18
Coarse Dispersions

Particulate systems have been classified previously (Table 15–1, p. 394) on the basis of size into molecular dispersions (Chapter 5), colloidal systems (Chapter 15), and coarse dispersions (this chapter). The present discussion 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. These topics have been introduced in the four previous chapters.

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 μm, and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity.

Suspensions contribute to pharmacy and medicine by supplying insoluble and often 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 may be classified into three groups: orally administered mixtures, externally applied lotions, and injectable preparations.

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 radioopaque 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 since 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 are 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 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. Since this ideal situation is seldom realized, it is appropriate to add the statement 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 a 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 flocculates 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 ΔG brought about by dividing the solid into smaller particles and consequently increasing the total surface area ΔA is given by

$$\Delta G = \gamma_{SL} \cdot \Delta A \qquad (18-1)$$

in which γ_{SL} is the interfacial tension between the liquid medium and the solid particles.

Example 18–1. Compute the change in the surface free energy of a solid in a suspension if the total surface is increased from 10^6 cm^2 to 10^7 cm^2. Assume that the interfacial tension between the solid and the liquid medium is $\gamma_{LS} = 100$ dyne/cm.

The initial free energy is

$$G_1 = 100 \times 10^6 = 10^8 \text{ erg/cm}^2$$

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

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

The change in the free energy, ΔG_{21}, is $10^9 - 10^8 \cong 10^9$ erg/cm^2. The free energy has been increased by 10^9, which makes the system more thermodynamically unstable.

In order to approach a stable state, the system tends to reduce the surface free energy; equilibrium is reached when $\Delta G = 0$. This condition may be accomplished, as seen from equation (18–1), by a reduction of interfacial tension, or it may be approached by a decrease of the interfacial area. The latter possibility, leading to flocculation or aggregation, may 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 in 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 has been considered in detail in Chapter 14, which dealt with interfacial phenomena. The student is advised to review, at this point, the section dealing with the electrical properties of interfaces (pp. 386–388) since particle charge, electrical double layer formation, and zeta potential are all relevant to the present topic.

The potential energy of two particles is plotted in Figure 18–1 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. In order to resuspend and redisperse these particles, it is again necessary to overcome the high energy barrier. Since 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

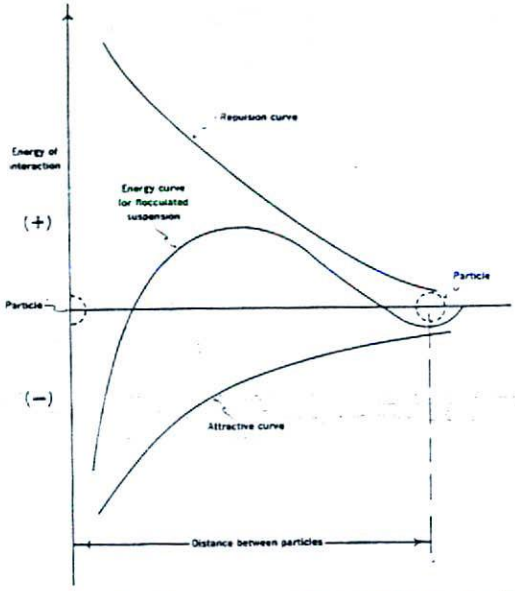

Fig. 18–1. Potential energy curves for particle interactions in suspension (from A. Martin, J. Pharm. Sci., 50, 514, 1961, reproduced with permission of the copyright owner.)

form the loosely structural flocs. These concepts evolve from the DLVO theory for the stability of lyophobic sols (p. 408). Schneider et al.[4] prepared a computer program to calculate 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. As discussed in Chapter 16, the velocity of sedimentation is expressed by Stokes' law:

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

in which v is the terminal velocity in cm/sec, d is the diameter of the particle in cm, ρ_s and ρ_o are the densities of the dispersed phase and dispersion medium, respectively, g is the acceleration due to gravity, and η_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 workers feel that the concentration must be less than 0.5 g/100 mL before Stokes' 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' law no longer applies.

Under these circumstances, some estimation of physical stability may 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. Stokes' equation may be written in other forms. One of there proposed modifications is as follows:[5]

$$v' = v\epsilon^n \qquad (18\text{–}3)$$

where v' is the rate of fall at the interface in cm/sec and v is the velocity of sedimentation according to Stokes' law. The term ϵ 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 18–2. The average particle diameter of calcium carbonate in aqueous suspension is 54 μm. The densities of $CaCO_3$ and water, respectively, are 2.7 and 0.997 g/cm³. 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' law (equation (18–2)),

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

Taking logarithms on both sides of equation (18–3), $\ln v' = \ln v + n \ln \epsilon$.

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 $v' = v$. 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 μm (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) has been worked out by Burton.[6]

It may 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 cps. 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' law, the larger particles settle more rapidly than the smaller particles. No clear boundary is formed (unless only one size particle is present), and the supernatant remains turbid for a considerably longer period of time. Whether or not 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 may 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

$$F = V_u/V_o \qquad (18\text{–}4)$$

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 18–2*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. 18–2*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 are so loose and fluffy that the volume they are able to encompass is greater than the original volume of

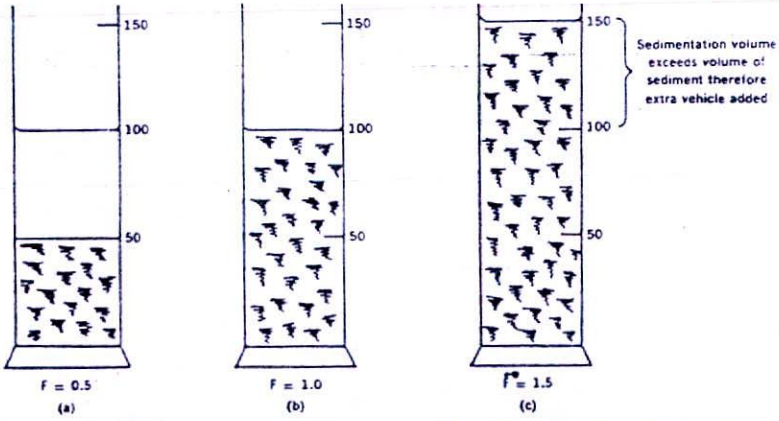

Fig. 18–2. Sedimentation volumes produced by adding varying amounts of flocculating agent. Examples *(b)* and *(c)* are pharmaceutically acceptable.

suspension. This situation is illustrated in Figure 18–2c, in which sufficient extra vehicles has been added to contain the sediment. In example shown, $F = 1.5$.

The sedimentation volume gives only a qualitative account of flocculation since it lacks a meaningful reference point.[7] A more useful parameter for flocculation is β, 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_∞, based on equation (18–4), we have

$$F_\infty = V_\infty/V_0 \qquad (18–5)$$

in which F_∞ is the sedimentation volume of the deflocculated, or peptized, suspension. The degree of flocculation, β, is therefore defined as the ratio of F to F_∞, or

$$\beta = F/F_\infty \qquad (18–6)$$

Substituting equations (18–4) and (18–5) in equation (18–6), we obtain

$$\beta = \frac{V_u/V_0}{V_\infty/V_0} = V_u/V_\infty \qquad (18–7)$$

The degree of flocculation is a more fundamental parameter than F since 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 18–3. Compute the sedimentation volume of a 5% (w/v) suspension of magnesium carbonate in water. The initial volume is $V_0 = 100$ 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_∞.

$$F = \frac{30}{100} = 0.30$$

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

FORMULATION OF SUSPENSIONS

The approaches commonly used in the preparation of physical stable suspensions fall into two categories—the use of 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 have been discussed in Chapter 17. 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 reformation 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 may be achieved. Whatever approach is used, the product must (1) flow readily from the container and (2) 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 may be ascertained easily by observing the contact angle (p. 384) 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, and 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, to enhance 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 concentra-

tion, the surfactant produces extensive flocculation. Glycerin and similar 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] has 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, attention may now be given to the various means by which controlled flocculation may 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 material 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 18–3 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 a negative direction, as shown in Figure 18–3. 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 floc-

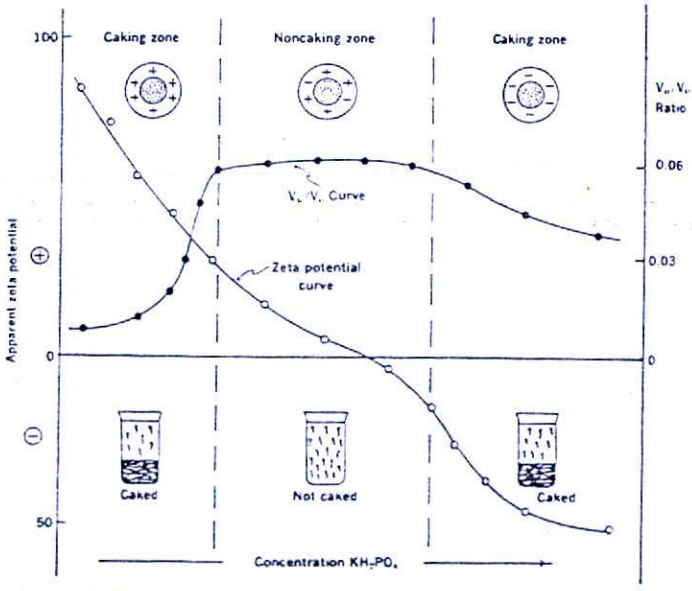

Fig. 18–3. Caking diagram, showing the flocculation of a bismuth subnitrate suspension by means of the flocculating agent, monobasic potassium phosphate. (From A. Martin and J. Swarbrick, in Sprowls, *American Pharmacy*, 6th Edition, Lippincott, Philadelphia, 1966, p. 205, reproduced with permission of the copyright owner.)

culation 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, 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 may 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 since these compounds may also act as wetting and deflocculating agents to achieve dispersion.

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.

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] has reviewed the control of floc structure in coarse suspensions by the addition of polymeric materials.

Hydrophilic polymers also act as protective colloids (p. 410), 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. (See page 513 for a discussion of liposomes.)

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 (CMC), Carbopol 934, Veegum, tragacanth, or bentonite have been employed, either alone or in combination.

This may 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 mentioned above. 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 for 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.

The student should note that this approach may be used regardless of the charge on the particle. The

sequence of events is depicted in Figure 18–4, which is self-explanatory.

Rheologic Considerations. The principles of rheology may 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 18–5, 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 18–5 were obtained by use of the modified Stormer viscometer described on page 464.

A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful since it forms a gel on standing and becomes fluid when disturbed.

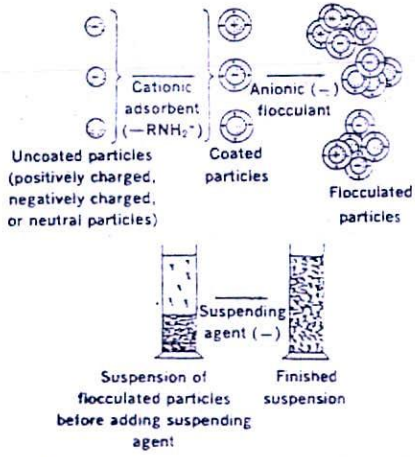

Fig. 18–4. The sequence of steps involved in the formation of a stable suspension (From A. Martin and J. Swarbrick; in Sprowls, *American Pharmacy*, 6th Edition, Lippincott, Philadelphia, 1966, p. 206, reproduced with permission of the copyright owner.)

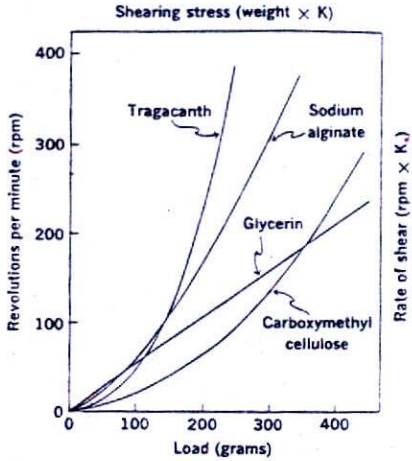

Fig. 18–5. Rheologic flow curves of various suspending agents analyzed in a modified Stormer viscometer.

Figure 18–6 shows the consistency curves for bentonite, Veegum (Vanderbilt Co.), and a combination of bentonite and sodium carboxymethylcellulose (CMC). 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 CMC 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 principles involved in the dispersion of solids by different types of equipment have been discussed by Oldshue.[17]

A suspension is prepared on the small scale by grinding or levigating the insoluble material in the

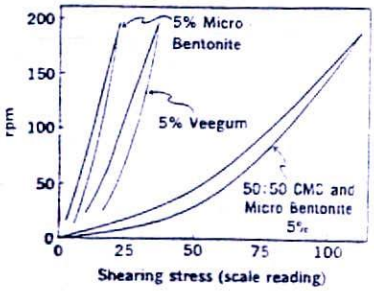

Fig. 18–6. Flow curves for 5% suspending agents in water showing thixotropy. The curves were obtained with the Ferranti–Shirley cone–plate viscometer.

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.[18] Dry grinding in ball mills is treated by Fischer, by Berry and Kamack and by Prasher.[18]

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 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 may 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 may 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 are able to 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 (see Fig. 15–12, p. 409). 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 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 may 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.[22] 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 the supersaturation of the solution required for the crystals to grow. This can be shown using the Kelvin equation (p. 440), as applied to a particle suspended in a saturated solution:[22]

$$\ln \frac{c}{c_o} = \frac{2\gamma M}{NkT\rho R} \qquad (18\text{–}8)$$

where c is the solubility of a small particle of radius R in an aqueous vehicle and c_o the solubility of a very large crystalline particle; γ is the interfacial tension of the crystal, ρ 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 $N \times k = 8.314 \times 10^7$ erg deg^{-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 (18–8), 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 18–4. Assume that the interfacial tension of a particle of drug in an aqueous vehicle is 100 erg/cm^2, its molecular weight 200 g/mole, and the temperature of solution 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 μm or 5×10^{-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 6×10^{-7} cm.

Using the Kelvin equation,

(*a*)

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

$$c/c_o = \text{antiln}(0.0024) = 1.002$$

(*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[23] designed a control unit to monitor crystal growth and studied the inhibition of growth by 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. 18–7). 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 since 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 may be used to estimate the critical flocculation concentration of sorbitol. Lucks et al.[24] 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.

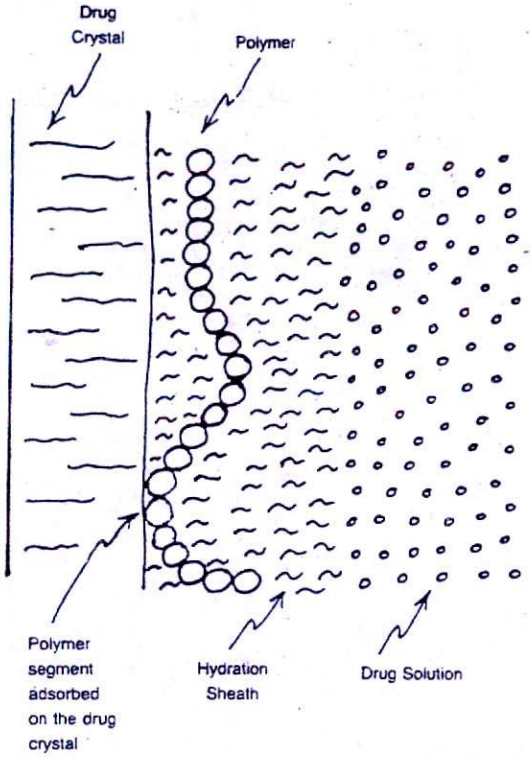

Fig. 18–7. Dissolution and crystallization of a drug in the presence of a polymer adsorbed on the drug crystal. (From K. H. Ziller and H. Rupprecht, Drug Dev. Ind. Pharm. 14, 2341, 1988, reproduced with permission of the copyright owner.)

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 μm, although particle diameters as small as 0.01 μ and as large as 100 μm are not uncommon in some preparations.

Emulsion type. Invariably, one liquid phase in an emulsion is essentially polar (e.g., aqueous), while 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 of the 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.[25] 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[26] 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 since 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 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 (1) the stability of the product and (2) 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 14.

When one liquid is broken into small particles, the interfacial area of the globules constitutes a surface that is enormous 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 μm (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 square meters. The surface free energy associated with this area is about 34×10^7 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 (16–15) and (16–17), p. 436, 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 γ_{ow} between mineral oil and water is 57 dyne/cm (erg/cm^2).

$$W = 57 \text{ erg/cm}^2 \times (6 \times 10^6 \text{ cm}^2)$$

$$= 34 \times 10^7 \text{ ergs} = 34 \text{ joules}$$

and since

$$1 \text{ cal} = 4.184 \text{ joules}$$

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

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 μm), the total surface is equivalent to an area slightly greater than that of a basketball court, or about 600 square meters! (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 may be divided into three groups, as follows:

(1) Surface-active agents, which are adsorbed at oil–water interfaces to form monomolecular films and reduce interfacial tension. These agents have been discussed in detail in Chapter 14, dealing with interfacial phenomena.

(2) Hydrophilic colloids (discussed in Chapter 15), which form a *multi*molecular film around the dispersed droplets of oil in an *o/w* emulsion.[27,28]

(3) 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 18–1.

Monomolecular Adsorption. Surface-active agents, or amphiphiles, reduce interfacial tension because of their adsorption at the oil–water interface to form monomolecular films. Since the surface free energy increase W equals $\gamma_{o/w} \times \Delta A$, and since 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 one sixtieth of that calculated earlier.

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

TABLE 18–1. *Some Typical Emulsifying Agents*

Name	Class	Type of Emulsion Formed
Triethanolamine oleate	Surface-active agent (anionic)	o/w (HLB = 12)
N-cetyl *N*-ethyl morpholinum ethosulfate (Atlas G-263)	Surface-active agent (cationic)	o/w (HLB = 25)
Sorbitan mono-oleate (Atlas Span 80)	Surface-active-agent (nonionic)	w/o (HLB = 4.3)
Polyoxyethylene sorbitan mono-oleate (Atlas Tween 80)	Surface-active agent (nonionic)	o/w (HLB = 15)
Acacia (salts of *d*-glucuronic acid)	Hydrophilic colloid	o/w
Gelatin (polypeptides and aminoacids)	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

significance is the fact that the dispersed droplets are surrounded by a coherent monolayer that helps to 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 (see p. 387), 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[29] 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 18–8. The combination of sodium cetyl sulfate and cholesterol leads to a complex film (Fig. 18–8*a*) that produces an excellent emulsion. Sodium cetyl sulfate and oleyl alcohol do not form a closely packed or condensed film (Fig. 18–8*b*), and consequently, their combination results in a poor emulsion. In Figure 18–8*c*, cetyl alcohol and sodium oleate produce a close-packed film, but complexation is negligible, and again a poor emulsion results.

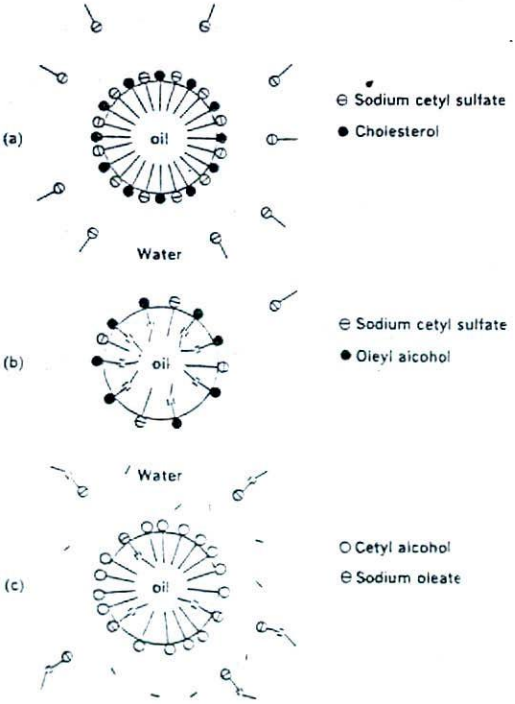

Fig. 18–8. Representations of combinations of emulsifying agents at the oil–water interface of an emulsion. (After J. H. Schulman and E. G. Cockbain, Trans. Faraday Soc. 36, 651, 1940.)

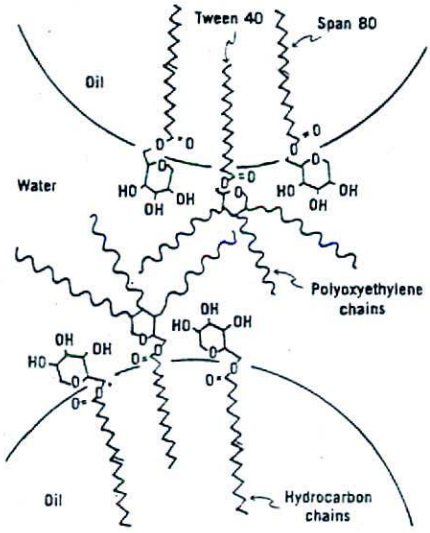

Fig. 18–9. Schematic of oil droplets in an oil–water emulsion, showing the orientation of a Tween and a Span molecule at the interface. (From J. Boyd, C. Parkinson and P. Sherman, J. Coll. Interface Sci. 41, 359, 1972, reproduced with permission of the copyright owner.)

Atlas-ICI* recommends that a hydrophilic Tween be combined with a lipophilic Span, varying the proportions so as to produce the desired *o/w* or *w/o* emulsion.[30] Boyd et al.[31] discussed the molecular association of Tween 40 and Span 80 in stabilizing emulsions. In Figure 18–9, the hydrocarbon portion of the Span 80 (sorbitan mono-oleate) 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 may be applied in the use of combinations such as

*Atlas surfactants, ICI United States, Inc., Wilmington, Del.

sodium stearate and cholesterol, sodium lauryl sulfate and glyceryl monostearate, and tragacanth and Span. Chun et al.[32] determined the hydrophile–lipophile balance 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 may be predicted from a knowledge of the hydrophile–lipophile balance, as discussed in a previous chapter (p. 371). 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[33] suggested an explanation for emulsion type and stability and devised a general scheme for emulsion formulation based on the Hildebrand and Hansen solubility parameters (pp. 224, 225).

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 may be regarded as surface active since they appear at the oil–water interface. They differ, however, from the synthetic surface-active agents in that (1) they do not cause an appreciable lowering of interfacial tension, and (2) they form a multi- rather than a monomolecular film at the interface. Their action as emulsifying agents is due mainly to the latter effect, for 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. Since 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 eye-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' Law. Those factors that find importance in the creaming of an emulsion are related by Stokes' law, equation (18–2) (p. 479). The limitations of this equation to actual systems have been discussed previously for suspensions (p. 479), 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 more dense than the continuous oil phase. This effect may 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 may 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 four.

Example 18–5. 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 μm or 5×10^{-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 per day?

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

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

and since a 24-hour 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' equation may 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 may 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 μm or one fifth of the original value, the rate of creaming is reduced to 0.014 cm per day or about 5 cm per year. Actually, when the particles are reduced to a diameter below 2 to 5 μm, Brownian motion at room temperature exerts sufficient influence so that the particles settle or cream slower than predicted by Stokes' 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, since 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 α-bromonaphthalene, bromoform, and carbon tetrachloride, which, however, cannot be used in medicinal products. Mullins and Becker[34] added a food grade of a brominated oil to adjust the densities in pharmaceutical emulsions.

Equation (18–2) 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[35] has 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, since creaming is a reversible process, whereas breaking is irreversible. The cream flocculates may be redispersed easily, and a uniform mixture is reconstituted from a creamed emulsion by agitation, since 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, since 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[36] 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 may 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[37] have shown 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 (p. 443), 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[38] and others have shown 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 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[39] used lecithin to stabilize perfluocarbon 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.[10] 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.[41] Johnson et al.[40] 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 18–10.

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.[42] 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.[43] have 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

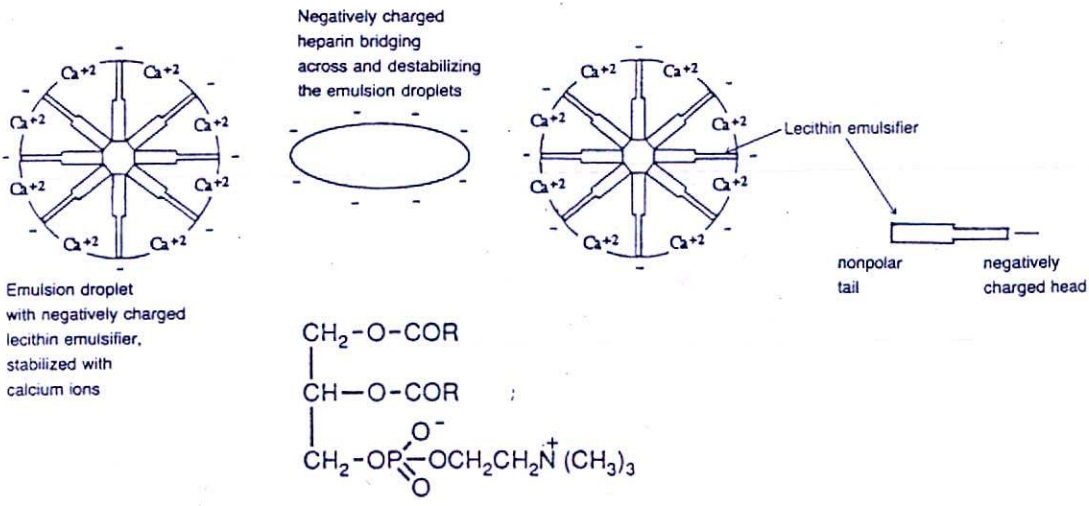

Fig. 18–10. Parenteral emulsion droplets in the presence of the negatively charged emulsifier lecithin, and stabilized by electrostatic repulsion by calcium ions. The emulsion may be flocculated and destabilized by the bridging effect of heparin, a negatively charged polyelectrolyte, which overcomes 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, reproduced with permission of the copyright owner.)

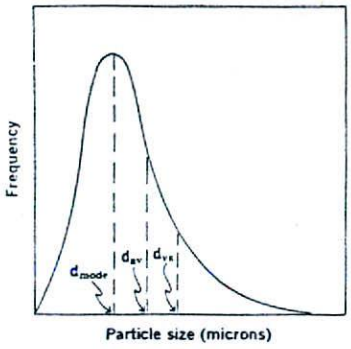

Fig. 18–11. Particle size distribution of an emulsion. Such curves ordinarily are skewed to the right as shown in the figure, and the mode diameter, i.e., the highest point on the curve or the most frequent value, is seen to occur at the lower end of the scale of diameters. The arithmetic mean diameter 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 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,[44] the only precise method for determining stability involves a size-frequency analysis of the emulsion from time to time as the product ages. For 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 μm, 1.0 to 1.9 μm, 2.0 to 2.9 μm, etc., is made as shown in Figure 18–11. 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.[45] 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[46] 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[46] 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, since 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.,[31] however, deemed this method unsatisfactory since the globules may 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[44] 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–freezing cycles, and centrifugation.

Merrill[47] introduced the centrifuge method to evaluate the stability of emulsions. Garrett, Vold, and others[48] have used the ultracentrifuge as an analytic technique in emulsion technology. Coulter counting (p. 434), turbidimetric analysis, and temperature tests have also been used in an effort to evaluate new emulsifying agents and to determine the stability of pharmaceutical emulsions. Garti and Magdassi[49] developed a method to evaluate the stability of oil–water viscous emulsions (ointments and cosmetic creams) containing nonionic surfactants. The method is based on electrical conductivity changes (see pp. 127–128 for conductivity) during nondestructive short heating–cooling–heating cycles. Conductivity curves are plotted during the temperature cycling. A stability index is defined as Δ/h, where h is the change in the conductivity between 35° and 45° C and Δ is the conductivity interval within the two heating curves at 35° C, as shown in Figure 18–12. 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 HLB's, emulsifier concentrations, and oil phase concentrations. The authors reviewed earlier work on electrical 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 may also be produced by alterations in phase–volume ratio. In the manufacture of an emulsion, one can mix an *o/w*

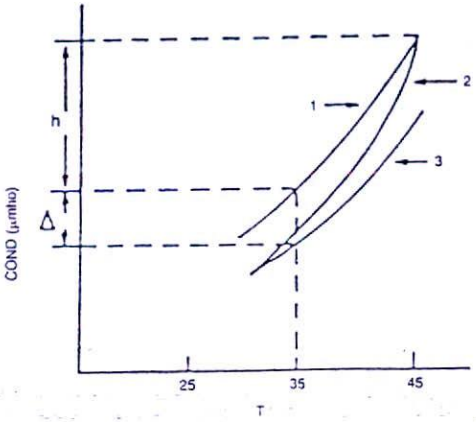

Fig. 18–12. A conductivity versus temperature plot involving successively (1) heating, (2) cooling, and (3) heating. (From N. Garti and S. Magdassi, Drug Dev. Ind. Pharm. 8, 475, 1982, reproduced with permission of the copyright owner.)

emulsifier with an oil and then add a small amount of water. Since the volume of the water is small compared with 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

While 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.[50] 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 are 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 since 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 of the text. The distribution of solutes between immiscible solvents was presented in Chapter 10, and the preservative action of weak acids in oil–water systems was introduced on page 240. Binding of molecules was discussed in Chapter 12, and the student should consult that chapter for information regarding the types of interaction that are possible between preservative molecules and the components of emulsions, such as nonionic surfactants. 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.[50]

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 usage 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 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 have been discussed in Chapter 17. Most emulsions, except dilute ones, exhibit non-Newtonian flow, which complicates interpretation of data and quantitative comparisons between different systems and formulations. In a comprehensive review,

Sherman[51] has 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[51] and the book *Rheology of Emulsions*.[52]

The factors related to the dispersed phase include the phase–volume ratio, 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; the wider the particle size distribution, the lower 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 points 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, since 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 or macroemulsions, an emulsifying adjunct or cosurfactant is used in the preparation of microemulsions. An anionic surfactant, sodium lauryl sulfate or potassium oleate, may 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[53] showed that by choosing a surfactant and cosurfactant that have similar HLB values, solubilization of an organic liquid in water may be increased and the microemulsion droplet size enlarged 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.

The microemulsion region is usually characterized by constructing ternary-phase diagrams, as shown in Figure 18–13, the axes representing water, mineral oil, and a mixture of surfactant and cosurfactant at differ-

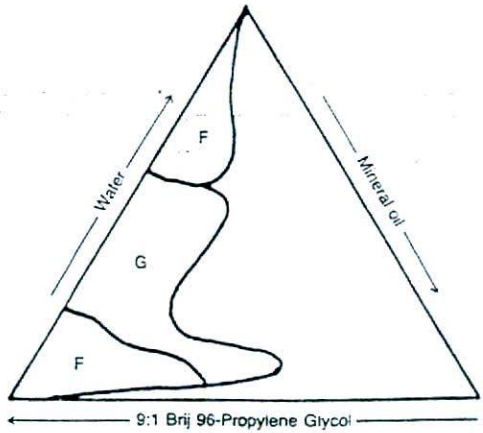

Fig. 18–13. A ternary-phase diagram of water, mineral oil, and a mixture of surfactants showing the boundary of the microemulsion region. The zones within the microemulsion region are labeled F for fluid and G for gel. (From N. J. Kale and L. V. Allen, Jr., Int. J. Pharm. 57, 87, 1989, reproduced with permission of the copyright owner.)

ent ratios.[54] 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[54] 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 18–13 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 (see Chapter 15, p. 399). Since 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.[54] Attwood and Ktistis[55] have shown that the extrapolation procedure often cannot be applied, since many microemulsions exhibit phase separation on dilution. They described a procedure to overcome these difficulties and to obtain true particle diameter using light scattering.

Microemulsions have been studied as drug delivery systems. They can be used to increase bioavailability of drugs poorly soluble in water by incorporation of the drug into the internal phase. Halbert et al.[56] 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.[57] 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.[58] compared delivery through hairless mouse skin of cetyl alcohol and octyl dimethyl 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 antiinflammatory drugs. Microemulsions presently are used in cosmetic science,[59] foods, dry cleaning, and wax polishing products.[60]

SEMISOLIDS

Gels. A gel is a solid or 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.

Gels may be classified either as two-phase or as 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 (Figure 18–14*a*, *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 (Figure 18–14*c*). 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 18–14*d*. Examples of such gels are tragacanth and carboxymethylcellulose. These gels are considered to be one-phase systems since no definite boundaries exist between the dispersed macromolecules and the liquid.

Gels may be classified as *inorganic* and *organic*. Most inorganic gels can be characterized as two-phase sys-

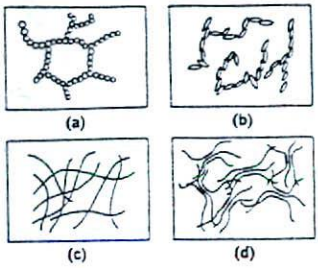

Fig. 18–14. Representations of gel structures. (*a*) Flocculated particles in a two-phase gel structure. (*b*) Network of elongated particles or rods forming a gel structure. (*c*) Matted fibers as found in soap gels. (*d*) Crystalline and amorphous regions in a gel of carboxymethylcellulose. (After H. R. Kruyt, *Colloid Science*, Vol. II. Elsevier, New York, 1949.)

tems, while organic gels belong to the single-phase class since 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, while petrolatum falls in the latter group.

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.[61] 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 may be expressed in general as

$$F = \frac{M_t}{M_0} = kt^n \qquad (18\text{–}9)$$

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 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.[62] Morimoto et al.[63] 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 hours.

Example 18–6. The release fraction F of indomethacin is 0.49 at $t = 240$ min. Compute* the diffusional exponent, n, knowing that $k = 3.155\%\ \text{min}^{-n}$.

*See Problem 18–11 for calculation of the rate constant, k.

Since the rate constant k is expressed as percent, the fractional release, F, is also expressed in percentage units in equation (18–9), that is, 49%. Taking the ln on both sides of equation (18–9),

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

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

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

Therefore, with the exponent of t equal to 0.5, equation (18–9) 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 term "*bleeding*" used 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[64] 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 hr gives the swelling isotherms (Fig. 18–15). The horizontal portions of the two isotherms correspond to equilibrium swelling. To

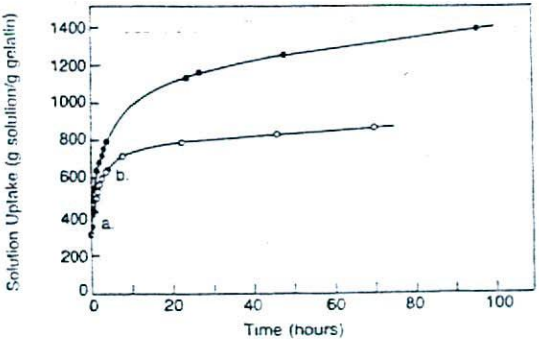

Fig. 18–15. Swelling isotherms of gelatin at two temperatures: ● at 25° C; ○ at 20° C. Swelling is measured as the increase in weight of gelatin strips in buffer solution after various times. The points a and b of this figure are discussed on p. 498. (From C. M. Ofner, III and R. Schott, J. Pharm. Sci. 75, 790, 1986, reproduced with permission of the copyright owner.)

obtain a linear expression, t/W is plotted against t (the plot is not shown here) according to the equation

$$\frac{t}{W} = A + Bt \qquad (18-10)$$

Rearranging and differentiating equation (18–10), we obtain

$$\frac{dW}{dt} = \frac{A}{(A + Bt)^2} \qquad (18-11)$$

As $t \rightarrow 0$, equation (18–11) gives the *initial swelling rate*, $dW/dt = 1/A$, which is the reciprocal of the intercept of equation (18–10). The reciprocal of the slope, $1/B = W_\infty$, is the *equilibrium swelling*, that is, the theoretical maximum uptake of buffer solution at t_∞.

Example 18–7. 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 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

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

Equation (18–10) represents a second-order process. When the constants A and B are used to back-calculate 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 (see Fig. 18–15). Ofner and Schott[64] attributed the deviations to the partially crystalline structure of gelatin. Thus, the first part of the curve (a) in Figure 18–15 corresponds to the swelling of the amorphous region, which is probably complete at times corresponding to maximum curvature, namely 6 to 10 hours 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) in Fig. 18–15).

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 charge the dissolution rate of soft gelatin capsules. Ofner and Schott[65] 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_∞ substantially, while the nonionic and anionic compounds increased it. The researchers suggested that the cationic additives such as quarternary 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 since diffusion of drugs in hydrogels depends on the water content in the hydrogel. Kou et al.[66] used phenylpropanolamine as a model compound to study its diffusion in copolymers of 2-hydroxyethyl methacryiate and methacrylic acid cross-linked with tetraethylene glycol dimethacryiate. The drug diffusivity D in the gel matrix is related to the matrix hydration by the relationship

$$\ln D = \ln D_o - K_f\left(\frac{1}{\mathrm{H}} - 1\right) \qquad (18-12)$$

where D_o 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

$$\mathrm{H} = \frac{\text{equilibrium swollen gel weight} - \text{dry gel weight}}{\text{equilibrium swollen gel weight}}$$

According to equation (18–12), a plot of ln D against $1/(\mathrm{H} - 1)$ should be linear with slope K_f and intercept ln D_o (see *Problem 18–14*).

Example 18–8. 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 $D_o = 1.82 \times 10^{-6}$ cm²/sec, and K_f, the constant of equation (18–12), = 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, since 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 18–2. 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

*The data are calculated from the slope and intercept given in Table III in reference 65.

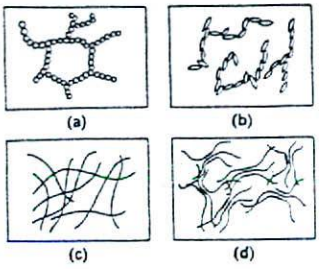

Fig. 18–14. Representations of gel structures. (*a*) Flocculated particles in a two-phase gel structure. (*b*) Network of elongated particles or rods forming a gel structure. (*c*) Matted fibers as found in soap gels. (*d*) Crystalline and amorphous regions in a gel of carboxymethylcellulose. (After H. R. Kruyt, *Colloid Science*, Vol. II, Elsevier, New York, 1949.)

tems, while organic gels belong to the single-phase class since 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, while petrolatum falls in the latter group.

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.[61] 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 may be expressed in general as

$$F = \frac{M_t}{M_0} = kt^n \qquad (18-9)$$

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 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.[62] Morimoto et al.[63] 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 hours.

Example 18–6. The release fraction F of indomethacin is 0.49 at $t = 240$ min. Compute* the diffusional exponent, n, knowing that $k = 3.155\%\ \text{min}^{-n}$.

*See Problem 18–11 for calculation of the rate constant, k.

Since the rate constant k is expressed as percent, the fractional release, F, is also expressed in percentage units in equation (18–9), that is, 49%. Taking the ln on both sides of equation (18–9),

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

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

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

Therefore, with the exponent of t equal to 0.5, equation (18–9) 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 term "*bleeding*" used 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[64] 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 hr gives the swelling isotherms (Fig. 18–15). The horizontal portions of the two isotherms correspond to equilibrium swelling. To

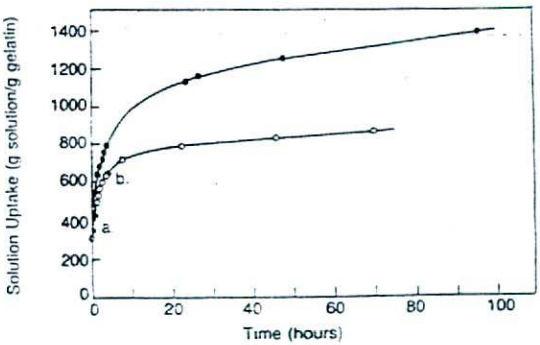

Fig. 18–15. Swelling isotherms of gelatin at two temperatures: ● at 25° C; ○ at 20° C. Swelling is measured as the increase in weight of gelatin strips in buffer solution after various times. The points a and b of this figure are discussed on p. 498. (From C. M. Ofner, III and H. Schott, J. Pharm. Sci. 75, 790, 1986, reproduced with permission of the copyright owner.)

not lose water readily by evaporation since water is the internal phase. While 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 may be expressed in terms of the *water number*, first defined in 1935 by Casparis and Meyer[67] as the maximum quantity of water that is held (partly emulsified) by 100 g of a base at 20° C. The test consists of 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 was 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 (p. 466) is particularly well adapted for the analysis of semisolid emulsions and suspensions. The Stormer viscometer (p. 464), consisting of a stationary cup and rotating bob, is also satisfactory for semisolids when modified as suggested by Kostenbauder and Martin.[68]

Consistency curves for the emulsifiable bases, hydrophilic petrolatum and hydrophilic petrolatum in which water has been incorporated, are shown in Figure 18–16. It will be observed that the addition of water to hydrophilic petrolatum has lowered the yield-point (the intersection of the extrapolated down-curve 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 18–17 and 18–18 show the changes of plastic viscosity and thixotropy of petrolatum and Plastibase as a function of temperature.[69] The modified Stormer viscometer was used to obtain these curves. As observed in Figure 18–17, 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

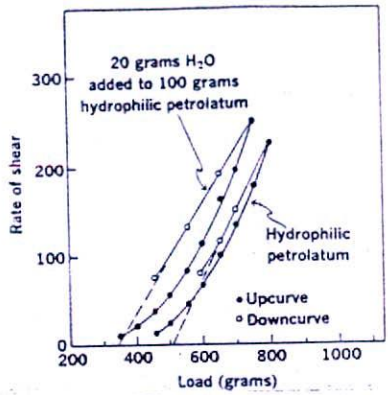

Fig. 18–16. Flow curves for hydrophilic petrolatum and hydrophilic petrolatum containing water. (After H. B. Kostenbauder and A. Martin, J. Am. Pharm. Assoc., Sci. Ed. 43, 401, 1954.)

"softness" when rubbed between the fingers. Curves of yield value versus temperature were found to follow approximately the same relationship. The curves of Figure 18–18 suggest strongly that it is the alternation of thixotropy with temperature that differentiates the two bases. Since thixotropy is a consequence of gel structure, Figure 18–18 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,

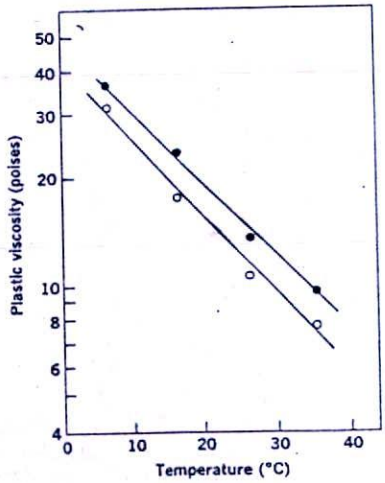

Fig. 18–17. The temperature coefficient of plastic viscosity of Plastibase, ● (E. R. Squibb and Sons) and petrolatum, ○. (After A. H. C. Chun, M. S. Thesis, Purdue University, June, 1956.)

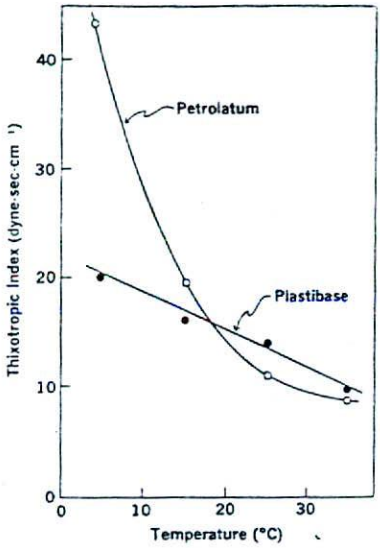

Fig. 18–18. The temperature coefficient of thixotropy of Plastibase (E. R. Squibb and Sons) and petrolatum. (After A. H. C. Chun, M. S. thesis, Purdue University, June, 1956.)

the worker in the production plant can better control the uniformity of the finished product, and the dermatologist and 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[70] 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,

$$-df/dt = k_f f^2 \qquad (18-13)$$

The integral form of equation (18–13) is

$$\frac{1}{f} - \frac{1}{f_0} = k_f t \qquad (18-14)$$

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, where g stands for gram. The quantities f_0 and k_f can be computed from the intercept and the slope of equation (18–14) at a given temperature.

Example 18–9. The rigidity degradation of a 6% pharmaceutical-grade gelatin USP was studied[70] 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 $t = 0$ the intercept $1/f_0 = 0.0167\ g^{-1}$; $f_0 = 59.9$ g. The slope $= k_f = 1.5 \times 10^{-4}\ g^{-1}\ hr^{-1}$. Using the regression equation, one is able to 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 hours.

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

$$k_f = Ae^{-E_a/RT} \qquad (18-15)$$

Thus, a plot of ln k_f against $1/T$ gives the Arrhenius constant A and the energy of activation E_a (see *Problem 18–15*).

Fassihi and Parker[71] 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 18–19. 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[72] has devised a "universe of topical medications" (Fig. 18–20), 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 18–20, one is confronted with the simple powder medication, used as a protective, drying agent, and lubricant and as a carrier for locally applied drugs.

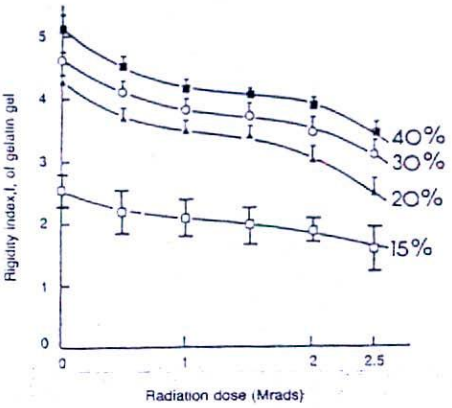

Fig. 18–19. Rigidity index of gelatin gel as a function of gamma irradiation at various concentrations (15–40%) of the gel. (From A. R. Fassihi and M. S. Parker, J. Pharm. Sci. 77, 876, 1988, reproduced with permission of the copyright owner.)

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.

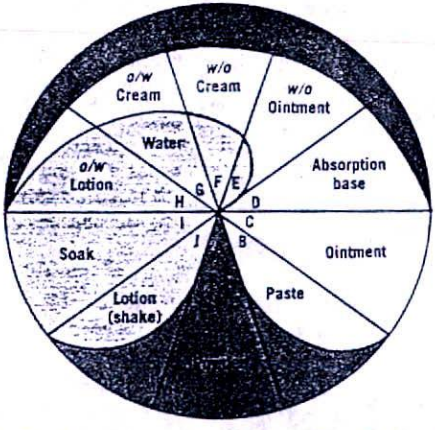

Fig. 18–20. Universe of topical medication. (From M. Katz, Design of topical drug products, in *Drug Design*, E. J. Ariens, Ed., Academic Press, New York, 1973, reproduced with permission of the copyright owner.)

DRUG KINETICS IN COARSE DISPERSE SYSTEMS

The kinetics of degradation of drugs in suspension[73] can be described as a pseudo–zero-order process (see Chapter 12, p. 286).

$$M = M_0 - k_1 V C_s t \qquad (18-16)$$

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 may be described as found in the section on solid state kinetics (see Chapter 12, p. 313). For very viscous dispersed systems, the kinetics of degradation may be partially controlled by the dissolution rate as given by the Noyes–Whitney equation (p. 331),

$$dc/dt = KS(C_s - C) \qquad (18-17)$$

where C_s is the solubility of the drug, C the concentration of solute at time t, S the surface area of the expanded solid, and K 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 may be written as

$$dc/dt = -kC + KS(C_s - C) \qquad (18-18)$$

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

$$C = [C_s KS/(k_1 + KS)]e^{-(k_1+SK)t} \qquad (18-19)$$

At large t values, C becomes

$$C = C_s KS/(k_1 + KS) \qquad (18-20)$$

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

$$M = M_0 - [k_1SKC_sV/(k_1 + KS)]t \quad (18-21)$$

where M_0 is the initial amount of drug in suspension. Equation (18–21) is an expression for a zero-order process, as is equation (18–16), but the slopes of the two equations are different. Since the dissolution rate constant, K, in equation (18–21) is proportional to the diffusion coefficient D (p. 331), K is inversely proportional to the viscosity of the medium; therefore, the more viscous the preparation the greater is the stability.

Example 18–10. The first-order decomposition rate of a drug in aqueous solution is 5.78×10^{-4} sec^{-1}, and the dissolution rate constant, K, is 3.35×10^{-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 $d_{vm} = 2 \times 10^{-4}$ cm. The density of the powder is 3 g/cm^3, and the solubility of the drug is 2.8×10^{-4} g/cm^3.

The initial amount of drug is

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

The number of particles N in 25 cm^3 can be computed from equation (16–4), page 430:

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

$$= 7.95 \times 10^{10} \frac{\text{particles}}{\text{gram}}$$

The number of particles in 1.25 grams 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 (18–21),

$$M = 1.25 - \left[\frac{5.78 \times 10^{-4} \times 1.25 \times 10^4 \times 3.35 \times 10^{-6} \times 2.8 \times 10^{-4} \times 25}{5.78 \times 10^{-4} + (3.35 \times 10^{-6} \times 1.25 \times 10^4}\right]$$

$$\times (2.6 \times 10^5 \text{ sec})$$

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

Kenley et al.[74] 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 (see p. 304)

$$k = k_o + k_H[H^+] + k_{OH}[OH^-] \quad (18-22)$$

where the k_i values represent the specific rates (catalytic coefficients) associated with the various catalytic species. Figure 18–21 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.[74]

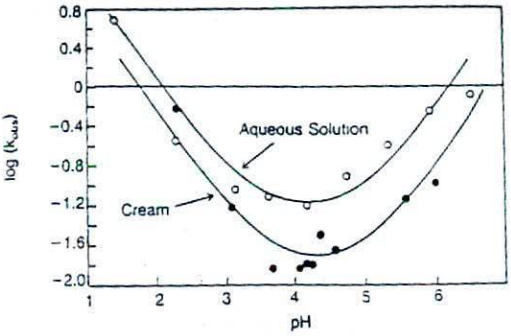

Fig. 18–21. pH–log(k_{obs}) profile for degradation of fluocinolone acetonide and triamcinolone acetonide at 50° C. Key: ● = experimentally determined k_{obs} (month^{-1}) for fluocinolone acetonide cream; ○ = triamcinolone acetonide solution. The solid lines were obtained from the calculated values of k_{obs} using equation (18–22). (From A. Kenley, M. O. Lee, L. Sukumar and M. Powell, Pharm. Res. 4, 342, 1987, reproduced with permission of the copyright owner.)

Since $\ln k = \ln A - E_a/RT$, where A is the Arrhenius factor and E_a is the energy of activation, equation (18–22) 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}:

$$k = \exp[\ln A_o - (E_{ao}/RT)] + \exp[\ln A_H - (E_{aH}/RT)][H^+] + \exp[\ln A_{OH} - (E_{aOH}/RT)][OH^-] \quad (18-23)$$

Equation (18–23) allows one to compute the degradation rate constant k at several temperatures and pH values.

Example 18–11. The natural logarithm of the Arrhenius parameters for neutral-, acid-, and base-catalyzed hydrolysis of fluocinolone acetonide in oil-in-water creams is $\ln A_O = 22.5$, $\ln A_H = 38.7$, and $\ln A_{OH} = 49.5$. The corresponding energies of activation are $E_{aO} = 17{,}200$, $E_{aH} = 22{,}100$, and $E_{aOH} = 21{,}100$ cal/mol. The H^+ and OH^- concentrations in equation (18–23) 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 (18–23),

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

$$(5.782 \times 10^{-3}) + (2.025 \times 10^{-3}) + (5.820 \times 10^{-4})$$

$$k = 8.39 \times 10^{-3} \text{ month}^{-1}$$

Teagarden et al.[75] 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 (p. 336):

$$Q = [D(2A - C_s)C_s t]^{1/2} \qquad (18-24)$$

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.[76] 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 (18–24)). This behavior was attributed to formation of 1:1 and 1:2 complexes between hexylresorcinol and ethyl myristate.

Example 18–12. The solubility of hexylresorcinol in petrolatum base is 0.680 mg/cm^3. After addition of 5% ethyl myristate, the solubility C_s of the drug is 3.753 mg/cm^3. Compute the amount Q of drug released after 10 hours. The diffusion coefficient D is 1.31×10^{-5} cm^2/sec and the initial concentration A is 15.748 mg/cm^3.

$$Q = \{1.31 \times 10^{-5}\ cm^2/sec\ [(2 \times 15.748\ mg/cm^3) - 0.68\ mg/cm^3]\}^{\frac{1}{2}} \times$$

$$[0.68\ mg/cm^3 \times (10 \times 3600)\ sec]^{\frac{1}{2}} = 0.099\ mg/cm^2$$

After addition of 10% ethyl myristate

$$Q = \{1.31 \times 10^{-5}\ cm^2/sec\ [(2 \times 15.748\ mg/cm^3) - 3.753\ mg/cm^3]\}^{\frac{1}{2}} \times$$

$$[3.753\ mg/cm^3 \times (10 \times 3600)\ sec]^{\frac{1}{2}} = 0.222\ mg/cm^2$$

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[77] 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:[78]

$$Q = 2\,C_0\sqrt{\frac{D_e t}{\pi}} \qquad (18-25)$$

in which 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,

$$D_e = \frac{D_1}{\phi_1 + K\phi_2}\left[1 + 3\,\phi_2\left(\frac{KD_2 - D_1}{KD_2 + 2D_1}\right)\right] \qquad (18-26)$$

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 $D_2 >> D_1$,

$$D_e = \frac{D_1(1 + 3\,\phi_2)}{\phi_1 + K\,\phi_2} \qquad (18-27)$$

D_e, the effective diffusion coefficient, is obtained from the release studies (equation (18–25)), and D_1 can be computed from equation (18–27) if one knows the volume fraction of the external and internal phases, ϕ_1 and ϕ_2, respectively. The drug is released according to two separate rates: an initial nonlinear and a linear diffusion-controlled rate (Fig. 18–22). The initial rates extending over a period of 30 minutes 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 absorption. In addition, the release of drug from the external phase contributes to the initial rates. Equation (18–25) is applicable only to the linear portion of the graph where the process becomes diffusion-controlled (see Fig. 18–22).

Example 18–13. Compute the amount of lonapalene released per cm^2 after t = 24 hours from a 0.5% *w/w* 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 ϕ_2 is 0.028, the diffusion coefficient of the drug in the external phase is $D_1 = 2.60 \times 10^{-5}$ cm^2/sec, and the partition coefficient K between the internal and external phases is 69.

From equation (18–27), the effective diffusion coefficient is

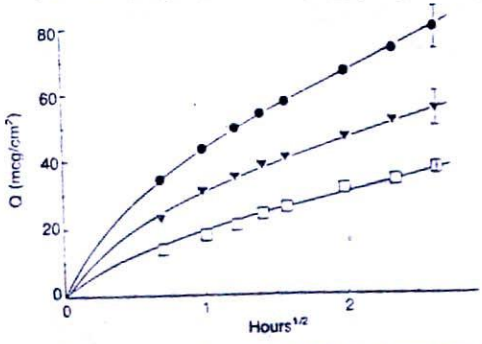

Fig. 18–22. Amount per unit area Q of lonapalene at time t from an emulsion-type ointment. Key: □ = 0.5%; ▼ = 1.0%; and ● = 2.0% drug. (From J. T. H. Ong and E. Manoukian, Pharm. Res. 5, 16. 1988, reproduced with permission of the copyright owner.)

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

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

Note that the sum of the volume fractions of internal and of external phases = 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 (18–25), the amount of lonapalene released after 24 hours 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 depends also on the solubility of the drug as influenced by the type of emulsion. Rahman et al.[79] 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 (18–25), 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.[80] 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.[81] Since 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.[81] found that the release of ethyl 4-biphenyl acetate, an antiinflammatory drug, from a lipid suppository base was enhanced by complexation of the drug with a hydrosoluble derivative of β-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.[82] 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.[83]

Nyqvist-Mayer et al.[84] 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 18–23. 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" (see pp. 68, 106). 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, 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:

$$R_T = R_a + R_m \tag{18–28}$$

or

$$R_T = \frac{1}{P} = \frac{h_m}{D_m K} + \frac{h_a}{D_a} \tag{18–29}$$

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

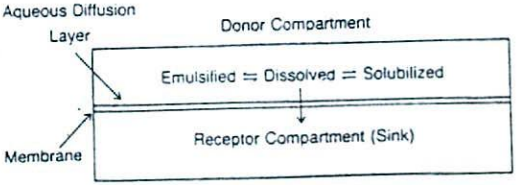

Fig. 18–23. Delivery of a eutectic mixture of lidocaine–prilocaine from an emulsion into a receptor compartment. (From A. A. Nyqvist-Mayer, A. F. Borodin and S. G. Frank, J. Pharm. Sci. 75, 365, 1986, reproduced with permission of the copyright owner.)

is the partition coefficient between the membrane and the aqueous layer. The subscripts a and m stand for aqueous layer and membrane, respectively. Equation (18–29) is analogous to equation (13–55) (p. 338) except that the constant 2 in the denominator has been eliminated in this case because we consider only one aqueous layer (Fig. 18–24).

Example 18–14. Compute the total permeability P of a 1:1.3 ratio of lidocaine–prilocaine in the form of a eutectic mixture. The thickness of the aqueous and membrane layers are 200 μm and 127 μm, 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, $D_m = 2.6 \times 10^{-7}$ 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 (18–29),

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

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

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

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.[84] Since 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

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

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

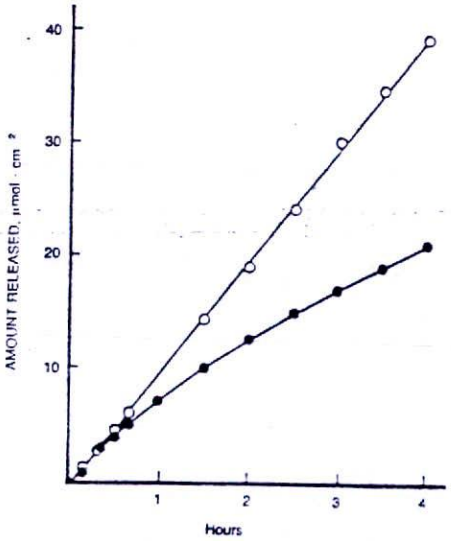

Fig. 18–24. Release of lidocaine–prilocaine from an emulsion (○) and from a gel (●). (From A. A. Nyqvist-Mayer, A. F. Borodin and S. G. Frank, J. Pharm. Sci. 75, 365, 1986, reproduced with permission of the copyright owner.)

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 rate from the gel and the emulsion is compared in Figure 18–24. 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 hour, 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 (equation (18–24)). The release process is both membrane layer and aqueous layer controlled for nongelled systems (emulsions). See page 338 and 339 for a description of membrane and aqueous layer control. For gelled systems the initial release is also membrane layer and aqueous layer controlled, but later, at $t > 1$ hour, 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.

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Problems

18–1. A hypothetical suspension contains 10^3 spherical particles of diameter $d = 10^{-3}$ cm. (a) Assuming that the interfacial tension between the solid and the liquid is γ_{SL} = 100 dyne/cm, compute the total surface free energy, G. (b) The solid particles are divided to obtain 100 particles from each initial particle. Compute the increase in the total surface area and the total surface free energy G' for the divided particles. *Hint:* Compute the volume of a particle to get its new radius and surface area. Assume that the density of the particle is unity.

Answers: (a) $G = 0.314$ erg; (b) $G' = 1.45$ erg

18–2. A coarse powder with a true density of 2.44 g/cm^3 and a mean diameter d of 100 μm was dispersed in a 2% carboxymethylcellulose dispersion having a density ρ_o of 1.010 g/cm^3. The viscosity of the medium at low shear rate was 27 poises. Using Stokes' law, calculate the average velocity of sedimentation of the powder in cm/sec.

Answer: 2.9×10^{-4} cm/sec

18–3. Using Stokes' law, compute the velocity of sedimentation in cm/sec of a sample of zinc oxide having an average diameter of 1 μm (radius of 5×10^{-5} cm) and a true density ρ of 2.5 g/cm^3 in a suspending medium having a density ρ_o of 1.1 g/cm^3 and a Newtonian viscosity of 5 poises.

Answer: 1.5×10^{-7} cm/sec

18–4. (a) Using the modified Stokes' expression, equation (18–3), compute the n value and v_s of a suspension of kaolin that contains tragacanth as a flocculating agent. The variation of the rate of fall v' measured at the sedimentation boundary, and the initial porosity ϵ (dimensionless) are given in the following table:

Data for *Problem 18–4**

ϵ	0.90	0.95	0.97	0.99
v' (cm/sec)	0.00164	0.038	0.127	0.415

*Data estimated from K. S. Alexander, J. Azizi, D. Dollimore and F. A. Patel, Drug Dev. Ind. Pharm. 15, 2559, 1989.

(b) Compute the Stokes' diameter, d_{st}, of the flocs. The density of kaolin is 3.15 g/cm^3. Assume that the density and the viscosity of the aqueous medium, respectively, are 1 g/cm^3 and 0.01 poises. *Hint:* See the paper by Alexander et al. referred to in the table above. These workers obtain n as the slope and v_{st}, the Stokes velocity of sedimentation, as the intercept of a plot of log v' (y-axis) versus log ϵ

(z-axis). Using v and Stokes' law (equation (18–2)) yields the Stokes' diameter.

Answers: (a) n = 57.23 (dimensionless), v_{ss} = 0.70 cm/sec; (b) d_{ss} = 77 μm

18–5. Using the accompanying table, Data for Problem 18–5, and following the example shown in Figure 18–3, plot both H_u/H_o and the zeta potential, ζ, on the vertical axis against the concentration of $AlCl_3$. Note that sedimentation height is used here instead of volume. H_u is the ultimate height and H_o is the initial height of sedimentation. Draw vertical lines to separate the caking from noncaking regions of the diagram. Explain the changes in the H_u/H_o values, the changes in ζ potential, and the changes in the sign of the charge on the sulfamerazine particles as the concentration of aluminum chloride is increased. Discuss flocculation and deflocculation in relation to the caking and noncaking regions of the diagram. Graph paper with a five-cycle log scale on the horizontal axis is needed to accommodate the wide range of concentrations of the $AlCl_3$ solutions.

Answer: See pages 480 to 483 of the text.

18–6. From the data on griseofulvin given in the table below, plot both zeta potential, ζ, and V_u/V_o as shown in Figure 18–3. Draw vertical dashed lines on the graph and label each area to show: Caking Zone, Caked But Easily Dispersed Zone, Noncaking Zone, and the zone labeled Flocculated Initially but Potential Caking Later. The latter zone possibly forms caked suspensions over time. Discuss the V_u/V_o curve in relation to the ζ potential curve and their facility to differentiate the several zones of caking and noncaking. As the charge on the griseofulvin particles change with increasing concentration of $AlCl_3$, how is the caking of the suspension altered? You will

Data for *Problem 18–5:*
Sedimentation Height and Zeta Potential of Sulfamerazine in the Presence of Aluminum Chloride

$AlCl_3$ (mmole/liter)	H_u/H_o	ζ millivolts	Caking Condition
0.0	0.03	−63.4	Hard cake
0.2	0.03	−50.6	Hard cake
0.6	0.03	−38.6	Hard cake
1.0	0.08	−28.2	Slight cake
2.0	0.10	−25.4	No cake
6.0	0.10	−19.6	No cake
10.0	0.10	−14.0	No cake
20.0	0.09	−15.8	No cake
60.0	0.08	−4.0	No cake
100.0	0.08	+4.1	No cake
400.0	0.07	+3.7	No cake
600.0	0.06	−8.2	Viscous
1000	0.07	−13.5	Viscous

Data for *Problem 18–6:*
F Values and Zeta Potential of Griseofulvin Suspension in the Presence of Aluminum Chloride as Flocculating Agent*

$AlCl_3$ Sol'n (molarity)	ζ, Zeta Potential millivolts	*F* value V_u/V_o	Supernatant	Caking Conditions
0.0	−49.8	0.020	Opalescent	No flocculation, difficult to redisperse, caked
1×10^{-4}	−42.3	0.035	Opalescent	
5×10^{-4}	−27.9	0.140	Opalescent	Caked but easily redispersed
1×10^{-3}	−13.5	0.136	Clear	Floccule formation, easily redispersed, no caking
2×10^{-3}	−13.3	—	—	—
5×10^{-3}	−8.83	—	—	—
7.5×10^{-3}	−6.09	—	—	—
1×10^{-2}	0.0	0.144	Clear	Floccule formation, easily redispersed, no caking
1.5×10^{-2}	11.2	—	—	—
2.0×10^{-2}	11.7	0.121	Clear	Floccule formation initially but possible caking later
5.0×10^{-2}	21.1	0.123	Clear	
1×10^{-1}	24.1	0.140	Clear	

*From B. Milian-Hernandez, Thesis, University of Texas, 1981.

need graph paper with a four-cycle log scale on the horizontal axis (four-cycle semilog paper) for the concentration of the $AlCl_3$ solution.

18–7. Schott[88] studied the flocculation of bismuth subnitrate (diameter 3 μm) in aqueous suspension by bentonite platelets (diameter 0.2 μm). The negatively charged bentonite plates are adsorbed on and coat the much larger positively charged and lath-shaped (i.e., thin plate-like bodies) bismuth subnitrate particles. Use the data in the accompanying table to plot the sedimentation volume in milliliters and the zeta potential against the weight ratio of bentonite–bismuth subnitrate.

(a) Explain the significance of the sedimentation volume and the zeta potential curves.

(b) Show the regions of the diagram where caking and noncaking would be expected to occur.

(c) Explain how it is possible for bentonite to act as a flocculating agent similar to an electrolyte such as $AlCl_3$ or potassium phosphate.

Partial Answer: (b) See pages 482 to 483 of the text; (c) See J. Pharm. Sci. 65, 355, 1976.

Data for *Problem 18–7:*
Sedimentation Volumes and Zeta Potential of Bentonite–Bismuth Subnitrate Mixtures*

Mixture number	Bentonite % (W/W)	Bismuth Subnitrate %(W/W)	Weight Ratio†	Sediment Volume (after 18 hr)	ζ millivolts
1	0	13.18	0	5	—
2	0.00114	13.18	8.65×10^{-5}	5	+26.8
3	0.00568	13.18	4.3×10^{-4}	6	+30.2
4	0.0114	13.18	8.62×10^{-4}	6.5	+6.8
5	0.0568	13.18	4.35×10^{-3}	7	−10.4
7	0.2270	13.16	1.67×10^{-2}	12	−20.8
13	0.561	7.92	7.14×10^{-2}	43	−21.4
15	0.932	7.90	1.18×10^{-1}	59	−30.6
16	1.320	7.88	1.67×10^{-1}	85	−23.2

*The ratio, bismuth subnitrate–bentonite, has been inverted in this problem and several values in Tables I, II, and III of Schott have been eliminated. The electrophoretic mobility values of Table III have been converted to ζ values.
†Weight ratio per cent of bentonite–bismuth subnitrate.

18–8. It is possible to determine the concentration of soap present as a monomolecular layer at the surface of the oil globules in an emulsion by centrifuging the emulsion, removing the cream layer, acidifying it, and titrating with sodium hydroxide. By the use of this method, the concentration of sodium oleate at the interface of a mineral oil emulsion was found to be 0.02 mole sodium oleate per liter of oil. The particles were found by a microscopic method to have a mean diameter of 1.0 μm (1×10^{-4} cm). Calculate the mean area of a soap molecule at the surface of an oil globule in the emulsion. Explain the discrepancy between the calculated value and the value, 25 $Å^2$, for the area of a soap molecule as found by the film balance method.

Answer: 50 $Å^2$. Apparently the film of molecules at the surface of an oil globule is not as condensed as that obtained in the film balance method. See pages 376 to 378 and Figures 14–18 and 14–19.

18–9. Mineral oil was dispersed as globules in an oil–water emulsion to form a total surface area of globules of 10^8 cm^2. If the presence of an emulsifying agent results in an interfacial tension between the oil and the water phase of 5 erg/cm^2, what is the total surface free energy of the system in calories, in SI units?

Answer: ΔG = 12 cal, 5×10^8 erg, 50.2 joule

18–10. A series of mineral oil emulsions was prepared using various combinations of Span 80 and Tween 80 (Atlas, ICI). The Span–Tween ratio of the best emulsion was found to be 40/60. Compute the HLB of this mixture. Span 80 has an HLB of 4.3 and Tween 80 an HLB of 15.0 (*Hint:* The HLB contributions of each emulsifier are obtained by multiplying the HLB of the agent by the fraction it contributes to the emulsifier phase.)

Answer: HLB = 10.7.

18–11. (a) Calculate the *required HLB*, abbreviated *RHLB*, for the oil phase in the oil-in-water lotion:

Mineral oil, light	10 g
Petrolatum	25
Stearic acid	15
Beeswax	5
Emulsifier	2
Preservative	0.2
Water	42.8
Perfume	q.s.

Hint: Multiply the percentage (actually the *fraction*, which is the percentage divided by 100) of each oil phase ingredient by its RHLB (Table 14–6) and sum to obtain the RHLB for the lotion.

(b) Calculate the amount in grams of an emulsifier pair, Tween 60 and Arlacel 60, to produce a stable oil-in-water emulsified lotion. The HLB of Tween 60 is 14.9 and that of Arlacel 60 is 4.7.

(c) State how you would combine the ingredients to produce a stable product.

Answers: (a) RHLB of the oil phase = 11.88; (b) Tween 60, 1.4 grams; Arlacel 60, 0.6 gram.

18–12. The rate constant k and the diffusional exponent n of equation (18–9) can be obtained respectively from the intercept and the slope of a plot of ln F versus ln t, where $F = (M_t/M_\infty) \times 100$ is the fractional release of drug from a gel (expressed as percentage), M_∞ being the initial amount of drug and M_t the amount released at time t. Assume the following results for the delivery of a drug from a gel:

Data for *Problem 18–12*

t (min)	10	20	50	100	200
F (%)	6.28	10.21	19.38	31.49	51.15

(a) Using regression analysis of ln F (dependent variable) versus ln t (independent variable) compute the rate constant k and diffusional exponent n. Does the release follow a Fickian model?

(b) What is the fractional release in percent at 73 minutes?

(c) Compute the time at which 100% of the drug is released from the gel.

Answers: (a) $n = 0.7$; $k = 1.251\%\ min^{-0.7}$; (b) $(M_t/M_\infty) \times 100 = F = 25.2\%$; (c) 523 min

18–13. Ofner and Schott[65] studied the effect of cetylpyridinium chloride, a cationic compound, on the swelling of gelatin. The weight, W, in grams of an aqueous buffered solution of cetylpyridinium chloride absorbed per gram of dry gelatin as a function of time is:

Data for *Problem 18–13*

t (hr)	0.5	1	1.5	2	3	4
W (g/g)	2.84	3.98	4.60	4.99	5.44	5.71

The regression equation is:

$$t/W = A + Bt$$

in which A is the intercept and B is the slope.

(a) Plot t/W (on the y axis) against time (on the x axis) and compute the *initial swelling rate* given by the reciprocal of the

intercept (1/*A*). Also, calculate the *equilibrium swelling* i.e., the maximum uptake of the solution of the cationic compound, which is given by the reciprocal of the slope (1/*B*). (See *example 18–7* and Figure 18–15.)

(b) Compute the percent increase or decrease in the *W* value for cetylpyridinium chloride in gelatin at 4 hours with respect to the increase in the *W* value for plain gelatin at the same time. For gelatin,

$$A = 0.0755 \frac{\text{hours} \times \text{gram gelatin}}{\text{gram solution}}$$

and $B = 0.132$ (gram gelatin)/(gram solution).

(c) Repeat part (b) for a buffered solution of an anionic compound, dicloxacillin sodium, with respect to plain gelatin. For this anionic compound,

$$A = 0.0310 \frac{\text{hour} \times \text{gram gelatin}}{\text{gram solution}}$$

and $B = 0.110$ (gram gelatin)/(gram solution). Regression analysis may be used in solving this problem.

Answers: (a) $1/A$ = initial swelling rate = 9.9 g/hr; $1/B$ = equilibrium swelling = 6.7 (g solution/g gelatin); (b) −13.7%, a decrease; (c) 28.2%, an increase

18–14. The diffusion coefficients *D* of phenylpropanolamine in swollen poly(hydroxyethyl methacrylate-co-methacrylic acid) hydrogels were measured at several pH values, corresponding to different gel hydration values, H[66]:

Data for *Problem 18–14*

pH	1	3	5	7
H (dimensionless hydration value)	0.352	0.337	0.639	0.880
$D \times 10^6$ cm²/sec	2.50	3.58	44.6	139.0

Compute the diffusion coefficient D_0 of phenylpropanolamine in water and the constant k_f of the system, using equation (18–12), page 498:

$$\ln D = \ln D_e - k_f\left(\frac{1}{H} - 1\right)$$

Answer: $k_f = 2.354$; $D_e = 1.81 \times 10^{-6}$ cm²/sec

18–15. The values of the ln of the rate constant k in grams^{-1} hours^{-1} for the rigidity breakdown of a 6% gelatin solution versus the reciprocal of absolute temperature was found to be:[76]

Data for *Problem 18–15*

$(1/T) \times 10^3$ °K^{-1}	2.90	2.95	3.00	3.10	3.15
ln k	−5.978	−6.429	−6.881	−7.783	−8.235

Compute the activation energy, E_a, for rigidity degradation. Express the result in the Arrhenius exponential form.

Answer: E_a = 17939 cal/mole; $k = 5.938 \times 10^8\, e^{-17939/RT}$ (gram^{-1} hour^{-1})

18–16. The results of a stability study of two brands, B and E, of ampicillin suspension at 5° C after reconstitution of the product are:

Data for *Problem 18–16*[*]

t (days)		2	4	6	8	10
[A] (mg/5 mL)	Brand B	284.49	268.97	253.46	237.94	222.43
	Brand E	294.37	288.74	283.11	277.48	271.85

[*]Data calculated from rate constants given in N. A. Boraie, S. A. El-Fattah and H. M. Hassan, Drug Dev. Ind. Pharm. 14, 831, 1988. The concentrations have been modified somewhat.

[A] is the concentration remaining at the various times, *t* (days). According to the labels, the products are stable for 2 weeks when refrigerated at 5° C. The USP requires that the products contain not less than 90% and not more than 120% of the label claim at this time.

(a) Compute the apparent zero-order rate constants, k_o (mg/5 mL)/day and the initial concentration in (mg/5 mL) of brands B and E at the time of reconstitution.

(b) Compute the time at which the products decompose to 90% of their original concentration (i.e., a decomposition of 10%). Do the suspensions meet the stated requirements under the storage conditions?

Answers: (a) k_o = 7.758 (mg/5 mL)/day (Brand B) and 2.815 (mg/5 mL)/day (Brand E); (b) t_{90} = 3.9 days (Brand B) and 10.6 days (Brand E) at 5° C. Product E satisfies the label claim.

18–17. Compute the energy of activation E_a for the neutral, acid-catalyzed, and base-catalyzed hydrolysis of fluocinolone acetonide in an oil–water emulsion. The rate constants are:[74]

Data for *Problem 18–17*

Temperature (°C)	80	50	40	23
k_{H^+} (M^{-1} month^{-1})	759	72.5	44.7	1.32
k_{OH^-} (M^{-1} month^{-1})	168	17.0	13.6	0.372
k_o (month^{-1})	0.133	0.0116	0.00079	0.00117

Answer: 22,203 cal/mole; 21,161 cal/mole; 18,968 cal/mole

18–18. The amount per unit area, *Q*, of hexylresorcinol released from petrolatum ointment containing 3% of ethyl myristate at various times, *t*, is:

Data for *Problem 18–18*

t (hr)	2	9	16	25
$Q \times 10^3$ mg/cm²	1.45	3.07	4.10	5.12

Plot *Q* (vertical axis) against $t^{1/2}$. Compute the release rate (mg cm^{-2} hr$^{-1/2}$) of the drug from the slope, according to the Higuchi equation 18–24. Compute the diffusion coefficient knowing that *A* is 20 mg/cm³ and the apparent solubility C_s of the drug in the ointment is 2.121 mg/cm³. *A* is the total concentration of the drug, dissolved and undissolved.[76]

Answer: Release rate = 1.02×10^{-3} mg cm^{-2} h$^{-1/2}$; $D = 1.3 \times 10^{-6}$ cm²/hr or 3.6×10^{-12} cm²/sec

18–19. The diffusion coefficient of salicylic acid dispersed in a Plastibase vehicle was found to vary with the particle size of salicylic acid. For particles of 88 μm in diameter, $D = 1.11 \times 10^{-6}$ cm²/sec; and for particles of 5.1 μm in diameter, $D = 1.85 \times 10^{-6}$ cm²/sec, where *D* is the diffusion coefficient. (The diffusion coefficients and solubility are from Al-Khamis et al.[86]) Compute the amount of drug released per unit area at t = 9 hr for both particle sizes using the Higuchi expression, equation (18–24). The initial amount of drug is A = 600 μg/cm³, and the solubility of the drug in the vehicle is C_s = 495 μg/cm³. Is the drug release larger or smaller when the particle size is reduced?

Answer: *Q* (88 μm) = 112 μg/cm²; *Q* (5.1 μm/cm²) = 145 μg/cm²

18–20. In an effort to determine the amount of emulsifier (a soap such as sodium stearate) required to prepare a stable mineral oil emulsion, one must ask the following questions. (Answer each question, (a) through (g), to arrive at the grams of soap for a 100 cm³ emulsion containing oil globules of 1 μm (1×10^{-4} cm) diameter. The emulsion contains 50 cm³ of oil.)

(a) The diameter of each oil globule is, on the average, 1 μm. What is the surface area of each globule? Show all calculations.

(b) If the cross-sectional area of a soap molecule is 25 Å, how many soap molecules can be placed on the surface of each oil droplet to cover it with a layer one molecule thick?

(c) If we produce an emulsion containing 50 cm^3 of oil and 50 cm^3 of water with the oil reduced to particles of 1 μm diameter, how many oil globules are there in the 100 cm^3 emulsion? The density of the oil is 0.90 g/cm^3.

(d) How many molecules of soap (sodium stearate) are required to cover all the mineral oil globules with a monolayer of soap molecules?

(e) What is the weight in grams of each of the soap molecules? *Hint:* You will need the molecular weight of sodium stearate.

(f) How many grams of soap (sodium stearate) are required to cover the 50 cm^2 of oil droplets with a monolayer of soap molecules?

(g) Soap-stabilized commercial emulsions ordinarily contain 1 to 2 percent of soap. Therefore, 1 to 2 grams should be plenty for a 100 cm^3 emulsion containing oil particles of 1 μm diameter. If the oil particles were larger, say 10 μm on the average, would we need more or less soap to cover the 50 cm^3 of oil globules with a layer one soap molecule thick?

Answers: (a) 3.14×10^{-4} cm^2/oil globule. (b) 12.5 million soap molecules around each oil globule. (c) Approximately 100 trillion droplets of oil. (d) 1.26×10^{21} soap molecules for the 100 cm^3 emulsion (which contains 50 cm^3 of oil). (e) Approximately 50×10^{-23} gram soap molecule. (f) About 0.6 grams of soap for this 100 cm^3 mineral oil emulsion.

18–21. Name one commercial product or a USP-NF preparation as an example of each class of topical medication found in Figure 18–20, *A* through *J*.

Partial Answer: For *D*, absorption bases, hydrophilic petrolatum of the USP-NF is a good example.