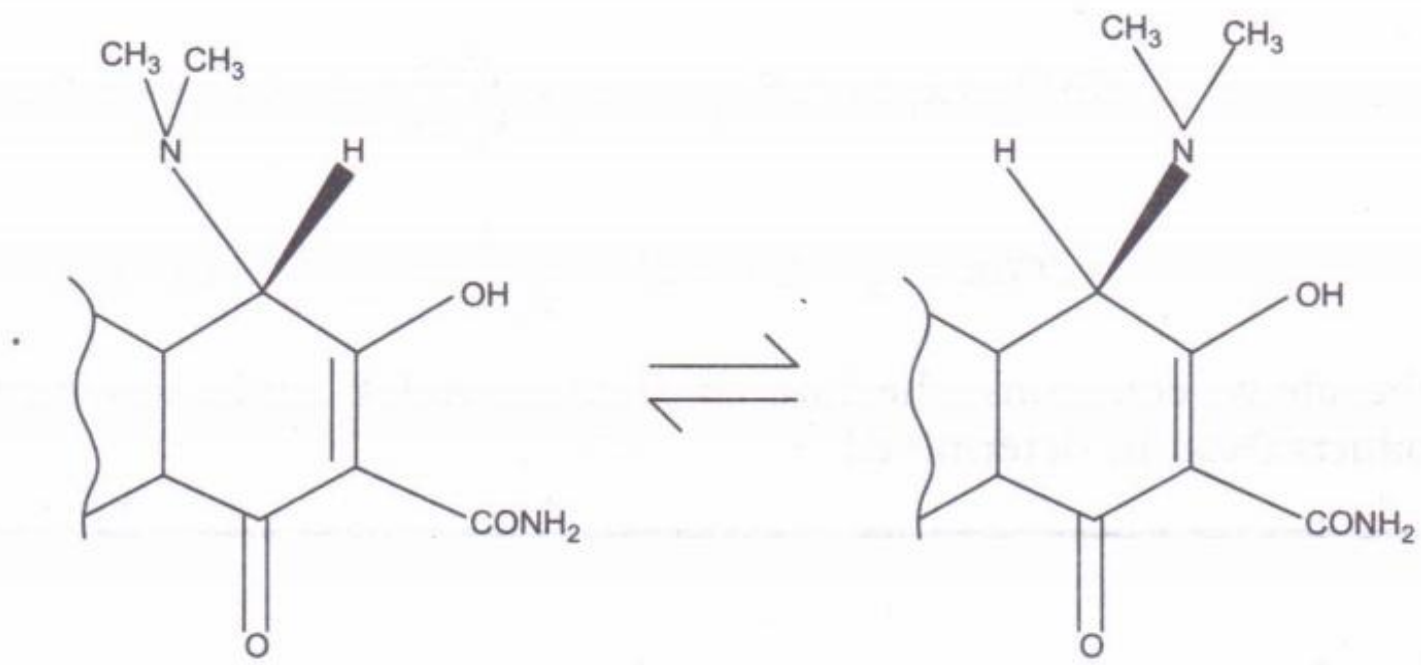
### *Example*

Reversible isomerization (epimerization) of tetracycline at a pH range of 2–6 forms epitetracycline, which shows much less therapeutic activity than the natural form.




A somewhat more complicated reversible reaction is one in which the forward reaction is of a first-order type and the reverse reaction of a second-order type, as demonstrated by the following reaction

$$A \underset{k^1}{\overset{k}{\rightleftharpoons}} B + C \tag{12.30}$$

When the forward and reverse reactions are both of the second-order type, the reaction takes on the following form:

$$A + B \underset{k^1}{\overset{k}{\rightleftharpoons}} C + D \tag{12.31}$$

Reversible reactions of this type are quite common, but usually, the reverse reaction is ignored because the concentration is not significantly affected. An example of this is expressed by the following reaction:

$$CH_3COOH + C_2H_5OH \rightleftharpoons CH_3COOC_2H_5 + H_2O \tag{12.32}$$

## Consecutive/Series Reactions

When the stages of a consecutive reaction occur at rates of about the same magnitude, each stage must be considered in the kinetics of the overall reaction. The simplest case is one in which both consecutive processes are of the first order, as illustrated by the following equation:

$$A \xrightarrow{k_2} B \xrightarrow{k_2} C \tag{12.33}$$

In the consecutive reaction, if $k_2$ is considerably greater than $k_1$, $B$ can be considered an unstable intermediate, and the rate-determining step for the overall reaction would be the conversion of $A$ to $B$. The overall reaction could then be treated by first-order kinetics. The rate of decomposition of such a reaction is given by the following equation:

$$-dA/dt = k_1 A \qquad A = A_0\, e^{-k_1 t} \tag{12.34}$$

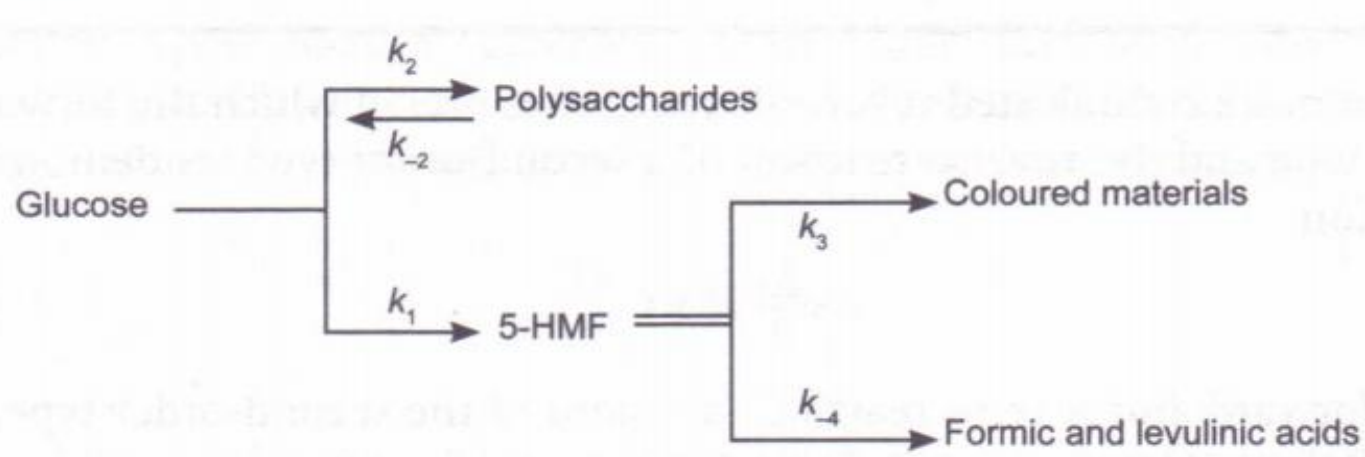
$$dB/dt = k_1A - k_2B \qquad B = \frac{A_0k_2}{k_2 - k_1}(e - k_1t - e - k_2t) \qquad (12.35)$$

$$-dC/dt = k_2B \quad C = A_0[1 + \frac{1}{k_1 - k_2}(k_2e^{-k_1t} - k_1e^{-k_2t})] \qquad (12.36)$$

Applying the above equations, the rate constant $k_1$ and $k_2$ and the concentration of breakdown products $C$ can be determined.

### *Example*

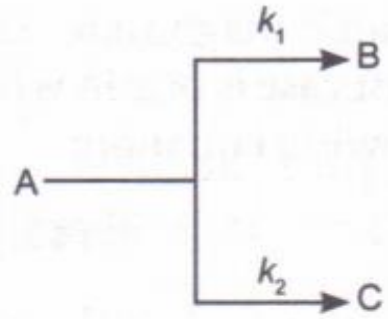
Degradation of glucose




Glucose is found to decompose by a first-order reaction. As glucose is depleted, the concentration of 5-hydroxymethylfurfural (5-HMF) increases rapidly in the beginning and then increases at a slower rate. The decomposition products of 5-HMF increase slowly at first and then increase at a greater rate. These later products are responsible for the discolouration of glucose solution when the solutions are sterilized at higher temperatures.

## Side/Parallel Reactions

In some processes, the reactant can degrade by two or more reactions occurring simultaneously, as depicted by the following equation:




The corresponding rate equation is

$$\frac{-dA}{dt} = k_1A + k_2A = kA \qquad (12.37)$$

$$A = A_0\,e^{-k_2t} \qquad (12.38)$$

The rate of formation of product B can be expressed as

$$\frac{-\mathrm{d}B}{\mathrm{d}t} = k_1 A + k_1 A_0 e^{-k_2 t} \tag{12.39}$$

The integration of these two equations gives

$$B = B_0 \frac{k_1}{k} A_0 (1 - e^{-kt}) \tag{12.40}$$

Here, $B_0$ is zero because the product is not formed before the reactant A begins to decompose. Therefore,

$$B = \frac{k_1}{k} A_0 (1 - e^{-kt}) \tag{12.41}$$

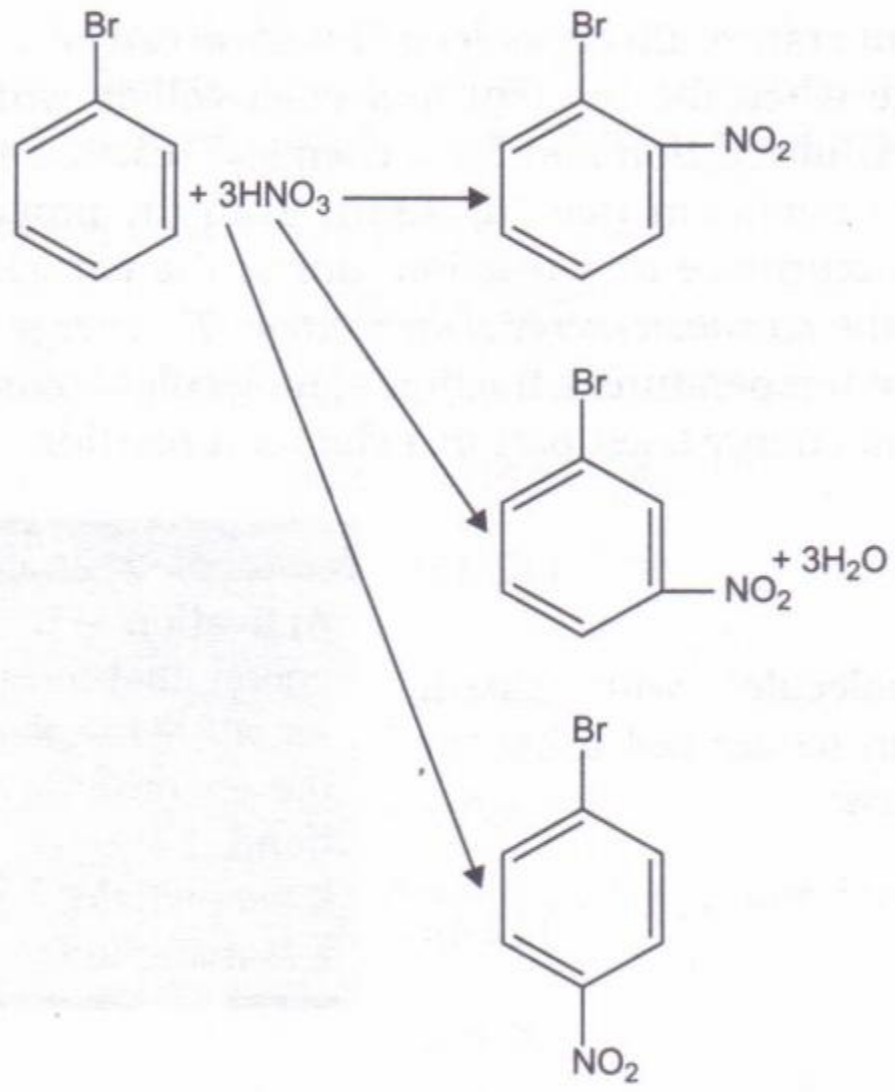
Similarly for product *C*

$$C = \frac{k_2}{k} A_0 (1 - e^{-kt}) \tag{12.42}$$

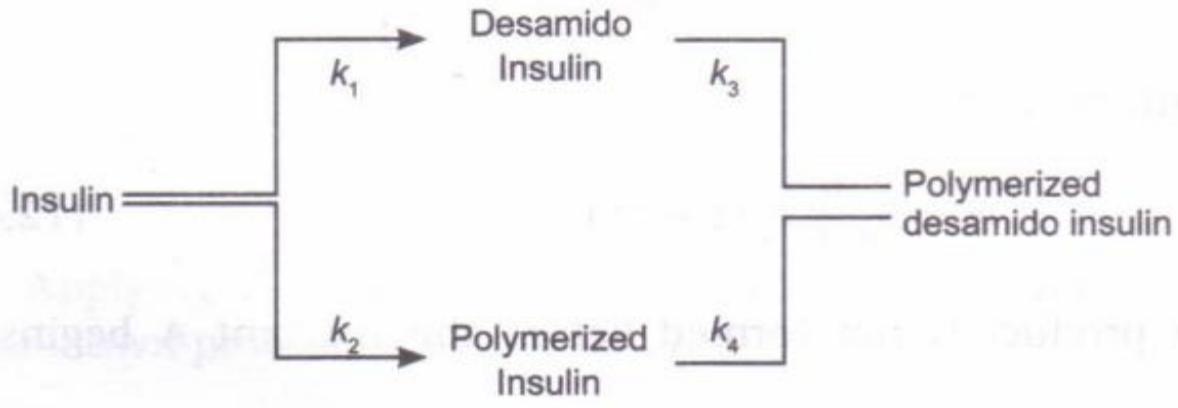
A plot of concentration B or C against $(1 - e^{-kt})$ should yield a straight line with slope equal to $\frac{k_1}{k} A_0$ or $\frac{k_2}{k} A_0$

## Examples

1. Nitration of bromobenzene to produce *ortho-*, *meta-* and *para*-nitrobenzene:



2. Deamidation and polymerization of insulin:




## FACTORS INFLUENCING REACTION RATES

### Temperature

According to rule-of-thumb methods, the rate of reaction is said to double for each 10°C increase in temperature. The manner in which temperature affects reaction rates may be understood by considering two theories: collision theory and transition-state theory.

**HIGHLIGHTS**

- Temperature
- Medium
  - Solvent
  - Ionic strength
  - Dielectric constant
- pH
- General acid–base catalysis

### *Collision theory*

The manner by which temperature affects molecular motion can be understood by considering that a reaction is possible when the reactant molecules collide with each other. Not every collision leads to a successful reaction and for a chemical reaction to occur the two species must collide in the right orientation (see Fig. 12.6). Even the proper orientation of species does not guarantee the occurrence of a reaction, unless the particles collide with a certain minimum energy, called the *activation energy of the reaction* ($E_a$, energy for bonds to break). The net result is that at a given temperature, a fraction of molecules having a given kinetic energy greater than the activation energy takes part in a chemical reaction.

$$F = \frac{N_i}{N_T} \tag{12.43}$$

The fraction of molecules with kinetic energies exceeding $E_a$ can be derived using the Boltzmann distribution law:

$$\frac{N_i}{N_T} = e^{-E_a/RT} \tag{12.44}$$

**HIGHLIGHTS**

**Activation Energy ($E_a$):** minimum energy that must be overcome in order for a chemical reaction to occur. It is the energy involved in the breaking of bonds.
If the particles collide with energy that is less than the $E_a$, no reaction will occur.

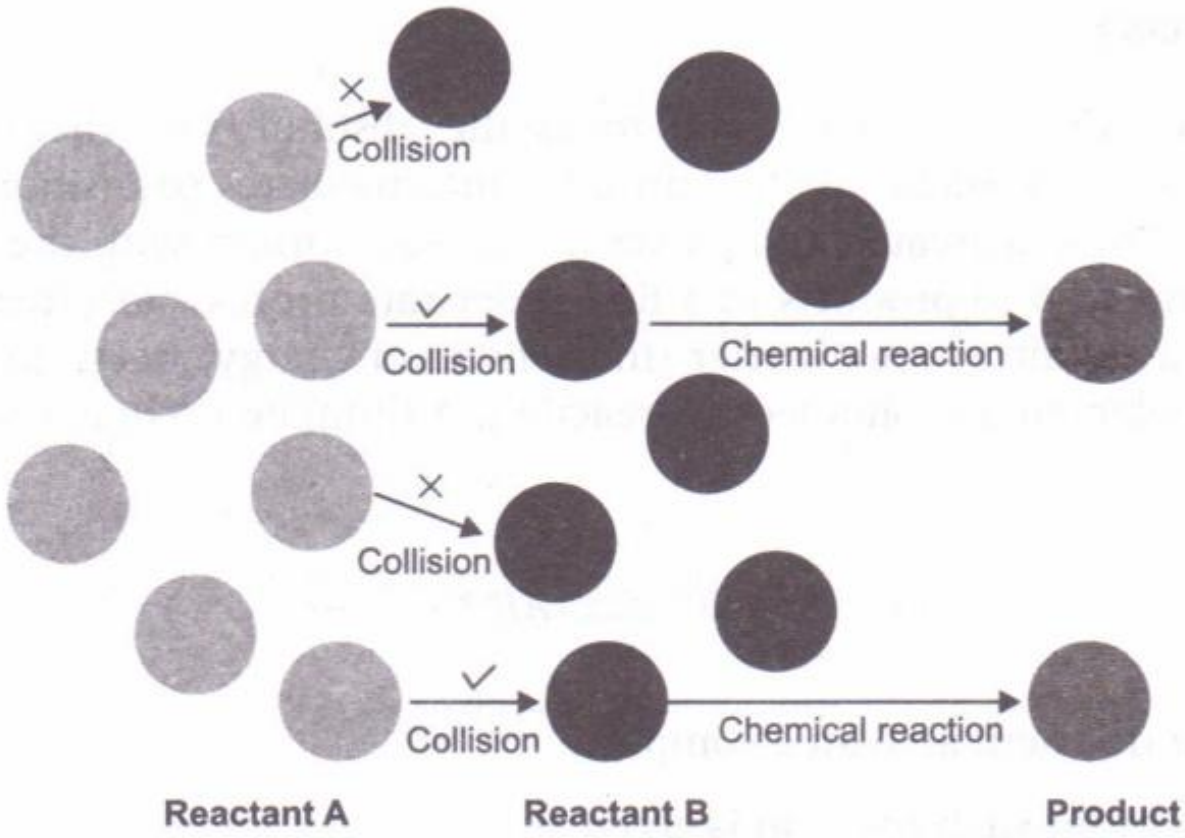



**Figure 12.6** Schematic representation of collision theory.

where $N_T$ is the total number of moles of a reactant and $N_i$, the moles having kinetic energy given by $E_a$.

Based on the collision theory, the rate of reaction depends on several variables:

1. $Z$, collision number (number of collisions per second per cubic centimeter) – a collision must occur between molecules for a reaction to occur.
2. $P$, probability factor (collision between molecules will lead to product) – since not every collision results in a chemical reaction.
3. $N_i$, (molecules having kinetic energy exceeding $E_a$)—molecules with kinetic energy exceeding the activation energy are involved in a chemical reaction.

Therefore, the rate can be expressed as follows:

$$\text{Rate} = PZN_i \tag{12.45}$$

Substituting the value of $N_i$ from Eq. (12.44), we get

$$\text{Rate} = (PZe^{-E_a/RT})N_T \tag{12.46}$$

Compared with the general rate law,

Rate = $k \times$ concentration of reactant

Concentration of reactant = $N_T$

Therefore,
$$k = PZe^{-E_a/RT} \tag{12.47}$$

Thus, collision theory interprets the Arrhenius frequency factor in terms of collision number and probability of collision (PZ).

$$A = PZ \tag{12.48}$$

### Transition-state theory

The transition-state theory, also referred to as the absolute rate theory, postulates that colliding molecules can combine to form unstable intermediates (transition state), known as *activated complexes*. These activated complexes are in equilibrium with the reactants and are spontaneously converted to products in a first-order rate process. In order for the activated complex to form, a certain energy barrier (the activation energy) needs to be overcome (see Fig. 12.7). For an elementary bimolecular reaction, a simplified scheme can be represented as follows:

$$A + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} (AB)^* \xrightarrow{k_3} C \tag{12.49}$$

where $(AB)^*$ is the transient activated complex.

Equilibrium constant for such reaction is given as

$$K^*_{AB} = \frac{k_1}{k_2} = \frac{[(AB)^*]}{[A][B]} \tag{12.50}$$

where $K^*_{AB}$ is the equilibrium constant.

Combined with the equilibrium assumption, the rate of the reaction can be written as follows:

$$\frac{\mathrm{d}[(AB)^*]}{\mathrm{d}t} = k_3[(AB)^*] \tag{12.51}$$

The transition-state theory assumes that the decomposition of the activated complex is the rate-determining step of the reaction and is given as follows:

$$k_3 = \frac{kT}{h} \tag{12.52}$$

where $h$ is the Planck constant and $k$ the Boltzman constant. Substituting Eq. (12.50) and Eq. (12. 52) into Eq. (12.51) yields

$$\frac{\mathrm{d}[(AB)^*]}{\mathrm{d}t} = \frac{kT}{h}[(AB)^*] = \frac{kT}{h}k^*_{AB}[A][B] \tag{12.53}$$

The thermodynamic relationship between the standard free energy change and the equilibrium constant of the activated complex is given as follows:

$$\Delta G^* = -RT \ln K^*_{\mathrm{AB}} = \Delta H^* - T\Delta S^* \tag{12.54}$$

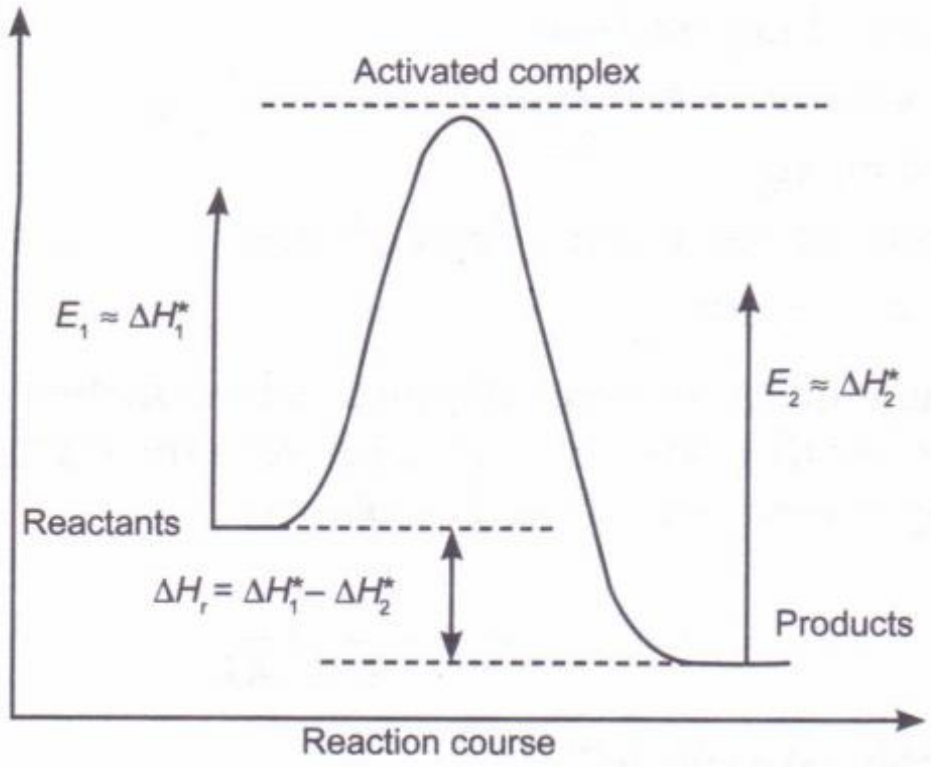



**Figure 12.7** Schematic diagram of the transition state for an exothermic reaction.

or

$$K_{AB}^* = \exp(-\Delta G^*/RT) = \exp(-\Delta H^*/RT)\exp(\Delta S^*/R) \tag{12.55}$$

Substituting Eq. (12.56) into Eq. (12.54) gives

$$\frac{d[(AB)^*]}{dt} = \frac{kT}{h} e^{-\Delta H^*/RT} e^{\Delta S^*/R}[A][B] \tag{12.56}$$

The term $e^{\Delta S^*/R}$ in Eq. (12.57) is less sensitive to the temperature effects and thus the rate constant $k$ for Eq. (12.57) is

$$k_1, k_2 \text{ or } k_3 = \frac{kT}{h} e^{-\Delta H^*/RT} e^{\Delta S^*/R} \propto \frac{kT}{h} e^{-\Delta H^*/RT} \propto Te^{-\Delta H^*/RT} \tag{12.57}$$

The enthalpy of activation is directly related to the Arrhenius activation energy.

$$E = \Delta H^* + RT \tag{12.58}$$

The difference between $E$ and $\Delta H^*$ is very small, and $\Delta H^*$ is replaced by $E$. Thus, Eq. (12.58) approximates to

$$k_1, k_2 \text{ or } k_3 \propto Te^{-E/RT} \tag{12.59}$$

### *Influence of temperature*

Based on the collision theory and the transition-state theory, the Arrhenius expression can be derived to account for the temperature dependence of the rate constant:

$$k = Ae^{-E_a/RT} \tag{12.60}$$

where $k$ = specific rate of degradation
$A$ = frequency factor or Arrhenius factor
$E_a$ = activation energy
$R$ = gas constant (1.987 calories degree$^{-1}$ mol$^{-1}$)
$T$ = absolute temperature

The constant of integration ($A$) or frequency factor in the Arrhenius equation is a measure of the frequency of collisions that can be expected between the reacting molecules for a given reaction. Logarithmically, it may be expressed as follows:

$$\log k = \log A - \frac{E_a}{2.303RT} \tag{12.61}$$

where log $A$ can be considered a constant.

In general, increase in temperature increases the collision frequency, which in turn increases the number of energetic particles that take part in a chemical reaction. The influence of temperature on the rate of reaction is depicted in Figure 12.8.

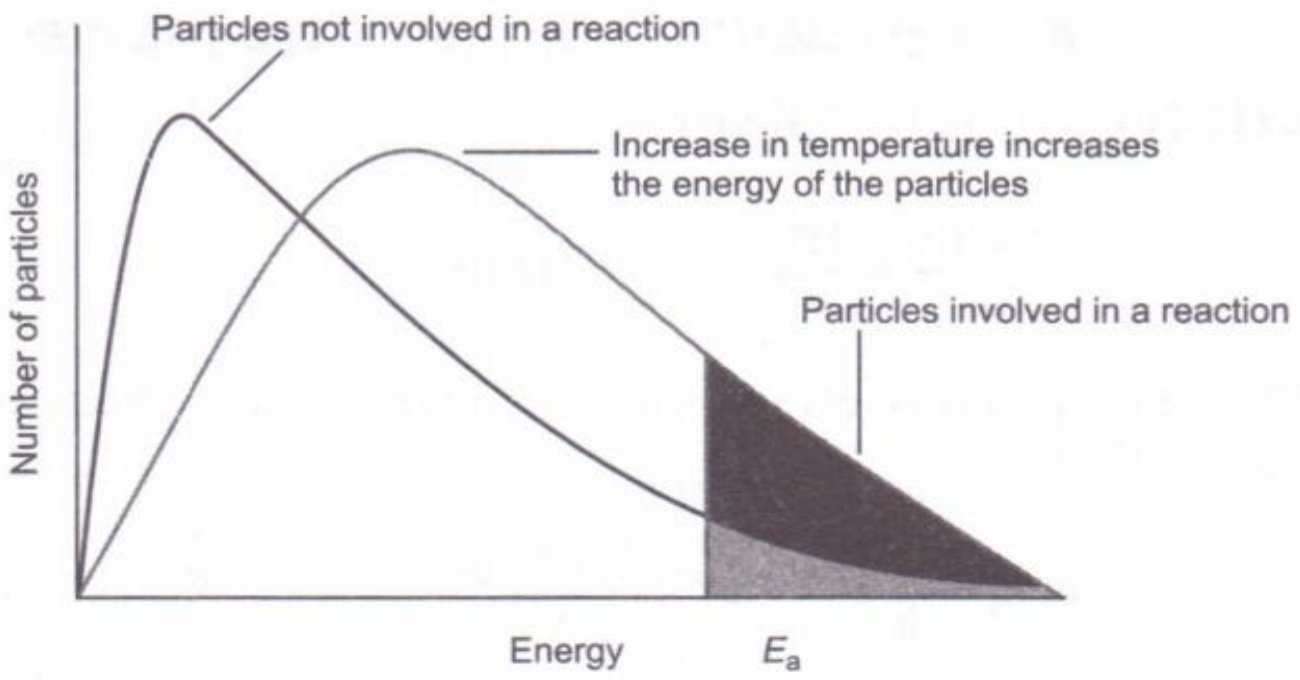



**Figure 12.8** Maxwell–Boltzmann Distribution.

Note: Majority of the particles do not have enough energy to react when they collide (light green). Increase in temperature changes the shape of the graph (red to blue) and increases the number of energetic particles (dark green).

## Calculation of $E_a$

### Method 1

From Eq. (12.62), a plot of log $k$ versus $1/T$ yields a slope equal to $-E_a/2.303R$, from which the value for the activation energy can be calculated (see Fig. 12.9).

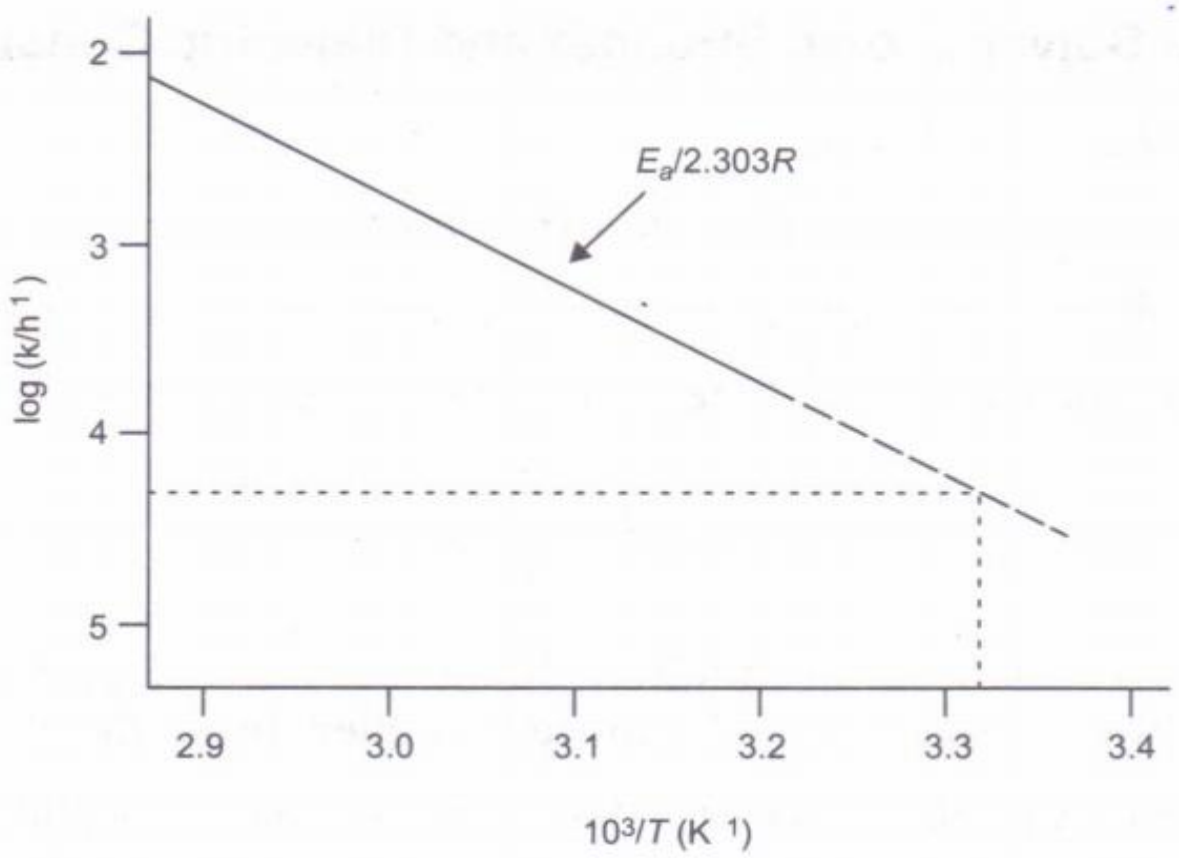



**Figure 12.9** Dependence of reaction rate on temperature.

### *Method 2*

$E_a$ can also be obtained by determining $k$ at two different temperatures ($T_1$ and $T_2$).

Upon integration of Eq. (12.62), between the limits $k_1$ and $k_2$ and $T_1$ and $T_2$, the following equation results:

$$\log\left[\frac{k_2}{k_1}\right] = \frac{E_a}{2.303R}\frac{T_2 - T_1}{T_2 T_1} \qquad (12.62)$$

**HIGHLIGHTS**

The *transition state theory* provides a better explanation of chemical reactivity and it accounts for the influences on reaction rate by various medium factors, such as *solvent, ionic strength* and *dielectric constant*.

### *Example 12.2 (Calculation of $E_a$)*

The rate constant for decomposition of drug at 393 K (120°C) is 1.173 $h^{-1}$ (or $3.258 \times 10^{-4}$ $s^{-1}$) and 413 K (140°C) is 4.860 $h^{-1}$. Calculate activation energy in kcal/mole and the frequency factor for the breakdown of drug within this temperature range.

### *Solution*

Based on Eq. (12.63), we obtain

$$\log\left(\frac{4.860}{1.173}\right) = \frac{E_a\,(413 - 393)}{(2.303 \times 1.987 \times 413 \times 393)}$$

$$E_a = 23 \text{ kcal/mole}$$

At 120°C, using Eq. (12.62), we obtain

$$\log\,(3.258 \times 10^{-4}) = \log A - \left\{\frac{23000}{(2.303 \times 1.987 \times 393)}\right\}$$

$$A = 2 \times 10^9 \text{ s}^{-1}$$

## Medium Effects: Solvent, Ionic Strength and Dielectric Constant

Based on the transition-state theory:

$$A + B \rightarrow [A\cdots B]^* \rightarrow \text{Product}$$

Solutions are ordinarily non-ideal; therefore, activity coefficients are included.

Rate constant for such a reaction in terms of activity coefficient is as follows:

$$k = k_0\left(\frac{\gamma_A \gamma_B}{\gamma^*}\right) \tag{12.63}$$

where $k_0$ is the rate constant in an infinitely dilute solution and $\gamma_A$, $\gamma_B$ and $\gamma^*$ are activity coefficients of reactant A, reactant B and activated complex, respectively.

When the solution is ideal, the activity coefficients become unity and $k = k_0$.

Eq. (12.64) can be written in logarithmic form as:

$$\log k = \log k_0 + \log \gamma_A + \log \gamma_B - \log \gamma^* \tag{12.64}$$

Using Eq. (12.65), the influence of solvent, ionic strength and dielectric constant on rate of reaction could be studied.

### *Solvent*

The activity coefficient of the non-electrolytic solute in a dilute solution is given by the following expression:

$$\log \gamma = \frac{V}{2.303RT}(\Delta S) \tag{12.65}$$

where $V$ is the molar volume of the solute and $\Delta S$ is the difference in the solubility parameters of solvent and solute.

Substituting Eq. (12.65) for activity coefficients in Eq. (12.64) gives:

$$\log k = \log k_0 + \frac{V}{2.303RT}(\Delta S_A + \Delta S_B - \Delta S^*) \tag{12.66}$$

where $\Delta S_A$, $\Delta S_B$ and $\Delta S^*$ are differences in the solubility parameter of solvent and reactant A, reactant B and activated complex, respectively.

Based on the above equation, the following can be derived:

- If the polarity of the product is similar to that of the solvent, the value is positive and the rate will be large in this solvent.
- If the polarity of the reactant is similar to that of the solvent, the value is negative and the rate will be small in this solvent.

In other terms, a polar solvent tends to increase the rate of those reactions where the product formed is more polar than the reactants. If on the other hand, the products are less polar than the reactants, the polar solvents tend to decrease the rate of such reactions.

### *Ionic strength*

According to Debye Huckel equation, the activity coefficient of an ion in a dilute aqueous solution is:

$$\log \gamma = 0.51 Z^2 \sqrt{\mu} \tag{12.67}$$

where $z$ is charge on ion and $\mu$ is the ionic strength.

Substituting Eq. (12.68) for the activity coefficients in Eq. (12.65), gives:

$$\log k = \log k_0 + 1.02\, Z_A Z_B \sqrt{u} \tag{12.68}$$

where $Z_A + Z_B$ are the charges carried by the reacting species in solution, $u$ the ionic strength, $k$ the rate constant of degradation and $k_0$ the rate constant at infinite dilution. Plotting the logarithm of the reaction rates versus the square root of the ionic strength, as illustrated in Figure 12.10, one can determine whether an increase in ionic strength increases, reduces or has no effect on the reaction rate.

Based on the above equation and graph:

- If one of the reactants is a neutral molecule ($Z_A Z_B = 0$), the rate of reaction is independent of ionic strength (i.e. changes in ionic strength by the addition of a salt would have no effect on the rate of reaction (constant slope as shown by curve 2, Fig. 12.10)).
- If the reaction is between similar charge ions (both either + or –),then an increase in ionic strength caused by the addition of a salt increases the rate of reaction (positive slope as shown by curve 1, Fig. 12.10).
- If the reaction is between oppositely charged ions (+ and –, or – and +), then an increase in ionic strength caused by the addition of a salt decreases the rate of reaction (negative slope as shown by curve 3, Fig. 12.10).

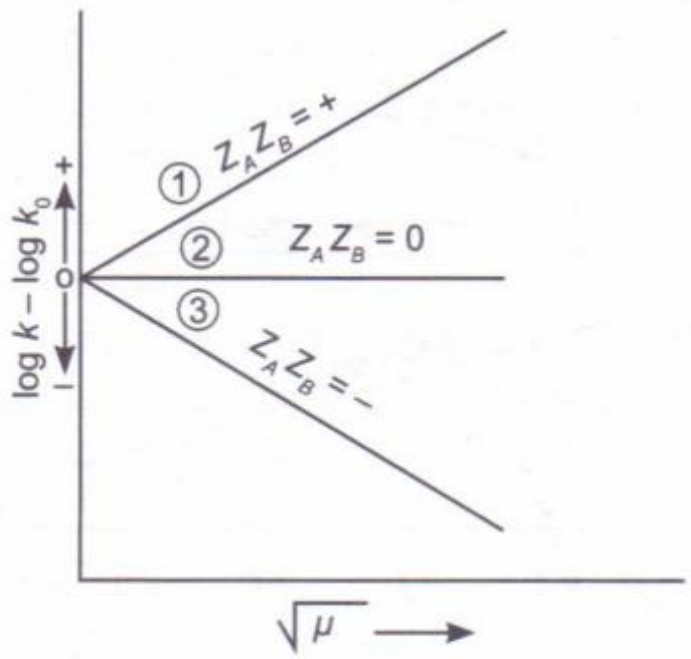



**Figure 12.10** Dependence of reaction rates on ionic strength.

### *Dielectric constant*

The dielectric constant (or relative permittivity) of a solvent is a measure of its polarity. Water has a high dielectric constant (~78 at room temperature); other solvents have much lower values (e.g. ~24 for ethanol). The following equation describes the effect of the dielectric constant, ε, on the rate constant of an ionic reaction:

$$\log k = \log k_{\varepsilon=\infty} - KZ_A Z_B/\varepsilon \qquad (12.69)$$

where $K$ is a constant for a particular reaction at a given temperature, $Z_A$ and $Z_B$ are the charge numbers of the two interacting ions.

Plotting log $k$ against the reciprocal of the dielectric constant of the solvent, as illustrated in Figure 12.11, can determine whether an increase in dielectric constant increases, reduces or has no effect on the reaction rate. Such a plot, according to Eq. (12.70), should yield a straight line with a positive slope for reactants of oppositely charged reactants (as $\varepsilon$ increases (right to left) for oppositely charged reactants, the slope becomes negative but since the graph is between log $k$ and $1/\varepsilon$, it appears positive) and a negative slope for similar charge reactants.

Based on the above equation and graph:

- If the reaction is between similarly charged ions (+ and +, or – and –), then a decrease in dielectric constant of the solvent decreases the rate of reaction (negative slope as shown by curve 3, Fig. 12.11).
- If the reaction is between oppositely charged ions (+ and –, or – and +), then a decrease in dielectric constant of the solvent causes an increase in the rate of reaction (positive slope as shown by curve 1, Fig.12.11).

In other words, if the reacting ions are of opposite charges, then the choice of a nonpolar solvent will result in the increase in rate of reaction. If the reacting ions are of similar charge, then the replacement of water with a solvent of lower dielectric constant will decrease the reaction rate. The particular solvent chosen to replace water must be nontoxic and alcohol–water or propylene glycol–water mixtures may be suitable for this purpose.

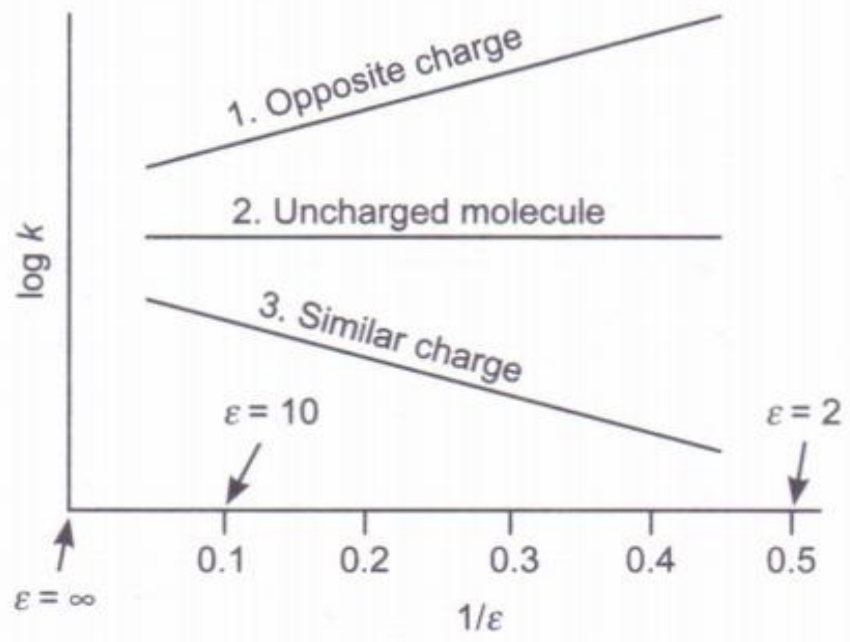



**Figure 12.11** Influence of dielectric constant on the rate constant for reactions between ions of different charges.

## pH-Specific Acid–Base Catalysis

In an aqueous environment, the decomposition of a number of drugs via hydrolysis occurs much more rapidly than that in the solid state, especially in the presence of hydrogen or hydroxyl ions. When the rate of reaction is expressed in an equation containing the hydrogen or hydroxyl ion terms, this reaction is called an *acid–base catalyzed hydrolysis*. The magnitude of the rate of acid–base catalyzed hydrolysis can vary considerably with pH. Hydrogen ion catalysis predominates at the lower pH range, whereas hydroxyl ion catalyzes at the higher pH range. At the intermediate pH range, the rate can be independent of pH or catalyzed by both hydrogen and hydroxyl ions.

When a drug compound decomposes by acid–base catalysis, the schematic process is as follows:

For specific acid catalysis $A + H^+ \xrightarrow{k_+} P$

For specific base catalysis $A + OH^- \xrightarrow{k_-} P$

For non catalysis (solvent) $A + H_2O \xrightarrow{k_0} P$

The overall rate expression is given as follows:

$$-\frac{d[A]}{dt} = k_+[H^+][A] + k_-[OH^-]A + k_0[A] = [A](k_+[H^+] + k_-[OH^-]) + k_0) \qquad (12.70)$$

For a given pH, the rate equation is as follows:

$$-\frac{d[A]}{dt} = k_{obs}[A] \qquad (12.71)$$

$$k_{obs} = k_+[H^+] + k_-[OH^-] + k_o \qquad (12.72)$$

To determine the influence of pH on the rate of reaction, the decomposition is measured at several hydrogen ion concentrations. Figure 12.12 illustrates the pH rate profile for the specific acid–base catalyzed hydrolysis. As pH increases from 1 to 7 (hydrogen concentration decreases), the rate of hydrolysis decreases. The term $k$ [$H^+$] is a dominating factor and is much larger than the sum of $k$ [$OH^-$] and $k_0$. A further decrease in hydrogen ion concentration results in a linear increase in the rate of hydrolysis since the term $k$ [$OH^-$] then influences most of the hydrolysis. Near pH 7, the minimum rate of hydrolysis occurs. This point of inflection is known as the *pH of optimum stability*. Either hydrogen or hydroxyl ions do not participate in the hydrolysis and the solvent (i.e., water) is responsible for hydrolysis. Knowledge of this point is extremely useful in the development of a stable dosage form, provided the pH is within safe physiologic limits.

It is clear from Figure 12.12 that the degradation of the drug is catalyzed by both the acid and base, which have slopes of –1 and +1, respectively.

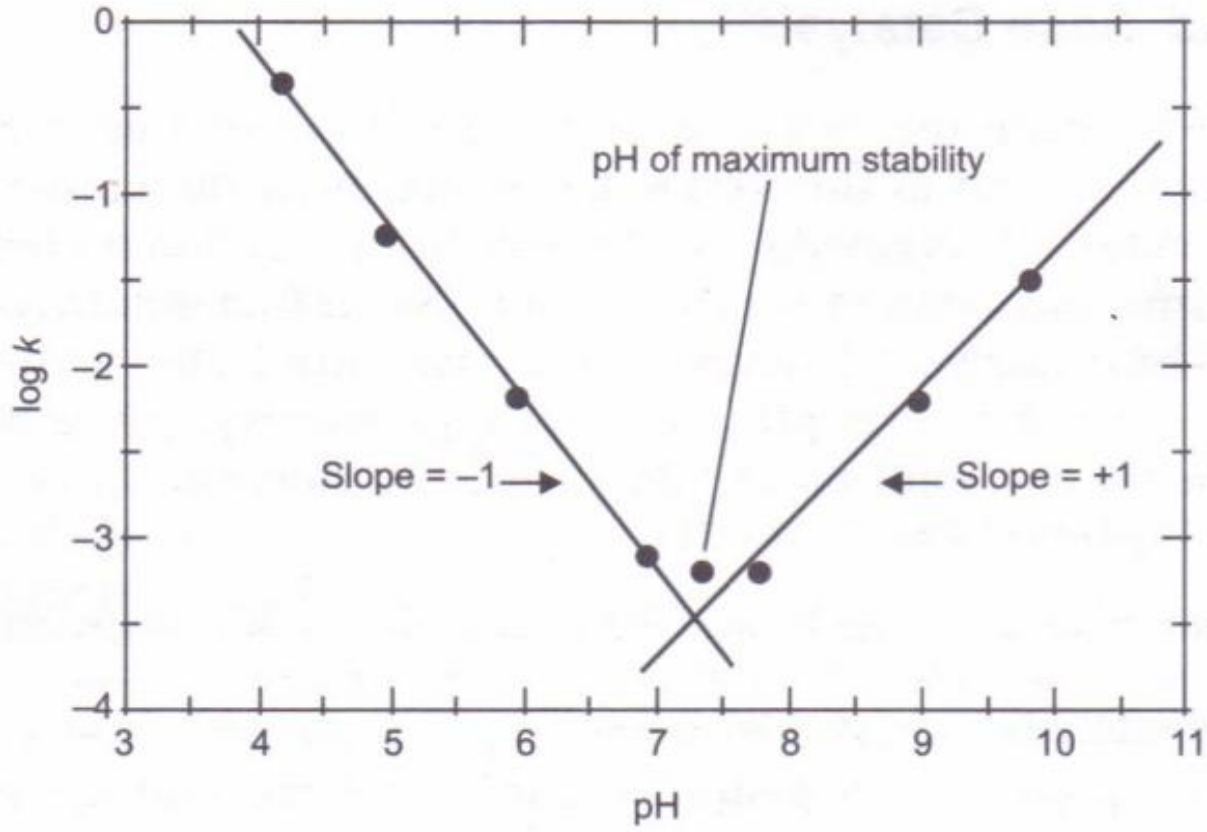



**Figure 12.12** pH rate constant profile for the specific acid–base catalyzed hydrolysis.

## General Acid–Base Catalysis

Buffer salts are commonly used in the formulation of pharmaceutical liquids to regulate the pH of the solution. Although these salts tend to maintain the pH of the solution at a constant level, they can also catalyze the degradation; the process is called *general acid–base catalyzed hydrolysis*. Therefore, it is necessary to evaluate the effect of buffer concentration on the stability of the preparation in addition to the effect of hydrogen and hydroxyl ion concentrations. Common buffer salts such as acetate, phosphate, and borate have been found to have catalytic effects on the degradation rate of drugs in solution. For example, the active ingredient in a solution prepared with acetate buffer may undergo hydrolysis due to acetic acid and acetate species as well as the hydrogen and hydroxyl ions. The rate equation for this case is as follows:

$$-\frac{d[A]}{dt} = k_+[H^+][A] + k_0[A] + k_-[OH^-][A] + k_{HA}[HA][A] + k_A[Ac^-][A] \quad (12.73)$$

$$k_{obs} = k_+[H^+] + k_0 + k_-[OH^-] + k_{HA}[HA] + k_A[Ac^-] \quad (12.74)$$

where $k_{HA}$ and $k_A$ are the rate constants of acetic acid (HA) and acetate ($Ac^-$), respectively.

# DECOMPOSITION AND STABILIZATION OF PHARMACEUTICALS

## Degradative Pathways

Decomposition of active ingredients in liquid, semisolid and solid dosage forms can occur through hydrolysis, oxidation–reduction, racemization, decarboxylation, ring cleavage and photolysis.

## Hydrolysis

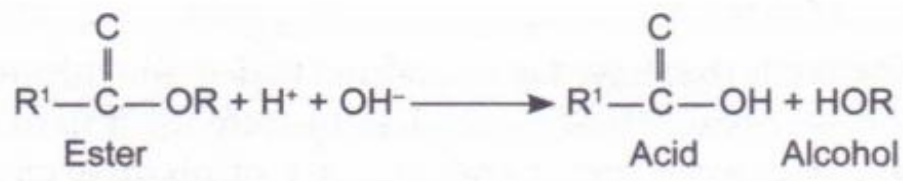
The term *hydrolysis* describes a chemical reaction in which a chemical bond is split via the addition of water. Drugs substances having ester and amide labile groups in their molecular structure degrade via hydrolysis in the presence of water. The degradation process by hydrolysis accelerates in the presence of hydrogen or hydroxyl ions, and hydrolytic reactions involve nucleophilic attack of the labile groups.

### *Ester hydrolysis*

The hydrolysis of an ester into a mixture of an acid and alcohol essentially involves the rupture of a covalent linkage between a carbon atom and an oxygen atom. Although hydrolysis can be affected in pure water, in the majority of cases, the presence of a catalyst such as mineral acids, alkalies or certain enzymes, all of which are capable of supplying hydrogen or hydroxyl ions, is needed to promote the reaction. The acid hydrolysis of an ester does not differ essentially from an alkali-catalyzed hydrolysis, except that it is reversible. On the other hand, the alkali-catalyzed hydrolysis of esters is irreversible.

For both the acid- and alkali-catalyzed hydrolysis, it is evident that the ester is cleaved at the acyl-oxygen linkage (i.e., between the oxygen of $C_2H_5(O—C_2H_5)$ and the carbonyl carbon $\left(\begin{matrix}O\\\|\\C\end{matrix}\right)$ This type of cleavage takes place for most ester hydrolytic reactions.

In practice, the general scheme employed to denote ester hydrolysis is as follows:



The general form of kinetic equations to express acid- or alkali-catalyzed hydrolysis is as follows:

$$\frac{d(\text{ester})}{dt} = -k(\text{ester})(H^+) \tag{12.75}$$

$$\frac{d(\text{ester})}{dt} = -k(\text{ester})(OH^-) \tag{12.76}$$

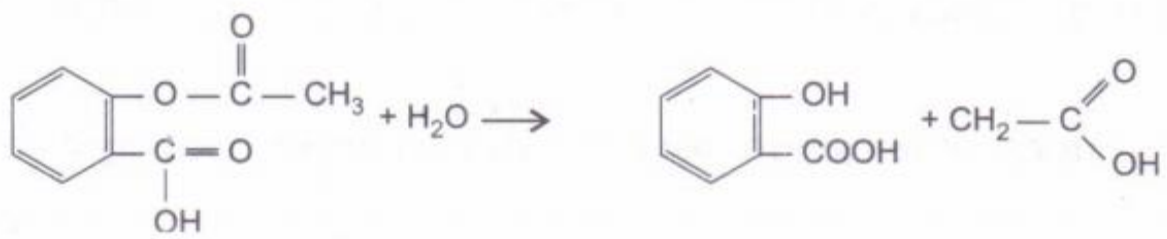
These equations denote second-order reactions, but in studying degradation reactions of this type, it is possible to treat them as pseudo-first-order reactions. This is done by keeping the $OH^-$ or $H^+$ at a considerably higher concentration than the ester concentration or by keeping the $H^+$ or $OH^-$ concentrations essentially constant using buffers. This would cause the previous equation to reduce to:

$$\frac{d(\text{ester})}{dt} = -k(\text{ester}) \tag{12.77}$$

which represents a kinetic expression for a first-order reaction. Whenever possible, first-order kinetic expressions have been employed in the study of degradation of drugs by ester hydrolysis, but at times, second-order kinetic expressions have also been employed.

### *Example: Degradation of aspirin*

Although the hydrolysis of aspirin proceeds through a complex mechanism, the use of pseudo-first-order kinetics is sufficient to define and study the degradation of aspirin. The marked instability of aspirin is due to two structural features: one, that it is an aromatic ester and is therefore more labile than an aliphatic ester and two, the ortho relationship of the acetoxy group to the carboxylate. Owing to this proximity, aspirin is prone to ester hydrolysis.

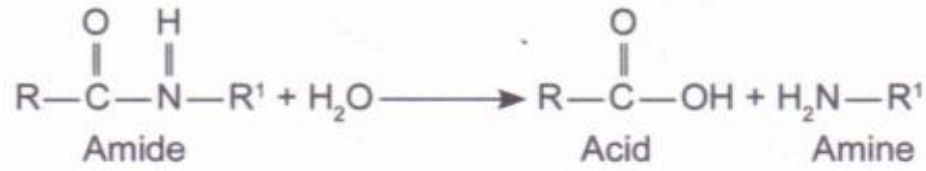



Other pharmaceutical materials that have been reported to degrade through ester hydrolysis are atropine, procaine and methyl p-amino-benzoate. These examples illustrate the importance of chemical kinetic studies in evaluating the degradative pathways and overall stability of pharmaceutical compounds containing an ester group in the molecule.

## Amide hydrolysis

Pharmaceutical compounds containing an amide group can undergo hydrolysis in a manner similar to that of an ester-type compound. Instead of the acid and alcohol that form because

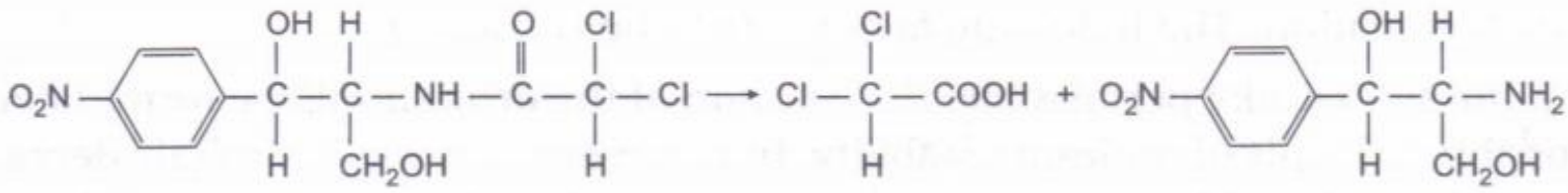
of ester hydrolysis, hydrolytic cleavage of an amide results in the formation of an acid and an amine. Owing to lesser electrophilicity of the carbon–nitrogen bond, amides are less susceptible than esters to hydrolysis. The amide group is hydrolyzed as follows:




Pharmaceuticals such as barbiturates, chloramphenicol, niacinamide, salicylamide and phenethicillin degrade by amide hydrolysis.

### *Example: Degradation of chloramphenicol*

Amide bonds in chloramphenicol undergo hydrolysis to liberate dichloroacetic acid and the primary amine.

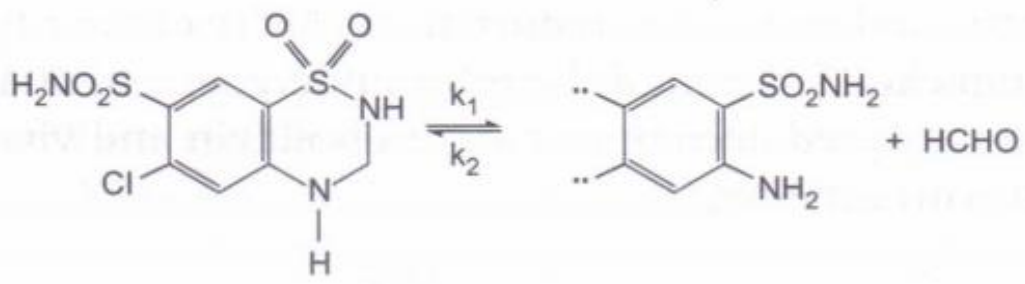



## Ring alteration

A hydrolytic reaction can proceed as a result of ring cleavage with subsequent attack by hydrogen or hydroxyl ion. Examples of drugs that have been reported to undergo hydrolysis by this mechanism include hydrochlorothiazide, pilocarpine and reserpine.

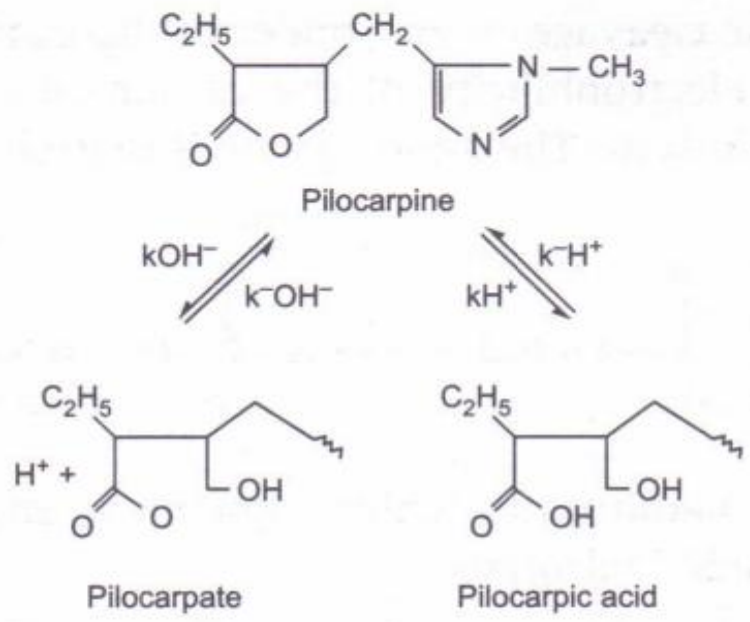
### *Example: Degradation of hydrochlorothiazide*

The hydrolysis of hydrochlorothiazide proceeds by ring opening to form an imine, which undergoes attack by water or hydroxide ion to yield a carbinolamine intermediate, which further decomposes to formaldehyde and 4-amino-6-chloro-m-benzenedisul-fonamide.




### *Example: Degradation of pilocarpine*

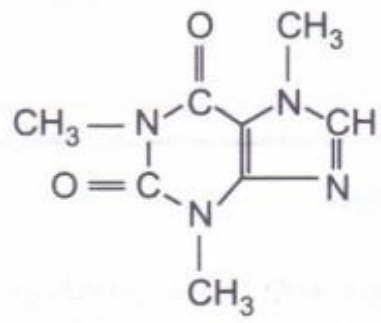
The hydrolysis of pilocarpine in an aqueous solution involves a cyclic equilibrium process catalyzed by hydroxyl ion and hydrogen ion, resulting in the formation of pilocarpate and pilocarpic acid.




### *Protection from hydrolysis*

Owing to the realization that a considerable number of drugs degrade through hydrolysis, further in-depth studies are required to enhance the stability of pharmaceuticals undergoing this type of degradation. The following factors are to be considered:

1. **pH:** If physiologically permissible, the solution of the drug should be formulated as close as possible to its pH of optimum stability. In the event that the hydrolytic degradation of the drug is catalyzed by the acid and basic species of the buffer salt in addition to $H^+$ and $OH^-$, the buffer concentration should be kept at a minimum.
2. **Type of solvent:** Partial or full replacement of water with a solvent of lower dielectric constant generally causes a considerable decrease in the rate of hydrolysis. Examples of these nonaqueous solvents are ethanol, glycols, glucose and mannitol solutions and substituted amides. The use of propylene glycol was found to retard the amide hydrolysis of pentobarbital.
3. **Complexation:** The hydrolytic rates may be influenced in two ways by complex formation, namely, by either polar or stearic effects.
   For example, the attachment of a large caffeine molecule on a benzocaine molecule can greatly affect the frequency and ease of encounter of the ester with various catalytic species ($H^+$, $OH^-$) through stearic hindrance. The reaction may also be affected by the electronic influence of the complexing agent, which can alter the affinity of the ester carbonyl ion for the catalytic species. Caffeine complexes with local anaesthetics, such as benzocaine, procaine and tetracaine, reduce the velocity of their hydrolytic degradation. In some cases, complexed fraction of the ester undergoes essentially no degradation. In another case, base-catalyzed decomposition of riboflavin and vitamin was decreased in a complexed form with caffeine.




Caffeine

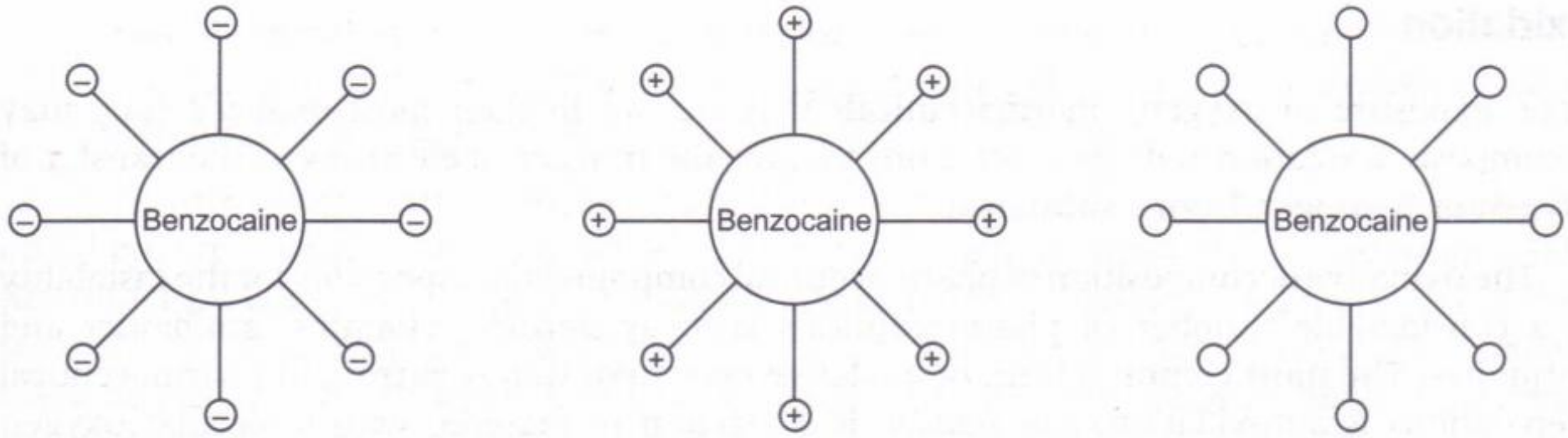



**Figure 12.13** Effect of surfactants on stabilization of benzocaine.

4. **Surfactants:** Anionic, cationic and nonionic surfactants also stabilize the drug against base catalysis (see Fig. 12.13). The use of anionic surfactant (5% solution of sodium lauryl sulfate) causes an 18-fold increase in the half-life of benzocaine. The anionic head group of the surfactant made a barrier to the approach of the hydroxyl group into the micelle and attack on the ester linkage. The cationic surfactant (2.46% solution of cetrimide) causes a 10-fold increase in the half-life of benzocaine. The negatively charged hydroxyl ion is attracted by cationic group of surfactant and therefore is unavailable to penetrate into micelles wherein the benzocaine is present.
   When a nonionic surfactant (3.3% solution) is used, only about a 4- to 5-fold increase in half-life was obtained for benzocaine, indicating that the nonionic surfactant is a less effective stabilizer than the anionic or cationic ones. The relatively high degree of hydration at the surface of the nonionic surfactant micelle could result in considerable hydrolytic attack within the micelle as well as in the aqueous phase.
5. **Modification of chemical structure:** Certain substituents added to the alkyl or acyl chain of aliphatic or aromatic esters cause a decrease in the hydrolytic rate due to stearic and/or polar effect. By increasing the length, or by branching, the acyl or alkyl chain, the rate of hydrolysis of the ester usually decreases. For example, the dipivalate ester of epinephrine helps protect the catechol ring from undergoing oxidation, thus enhancing the stability of the topical ophthalmic solution of epinephrine.
6. **Transient derivatives:** The stability of pharmaceuticals undergoing degradation through hydrolysis could be improved by reducing their solubility by forming less-soluble salts or esters of the drug. Transient derivatives are nontoxic additions to drug molecules, such as hydrolyzable esters, which remain intact long enough to improve the drug bioavailability and then undergo biotransformation or hydrolysis at physiologic pH to yield the active form of the drug. Monoesters of the antibiotics lincomycin and clindamycin have been prepared to render soluble and stable compounds suitable for injection. At pH 7.4, the antibiotics undergo biomodification to yield the active forms.

## Oxidation

Upon exposure to oxygen, pharmaceuticals that are not in their most oxidized state may decompose. Oxidation/reduction reactions involve the transfer of electrons or the transfer of oxygen or hydrogen from a substance.

The oxidative decomposition of pharmaceutical compounds is responsible for the instability of a considerable number of pharmaceuticals such as steroids, vitamins, antibiotics and hormones. The most common form of oxidative decomposition occurring in pharmaceutical preparations is autoxidation. *Autoxidation* is a reaction of material with molecular oxygen that occurs spontaneously and involves a free radical chain process. The autoxidation of an organic substance RH by a free radical chain process can be simply described as follows:

### *Initiation*

$$RH \xrightarrow[light,\ heat]{activation} R\bullet + (H)$$

### *Propagation*

$$R\bullet + O_2 \rightarrow RO_2$$

$$RO_2\bullet + RH \rightarrow ROOH + R\bullet$$

### *Hydroperoxide decomposition*

$$ROOH \rightarrow RO\bullet + \bullet OH$$

### *Termination*

$$RO_2\bullet + X \rightarrow \text{inactive products}$$

$$RO_2 + RO_2 \rightarrow \text{inactive products}$$

In an autoxidation process, free radicals, formed by thermal or photolytic cleavage of chemical bonds (e.g. peroxide, ROOH) or redox processes with metal ions present in raw material impurities, are involved. These radicals are highly unsaturated and readily take electrons from other substances, causing oxidation.

1. Heavy metals, particularly those possessing two or more valency states, with a suitable oxidation–reduction potential between them (copper, iron, cobalt and nickel) generally catalyze oxidative deteriorations. These metals reduce the duration of the induction period (the time in which no measurable oxidation occurs) and increase the maximum rate of oxidation.
2. Oxidation reactions are also catalyzed by hydrogen and hydroxyl ions. This can partly be ascribed to the fact that the redox potential for many reactions depends on pH.
3. Temperature, directly or indirectly, affects the rate of the reaction for an oxidation. For example, the transfer of a product from storage at 15–5°C causes the rate to be reduced

to half its initial magnitude, owing to the direct temperature dependence of the reaction. Simultaneously, the concentration of oxygen increases by about 25%, usually resulting in an increased rate of oxidation.

In autoxidative reactions, only a small amount of oxygen is needed to initiate the reaction, and thereafter, oxygen concentration is relatively unimportant. Most of these reactions follow first-order kinetic expressions but because of the complexity of oxidative processes and their sensitivity to trace metal and other impurities, it is difficult to reproduce them and to establish mechanisms for the reactions. Examples of drugs that degrade through oxidative pathways are given in Table 12.2.

**Table 12.2** Drugs susceptible to oxidation

| Drugs/Excipients | Functional Group |
|---|---|
| Amyl nitrite | Nitrites |
| Chlorpromazine | Thioethers |
| Clozapine | Amines |
| Diethyl ether | Ethers |
| Dimercaprol | Thiols |
| Fatty acids | Carboxylic acids |
| Morphine | Phenols |
| Paraldehyde, flavor | Aldehydes |
| Vitamin A | Conjugated Dienes |

*Rancidity,* which can affect nearly all oils and fats, is a widely known term covering many typical off-flavours formed by the autoxidation of unsaturated fatty acids present in an oil or fat. These off-flavours have a more or less distinct odour, which is due to the volatile compounds that are formed upon oxidation of the oils and fats. These volatile compounds are generally short-chain monomers that are formed by the cleavage of the nonvolatile hydroperoxide primary oxidation product. The free radical mechanism shown here depicts the oxidation of oils and fats that takes place in the presence of atmospheric oxygen, light and trace amounts of catalysts.

### *Protection from Oxidation*

The stability of pharmaceutical compounds undergoing oxidative degradation can be increased by several approaches.

1. **Low oxygen content:** Since, in many cases, oxidative degradation of a drug takes place in aqueous solution, it helps to keep the oxygen content of these solutions at a minimum. Oxygen content of water could be kept to a minimum by storing the freshly distilled water at 4°C in closed containers or by purging the boiled water with carbon dioxide or nitrogen. Since most oxidative degradations of pharmaceutical compounds are probably autoxidative in nature and involve chain reactions that require only a small amount of oxygen for initiating the reaction, reduction of oxygen concentration

alone is not sufficient in many cases to prevent degradation from occurring. The traces of oxygen left may be sufficient to start a chain reaction. Consequently, it is necessary to add agents such as antioxidants and chelating agents to obtain acceptable protection against oxidative degradation.

2. **Antioxidants:** Antioxidants are used to prevent the oxidation of active substances and excipients in the finished product. There are three main types of antioxidants:

   a. True Antioxidants (water insoluble): They act as chain inhibitors by reacting with free radicals. These antioxidants break up the chains formed during the propagation process by providing a hydrogen atom or an electron to the free radical. Examples include butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), α-tocopherol, propyl gallate and ascorbyl palmitate.

   b. Reducing Agents (water soluble): These antioxidants have a higher oxidative potential than the drug that they are designed to protect and get preferentially oxidized. Examples include ascorbic acid, sodium sulfite, sodium metabisulfite, sodium thiosulfate, cysteine hydrochloride and thioglycolic acid.

   c. Antioxidant Synergists (chelating agents): These agents tend to form complexes with the trace amounts of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments. These agents enhance the effect of antioxidants. Examples include EDTA, citric acid, dihydroxyethyl glycine and tartaric acid.

3. **pH:** It is also desirable to buffer solutions containing ingredients that are readily oxidizable to a pH in the acid range. This causes an increase of the oxidation potential of the system with a concurrent increase in stability when oxidations are catalyzed by hydrogen or hydroxyl ions. The pH of optimum stability in the acid range, however, must be determined experimentally for each drug.
4. **Solvents:** Solvents other than water may have a catalyzing affect on oxidation reactions when used in combination with water or alone. For example, aldehyde, ethers and ketones may influence free radical reactions significantly.

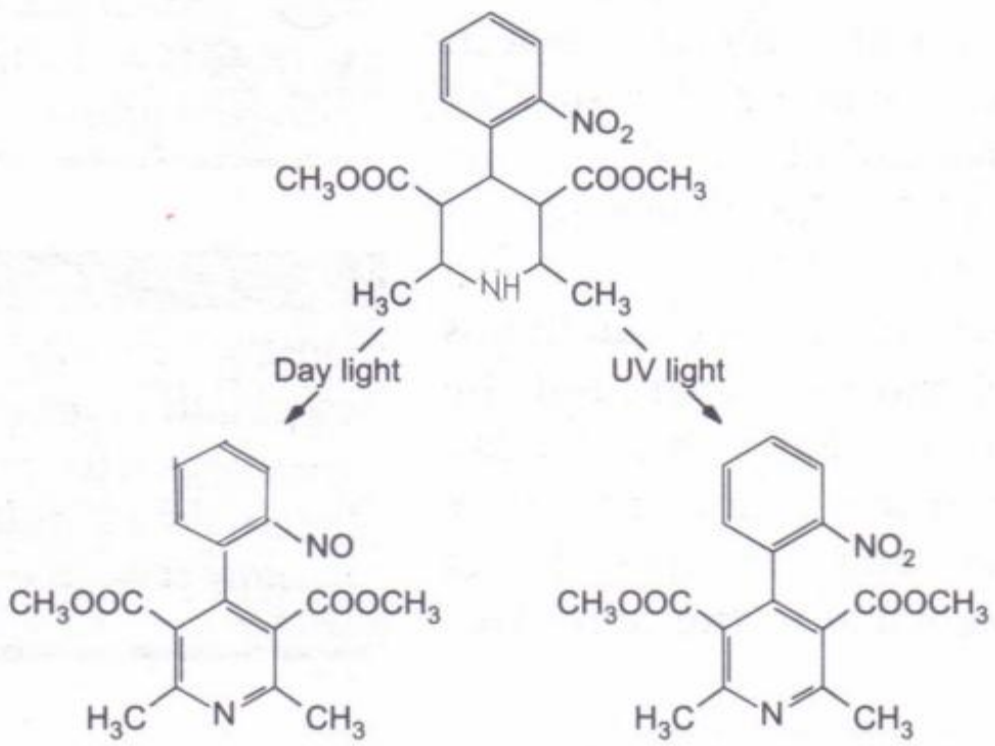
## Photolysis

Degradative reactions, such as oxidation–reduction, ring rearrangement, modification and polymerization, can be brought about by absorption of radiant energy in the form of light at particular wavelengths. According to the equation $E = 2.859 \times 10^5/\lambda$ Kcal/mol, the shorter the wavelength ($\lambda$) of light, the more energy absorbed per mole. Consequently, the radiations absorbed from the ultraviolet and violet portions of the light spectrum are more active in initiating chemical reactions. In a large number of systems that are photolyzed, free radicals are products that undergo subsequent reactions. If the molecules absorbing the radiation themselves participate in the main reaction, the reaction is said to be a *photochemical* one. Where the absorbing molecules do not themselves participate directly in the reaction, but pass on their energy to other molecules that do, the absorbing substance is said to be a

*photosensitizer.* The kinetics of photochemical reactions is more complicated than the kinetics of thermal reactions because more variables are involved. A photochemical reaction may be accompanied by a thermal reaction that is identical to the photochemical reaction opposite to it, or entirely different in character. A photochemical reaction may produce a catalyst, which then causes a thermal reaction to proceed at a measurable rate. A thermal reaction, once started, may continue after the illumination is stopped, giving an after effect.

The energy available in a photochemical reaction is much greater than that in a thermal reaction, and this fact often changes the character of the reaction. The photolysis of a drug substance may cause discolouration of the product and packaging materials in addition to chemical degradation. The pathways of photolysis are generally very complex and, therefore, in photodegradative reactions, second-order, first-order and zero-order reactions are possible. Alcoholic solutions of hydrocortisone, prednisolone and methylprednisolone are susceptible to light-catalyzed degradation. Chlorpromazine hydrochloride also undergoes photodecomposition through a semiquinone free radical intermediate following zero-order kinetics.

*Example: Degradation of nifedipine*




## Racemization

In such a reaction, an optically active substance loses its optical activity without changing its chemical composition. This reaction can be important to the stability of pharmaceutical formulations, since for a few drugs one of the optical forms is biologically more active than the other forms. For example, levo-adrenaline is 15–20 times more active than dextro-adrenaline. The racemization of a compound depends on the functional group bound to the asymmetric carbon atom; aromatic groups tend to accelerate the racemization process. Racemization reactions, in general, undergo degradation in accordance with first-order kinetic principles.

# STABILITY TESTING

Stability of a drug product is determined by evaluation of quality parameters with time under the influence of a variety of environmental factors such as temperature, humidity and light. A stable product is one that retains its chemical integrity and label potency (chemical properties) within the specified limits, retains its appearance, palatability, uniformity, dissolution and suspendability (physical properties), is resistant to microbial growth (microbiological stability) and whose therapeutic effect remains unchanged without any significant increase in toxicity, during the shelf life. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

## ICH Stability Guidelines

The International Conference on Harmonization (ICH) has published a comprehensive series of stability guidelines covering different aspects of stability. The storage conditions for stability evaluation of pharmaceutical products are summarized in Table 12.3. The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of Europe, Japan and the United States. The principle states that stability information generated in any one of the three regions of Europe, Japan and the United States would be mutually acceptable to the other two

**HIGHLIGHTS**

**ICH Q1A (R2):** Stability Testing of New Drug Substances and Products
**ICH Q1B:** Photostability Testing of New Drug Substances and Products
**ICH Q1C:** Stability Testing of New Dosage Forms

**HIGHLIGHTS**

During stability testing, accelerated condition of temperature and humidity are selected to increase rate of degradation of drug product and to generate the stability data in quick time period.

**Table 12.3** Storage conditions for stability evaluation of pharmaceutical products

| Storage conditions | Stability study type | | |
|---|---|---|---|
| | Long-term study | Intermediate study | Accelerated study |
| *1. Product intended for storage at room temperature* | | | |
| Temperature | 25 ± 2°C | 30 ± 2°C | 40 ± 2°C |
| Relative humidity | 60 ± 5% | 65 ± 5% | 75 ± 5% |
| *2. Product intended for storage in refrigerator* | | | |
| Temperature | 5 ± 3°C | – | 25 ± 2°C |
| Relative humidity | – | – | 60 ± 5% |
| *3. Product intended for storage in freezer* | | | |
| Temperature | –20 ± 5°C | – | 5 ± 2°C |
| Relative humidity | – | – | – |

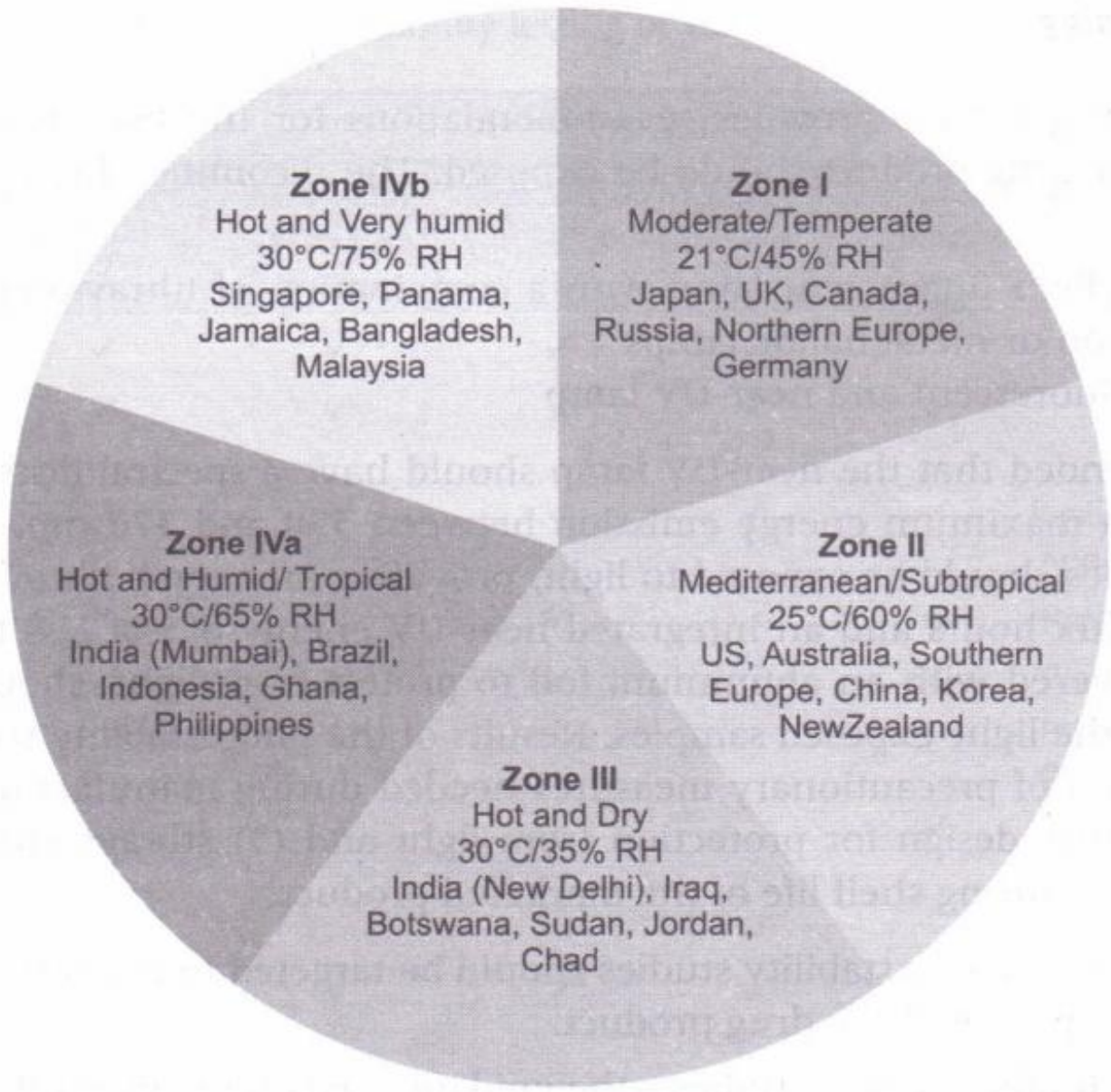



**Figure 12.14** Climatic (stability) zones and the associated temperatures and relative humidity values.

regions. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into various climatic zones as shown in Figure 12.14.

### *Thermal cycling studies*

Most heterogeneous systems such as suspensions, emulsions, creams, ointments, suppositories and inhalation aerosols may be adversely affected by variations in temperature conditions encountered during shipping and distribution. They may undergo precipitation, phase separation, crystallization, viscosity changes, sedimentation and so on. These types of drug products should be tested under cyclic temperature conditions to stimulate shipping and distribution conditions. Recommendations for thermal cycling studies are as follows:

1. For products exposed to freezing temperature variations: Three cycles of 2 days at refrigerated storage (2–8°C) followed by 2 days under accelerated conditions (40°C).
2. For products exposed to subfreezing temperature variations: Three cycles of 2 days at freezer temperature (–10 to –20°C) followed by 2 days under accelerated conditions (40°C).
3. For frozen drug products: Thawing under a hot water bath unless the drug is known to degrade at high temperatures.
4. For inhalation aerosols: Three to four cycles of 6 h per day, between freezer temperature (–10 to –20°C) and accelerated conditions (40°C/75% RH) for a period of up to 6 weeks.

### *Photostability studies*

The photostability guidance provides recommendations for the light exposure options to which the drug or drug product should be exposed. The recommended light sources are as follows:

1. Artificial daylight fluorescent lamp with a combination of ultraviolet (UV) and visible outputs, xenon or metal halide lamps
2. Cool white fluorescent and near-UV lamp

It is recommended that the near-UV lamp should have a spectral distribution from 320 to 400 nm with a maximum energy emission between 350 and 370 nm. For confirmatory studies, the samples should be exposed to light, providing an overall illumination of not less than 1.2 million lux hours and an integrated near-UV energy of not less than 200 Wh/m$^2$. Dark controls, covered with an aluminium foil to protect from light, should also be placed side by side with the light-exposed samples. Results of the photostability studies should help in (1) identification of precautionary measures needed during manufacture and packaging, (2) container closure design for protection from light and (3) storage conditions and light protection required during shelf life of the marketed product.

The testing frequency in stability studies should be targeted to generate data sufficient to establish a stability profile of the drug product.

- For long-term storage stability studies—the guidance recommends testing every 3 months over the first year, 6 months over the second year and annually thereafter through the proposed shelf life for drug products.
- For accelerated-storage stability studies—the guidance recommends sampling at 0, 3 and 6 months. When significant changes are likely to occur, increased testing is required with inclusion of a fourth sampling point.
- For intermediate-storage stability studies—if necessary, a minimum of 6 months of data from this study should be submitted with the application. When significant changes are likely to occur under accelerated storage conditions, testing at the intermediate storage condition for 12 months with sampling at time 0, 6, 9 and 12 is recommended.

Depending on the stage of stability, product type and dosage form, the product is analyzed at intervals for various parameters. These parameters may include assays for the active ingredient, measurement of known degradation products, dissolution time, appearance, etc. (Table 12.4).

However, the drug product is said to undergo significant change if the following factors are observed:

1. 5% change in assay from initial value is observed or if the product fails to meet the acceptance criteria for potency.
2. Any degradation product exceeding the acceptance criterion is observed.
3. Unexpected change in physical attribute such as colour, phase separation, resuspendability, caking or hardness is observed.
4. The product fails to meet the acceptance criterion for pH.
5. The product fails to meet the acceptance criterion for dissolution.

**Table 12.4** Evaluation parameters for stability testing of various dosage forms

| Product | Evaluation parameters | | | | | |
|---|---|---|---|---|---|---|
| | Appearance, colour, odour | Assay/Degradation product | Dissolution | Moisture | Microbial limit | Miscellaneous |
| Tablets | ✓ | ✓ | ✓ | ✓ | | Friability |
| Hard gelatin capsules | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Soft gelatin capsules | ✓ | ✓ | ✓ | ✓ | ✓ | Leakage, pellicle formation, pH |
| Oral solutions | ✓, Clarity | ✓ | ✓ | | ✓ | Preservative content, pH |
| Oral suspensions | ✓ | ✓ | ✓ | | ✓ | Preservative content, pH, redispersibility, rheology, particle size |
| Emulsions | ✓ | ✓ | ✓ | | ✓ | Preservative content, pH, rheology, globule size |
| Oral powders | ✓ | | | ✓ | | Reconstitution time |
| Aerosols, nasal spray | ✓ | ✓ | ✓ | ✓ | ✓ | Cosolvent assay, dose uniformity, aerodynamic particle size, leak rate, water content, valve delivery, packaging tests |
| Inhalation solution | ✓ | ✓ | | | | Particulate matter, pH, weight loss, sterility, packaging tests |
| Topical/ ophthalmic | ✓ | ✓ | | | | Clarity, pH, consistency, rheology, particle size, sterility |
| Small-volume parenterals | ✓, Clarity | ✓ | | ✓ | | Pyrogenicity, sterility, particulate matter, preservative content |
| Large-volume parenterals | ✓, Clarity | ✓ | | | | Pyrogenicity, sterility, particulate matter, volume, preservative content |

## EXPIRATION DATING OF PHARMACEUTICALS

The expiration dating or shelf life of a drug product is defined as the time interval that a drug product is expected to remain within an approved shelf-life specification, provided that it is stored according to label storage conditions and that it is in the original container closure system. The expiry is the actual date placed on the container or label of a drug product

designating the time during which a batch of the drug product is expected to remain within the approved shelf-life specification if stored under defined conditions and after which it must not be used. In general, this is answered through stability testing that monitors chemical and physical product attributes as a function of time, temperature and other environmental factors.

The important features to conducting stability studies and assigning expiration dates are listed as follows:

1. Expiration date related to the specific storage condition stated on the label must be derived on the data obtained from an appropriate stability-testing program using a reliable stability-indicating assay method.
2. The stability program should include:
   a. Numbers and sizes of containers per sample time;
   b. Testing of drug product in the marketed container-closure system at appropriate storage condition(s);
   c. An adequate number of batches, usually at least three production batches, to be placed on long-term stability testing for a new product initially and one production batch per year thereafter.
3. Tentative expiration dates can be assigned based on data from *accelerated stability studies*. A rule of thumb for solid dosage forms allows a 2-year tentative expiration date at room temperature if the drug has retained 90% of its original potency after 90 days of storage at 40°C and 75% relative humidity.
4. Long-term stability studies should be conducted to confirm the predicted expiration date.

## Accelerated Stability Studies (Shelf-Life Determination)

To assess the stability of a formulated product, it is usual to expose it to 'high stress', i.e. conditions of temperature and humidity that are known from experience to be likely causes of breakdown. High stress conditions accelerate the deterioration of the product and therefore reduce the time required for testing. This enables more data to be gathered in a shorter time, which in turn will allow unsatisfactory formulations to be eliminated early in a study, thereby reducing the time for a successful product to reach the market. It must be emphasized that extrapolations to 'normal' storage conditions must be made with care, and that the formulator must ensure that such extrapolations are valid. It is advisable therefore to run concurrently a batch under expected normal conditions to confirm later that these assumptions are valid. The objectives of such accelerated tests may be defined as follows:

- The rapid detection of deterioration in different initial formulations of the same product, which is useful when selecting the best formulation from a series of possible choices.
- The prediction of shelf life, which is the time a product will remain satisfactory when stored under expected or directed storage conditions.

- The provision of a rapid means of quality control, which ensures that no unexpected change has occurred in the stored product.

### *Prediction of shelf life from accelerated stability-testing data*

The Arrhenius equation has been used by pharmaceutical scientists in predicting room-temperature stability of drug products based on data obtained under exaggerated conditions (higher temperature rates of degradation). The main steps in the process are as follows:

1. Product to be evaluated is stored at several elevated temperatures (40, 50, 60 and 70°C).
2. At predesignated time points, drug assay is carried out to determine the concentration of drug remaining at each time point and at each elevated temperature.
3. Based on concentration–time data at each elevated temperature (stability data), the order of reaction is determined (substitution or graphical method)
4. Using the rate equation, values of the rate constant $k$ at each elevated temperature are calculated ($k_{40}$, $k_{50}$, $k_{60}$ and $k_{70}$).
5. The logarithms of different $k$ values are then plotted against the reciprocals of absolute temperature according to the Arrhenius plot.
6. The plot is linear (see Fig. 12.15) as depicted by the Arrhenius equation:

$$\log k = \log A - \frac{E_a}{2.303RT}$$

7. The plot is extrapolated to ambient temperature (room temperature, 25°C) to determine the value of $k_{25}$.
8. The shelf life or expiration date is then calculated using a particular shelf-life equation.

**HIGHLIGHTS**

**A reaction is**

- Zero order if concentration versus time plot is linear.
- First order if log concentration versus time plot is linear.

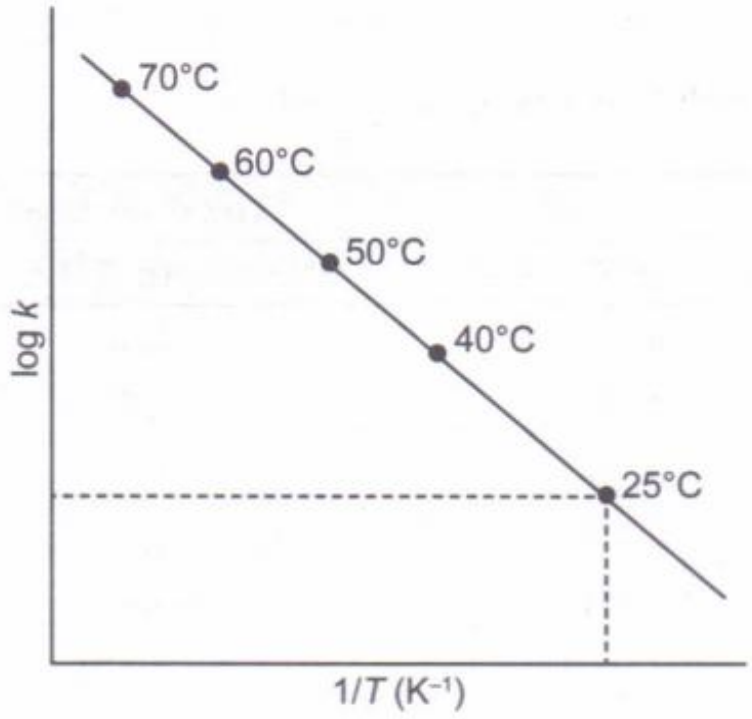



**Figure 12.15** Arrhenius plot to determine shelf life of the drug

### *Practical Example: Estimation of degradation from accelerated data: First-order case*

Table 12.5 shows the degradation data for drug product, obtained at elevated temperature conditions. All values are expressed as a percentage of the label claim. The assay values at 25°C are estimated as a function of time.

**Table 12.5** Assay degradation data for drug product

| Time (months) | Drug assay | | |
|---|---|---|---|
| | 30°C | 40°C | 50°C |
| 0 | 99.9 | 99.9 | 99.9 |
| 2 | 99.4 | 98.0 | 95.6 |
| 4 | 98.7 | 95.9 | 91.2 |
| 6 | 97.4 | 99.1 | 87.4 |

*Solution*

- For first-order kinetics, the first step is to obtain the log of concentrations (Table 12.6).
- The values are then graphed as a function of time where straight lines should be obtained as shown in Figure 12.16.
- The slope of each line corresponds to the value of $k_1$ (shown at the bottom part of Table 12.6).
- A plot of log $k_1$ versus $1/T$ is prepared with the three values of $k_1$, one for each temperature as shown in Figure 12.17. The absolute temperature should be used here.
- The value of $k_1$ can be extrapolated to T = 25°C ($1/T = 0.003354\ K^{-1}$) to then predict the drug product assay as a function of time. The values of slope and intercept are shown in the inset of Figure 12.17. The calculation is as follows:

$$\log k_{25} = -8237.4 \times 0.003354 + 21.639 = -5.990$$

$$k_{25} = 0.00250\ month^{-1}$$

**Table 12.6** Degradation data treated as first-order kinetics

| Time (months) | Log drug assay | | |
|---|---|---|---|
| | 30°C | 40°C | 50°C |
| 0 | 4.60 | 4.60 | 4.60 |
| 2 | 4.59 | 4.58 | 4.55 |
| 4 | 4.58 | 4.55 | 4.50 |
| 6 | 4.57 | 4.55 | 4.46 |
| $k_1$ | 0.00415 | 0.00847 | 0.02224 |
| log $k_1$ | −5.483 | −4.771 | −3.798 |
| 1/T | 0.00330 | 0.00319 | 0.00309 |

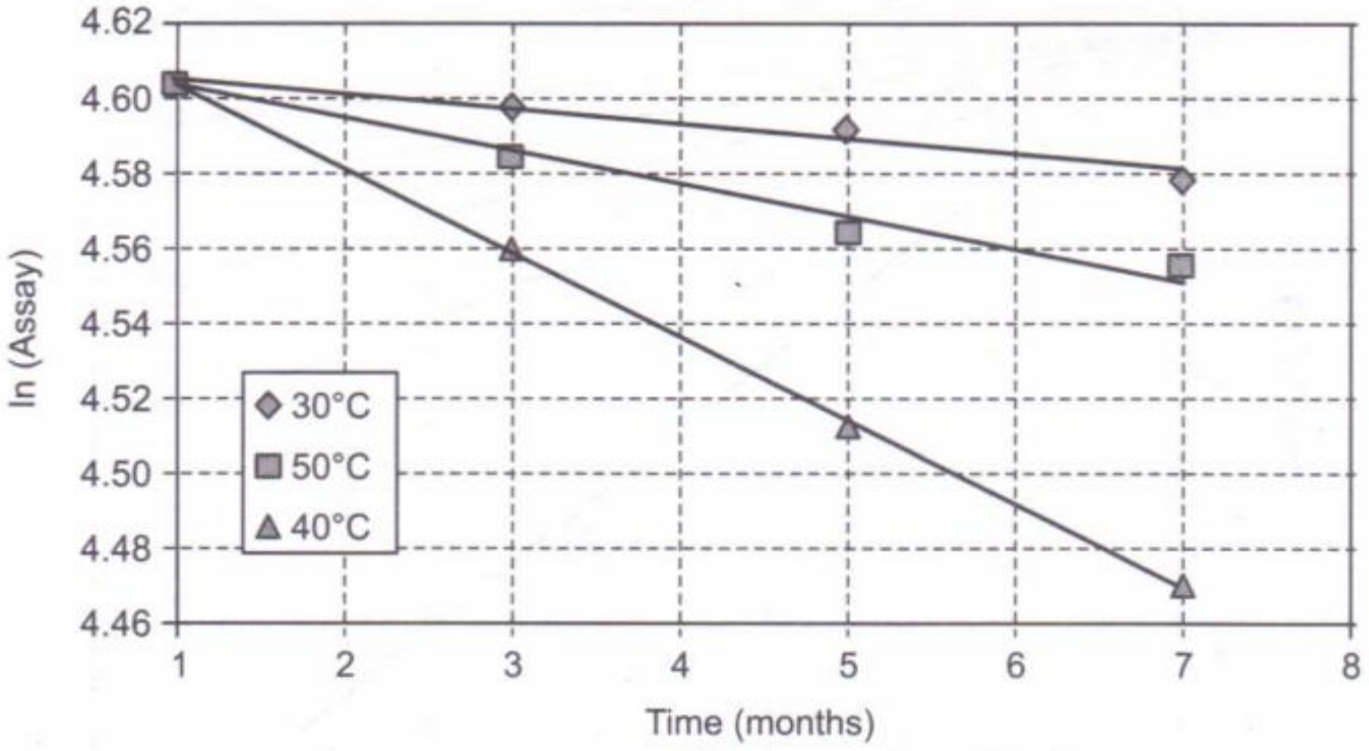



**Figure 12.16** Graphical representation of degradation data.

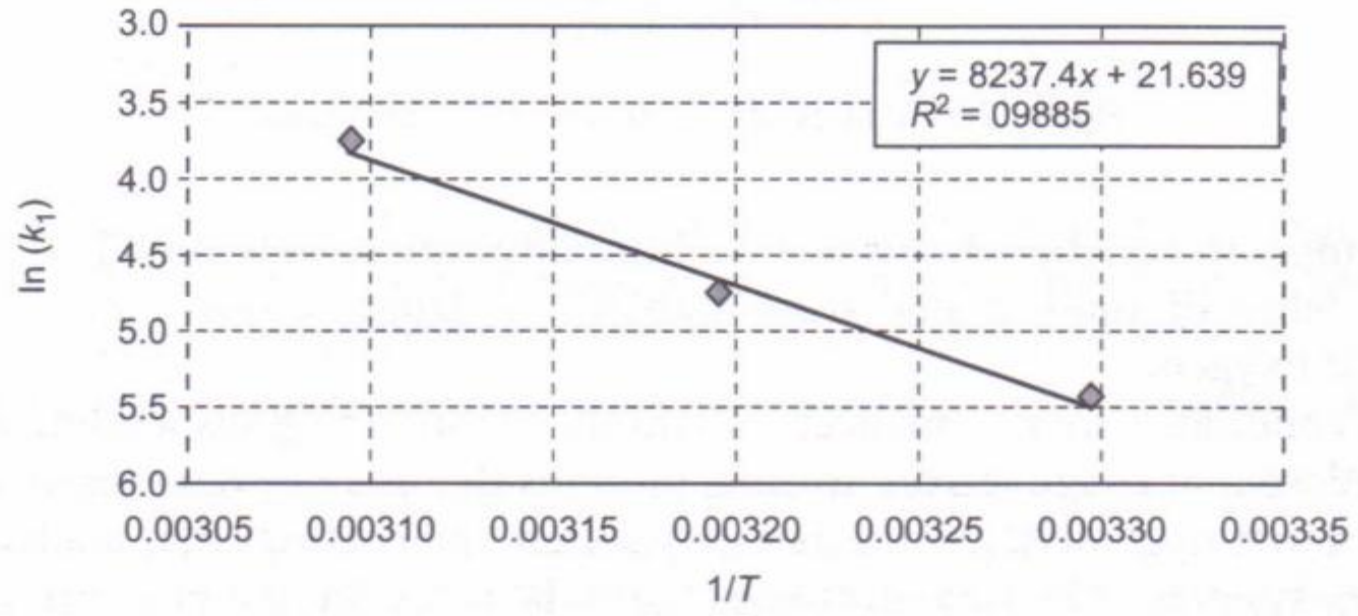



**Figure 12.17** Plot of log $k_1$ versus $1/T$.

## Limitations of Accelerated Stability Testing

There are many situations in which accelerated stability testing based on Arrhenius predictions can be erroneous or invalid as mentioned below:

- The Arrhenius equation involves only one rate constant and therefore applies to a simple decomposition mechanism.
- It cannot be used for complex reactions or heterogeneous processes involving phase boundaries (here additional factors, such as rate of dissolution, diffusion from within a matrix and melting, are important determinants of decomposition).
- If drug decomposition is due to photochemical reaction, freezing, excessive agitation or microbial contamination, an elevated temperature study is of little use in predicting the shelf life of the product.
- Higher temperatures may also reduce the moisture content of the product, thus slowing down the process of hydrolysis.

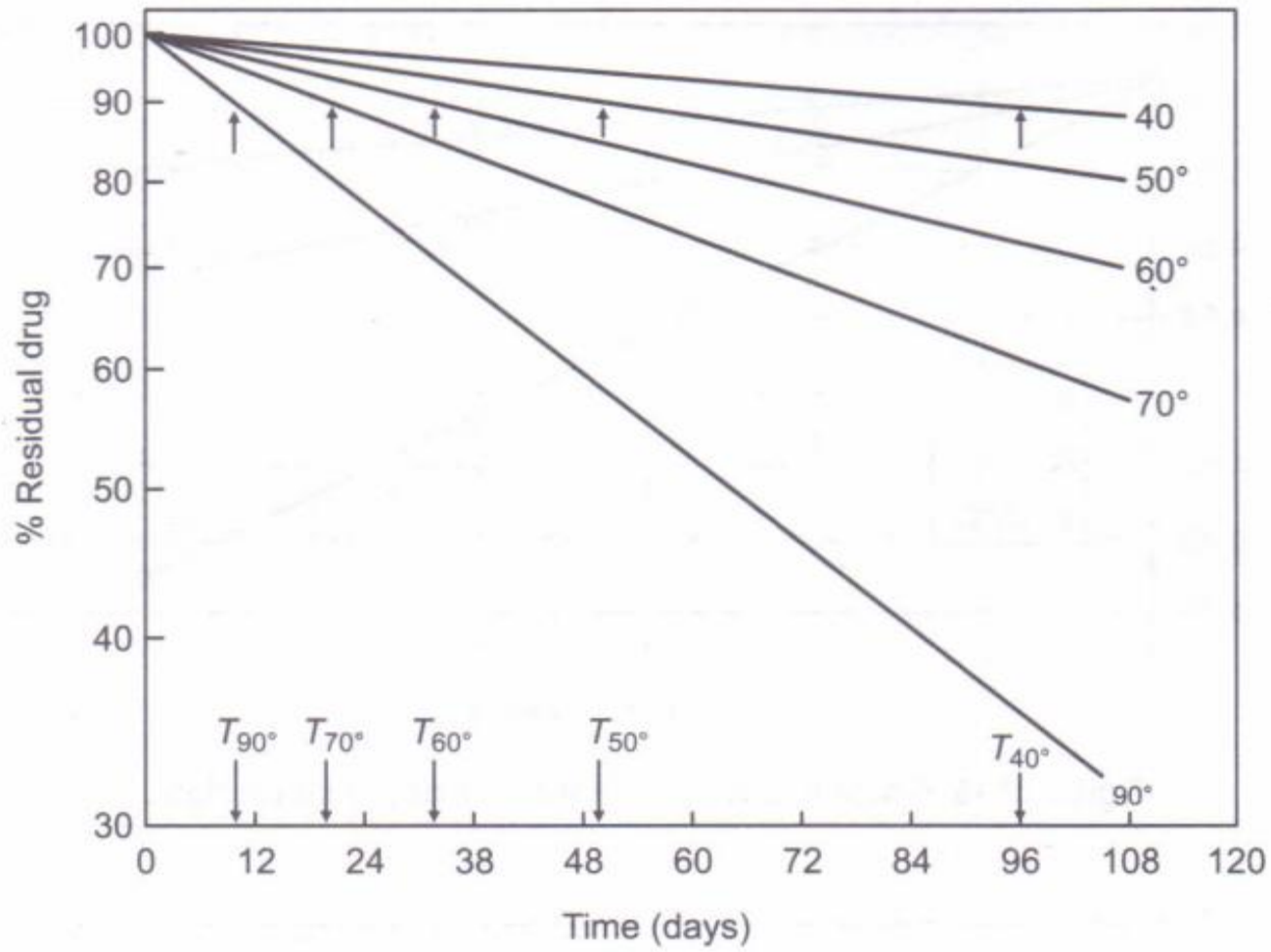



**Figure 12.18** Values of $T_{10\%}$ at several temperatures.

- At higher temperatures, there is less relative humidity and oxygen solubility, thus hindering the predictability of room-temperature stability of drugs sensitive to the presence of moisture and oxygen.
- Accelerated conditions are not applicable to products containing suspending agents such as methyl cellulose that coagulate on heating, proteins that may be denatured, ointment and suppositories that may melt, gelatin that may soften and coatings that might split.
- For disperse systems, viscosity decreases with increase in temperature, and physical characteristics may be altered, resulting in potentially large errors in the prediction of stability.
- In case of emulsions, breaking involves the coagulation of globules, which makes some emulsions more stable at elevated temperatures at which Brownian motion is increased.
- At certain temperatures, autocatalysis may occur to make room-temperature stability predictions from accelerated stability predictions impractical.

To conclude, a formulation developer should recognize the limitations of accelerated studies and in case where accelerated studies are not applicable, extended ageing test must be employed to obtain the desired stability information.

## OTHER TECHNIQUES FOR STABILITY PREDICTION

Simplified graphic techniques have been employed to predict the breakdown that may occur over prolonged periods of storage at normal shelf conditions. The plots in Figure 12.18 show

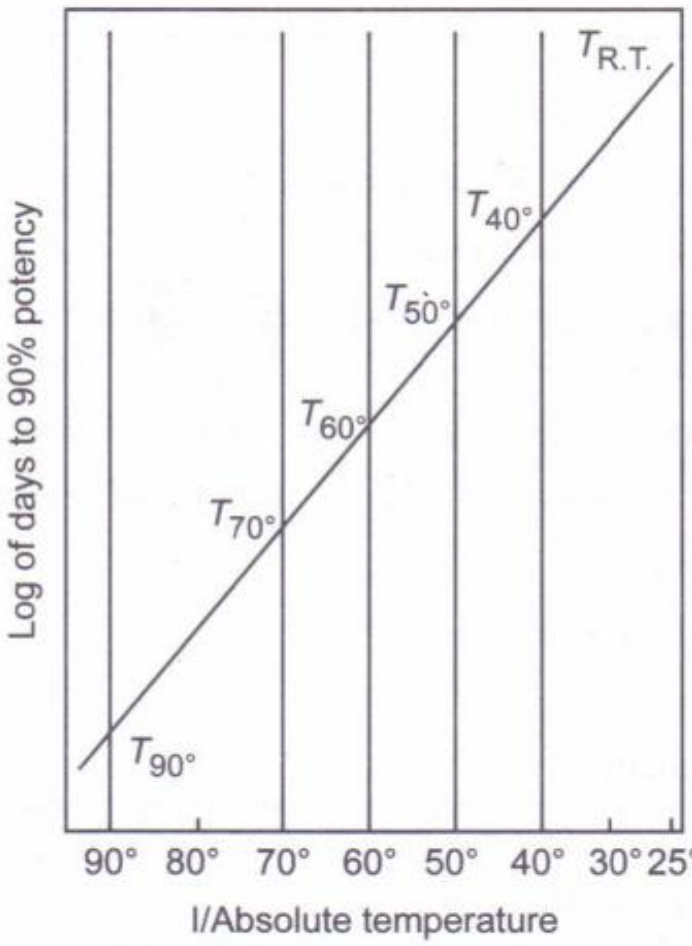



**Figure 12.19** Plot of $T_{10\%}$ values versus absolute temperature$^{-1}$.

that degradation is following a first-order reaction. The time required to reach 90% of the theoretic potency is noted for several temperatures (arrows on the curve). These time values at different temperatures are plotted in Figure 12.19 and the time for 10% loss of potency at room temperature can be obtained from the resulting straight line by extrapolation to 25°C.

To determine the overages required for the product to maintain at least 90% potency for a prescribed time, as a first step the loss line representative of the 90% potency value at room temperature is drawn (Figure 12.20). Then a line is drawn parallel to this from the desired shelf life back to 0 days. The plot in Figure 12.20 indicates that using a 10% overage, the product now takes about twice as long to fall below 90% of the labelled claim during shelf storage.

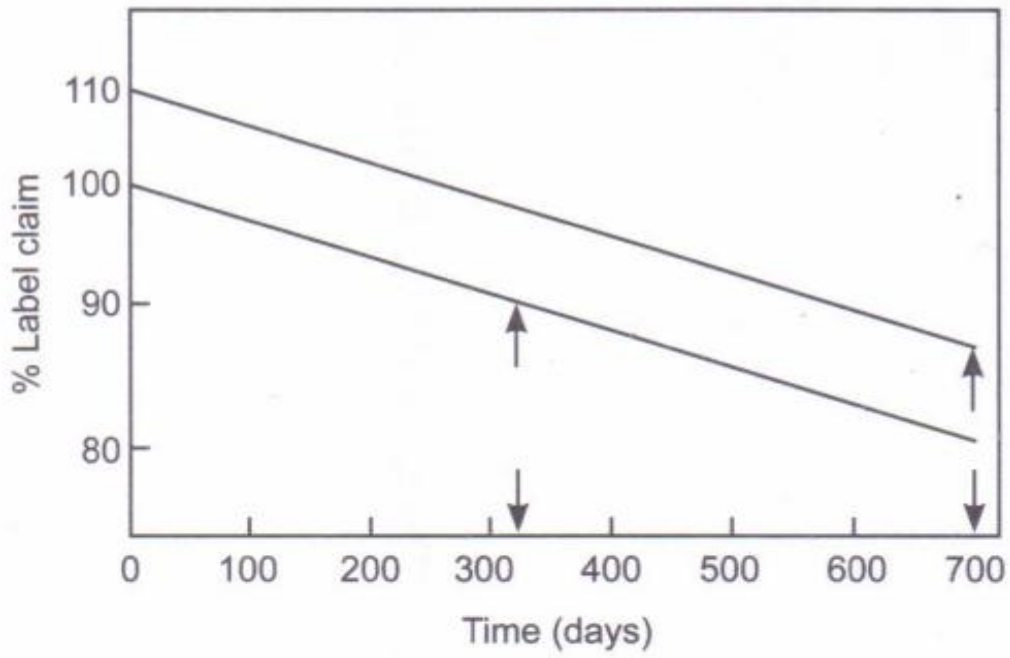



**Figure 12.20** Plot of average and normal loss curves.

**HIGHLIGHTS**

**Overages:** The amount of drug added to compensate for degradation during storage to improve shelf life of the product.

## Questions

1. Give proper justification for the following:
   a. Increase in reaction temperature by 10°C increases the rate of reaction by two- to three-fold.
   b. Suspensions show apparent zero-order kinetics.
   c. For a reaction between ions of opposite charge, an increase in dielectric constant of the solvent decreases the rate of reaction.
   d. In a reaction involving neutral molecules, the rate constant is independent of the ionic strength.
   e. If the polarity of the product is similar to solvent, the rate of reaction is large in this solvent.
2. Write short notes on the following:
   a. Order and molecularity of a reaction
   b. Complex reactions
   c. Factors influencing rate of reaction
   d. ICH stability guidelines
   e. Overages in pharmaceutical product
3. Derive rate equation, half-life and shelf life of zero-order and first-order reactions.
4. Discuss the procedure for accelerated stability testing and prediction of shelf life of a drug product.
5. Describe various degradation pathways of drug products and methods of preventing the same.
6. Solve the following numerical:
   a. A drug is hydrolyzed via a first-order reaction in a solution. The solubility of the drug in water is 3.5 mg/100 mL. A pharmacist made a suspension formulation of the drug containing 2.7 mg/mL. The shelf life of the suspension was 15 days. Calculate the half-life of the solution.
   b. Experimentally, it was found that the half-life for the hydrolytic degradation (first-order kinetics) of oxazepam in aqueous solution at pH 3.24 was 38.9 min at 80°C. However, 28% of the drug was hydrolyzed at 70°C after 25.4 min. Calculate the activation energy for the degradation, the degradation rate constant at 25°C, the shelf life at 25°C and what concentration of intact drug is left after 225 min at 25°C, expressed as a percentage.