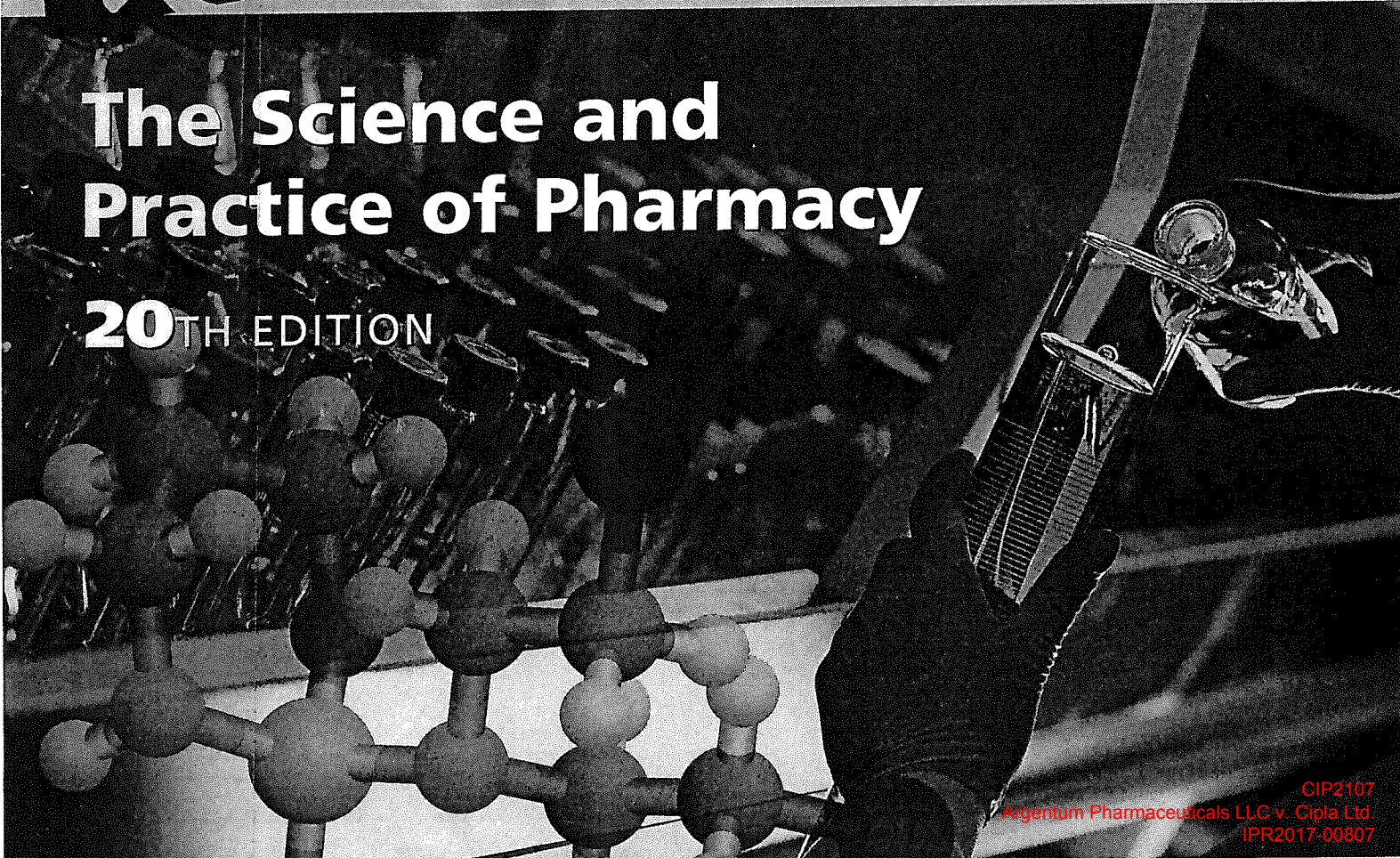




# REMINGTON

## The Science and Practice of Pharmacy

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# **Remington: The Science and Practice of Pharmacy**

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# Coarse Dispersions

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

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

## THE DISPERSION STEP

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

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

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

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

## INTERFACIAL PROPERTIES

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

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

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

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

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

## SUSPENSIONS

A *pharmaceutical suspension* may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, instilled intranasally, inhaled into the lungs, applied to the skin as topical preparations, or used for ophthalmic purposes in the eye. They are an important class of dosage form. Because some products occasionally are prepared in a dry form to be placed in suspension at the time of dispensing by the addition of an appropriate liquid vehicle, this definition is extended to include these products.

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

The three major concerns associated with suspensions are

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

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

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

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

Some workers restrict the term "flocculation" to the aggregation brought about by chemical bridging; aggregation involving a reduction of repulsive potential at the double layer is referred to as *coagulation*. Other workers regard flocculation as aggregation in the secondary minimum of the potential energy curve of two interacting particles and coagulation as aggrega-

tion in the primary minimum. In the present chapter the term *flocculation* is used for all aggregation processes, irrespective of mechanism.

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

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

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

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

## SETTLING AND ITS CONTROL

To control the settling of dispersed material in suspension, the pharmacist must be aware of those physical factors that will affect the rate of sedimentation of particles under ideal and nonideal conditions. Also important are the various coefficients used to express the amount of flocculation in the system and the effect flocculation will have on the structure and volume of the sediment.

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

DEFLOCCULATED	FLOCCULATED
<ol style="list-style-type: none"> <li>1. Particles exist in suspension as separate entities.</li> <li>2. Rate of sedimentation is slow, as each particle settles separately and particle size is minimal.</li> <li>3. A sediment is formed slowly.</li> <li>4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed that is difficult, if not impossible, to redisperse.</li> <li>5. The suspension has a pleasing appearance, as the suspended material remains suspended for a relatively long time. The supernate also remains cloudy, even when settling is apparent.</li> </ol>	<ol style="list-style-type: none"> <li>1. Particles form loose aggregates.</li> <li>2. Rate of sedimentation is high, as particles settle as a floc, which is a collection of particles.</li> <li>3. A sediment is formed rapidly.</li> <li>4. The sediment is packed loosely and possesses a scaffold-like structure. Particles do not bond tightly to each other and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.</li> <li>5. The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.</li> </ol>

## Sedimentation Rate

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

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

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

where  $v$  is the terminal velocity in cm/sec,  $r$  is the radius of the particles in cm,  $\rho_1$  and  $\rho_2$  are the densities (g/cm<sup>3</sup>) of the dispersed phase and the dispersion medium, respectively,  $g$  is the acceleration due to gravity (980.7 cm/sec<sup>2</sup>), and  $\eta$  is the Newtonian viscosity of the dispersion medium in poises (g/cm sec). Stokes' law holds only if the downward motion of the particles is not sufficiently rapid to cause turbulence. Micelles and small phospholipid vesicles do not settle unless they are subjected to centrifugation.

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

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

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

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

## Quantitative Expressions of Sedimentation and Flocculation

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

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

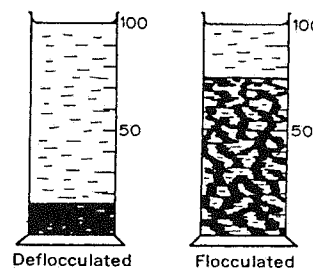


Figure 22-1. Sedimentation parameters of suspensions. Deflocculated suspension:  $F_\infty = 0.15$ . Flocculated suspension:  $F = 0.75$ ;  $\beta = 5.0$ .

$$F = V_w/V_0 \quad (4)$$

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

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

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

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

## FORMULATION OF SUSPENSIONS

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

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

Only the minimum amount of wetting agent should be used, compatible with producing an adequate dispersion of the particles. Excessive amounts may lead to foaming or impart

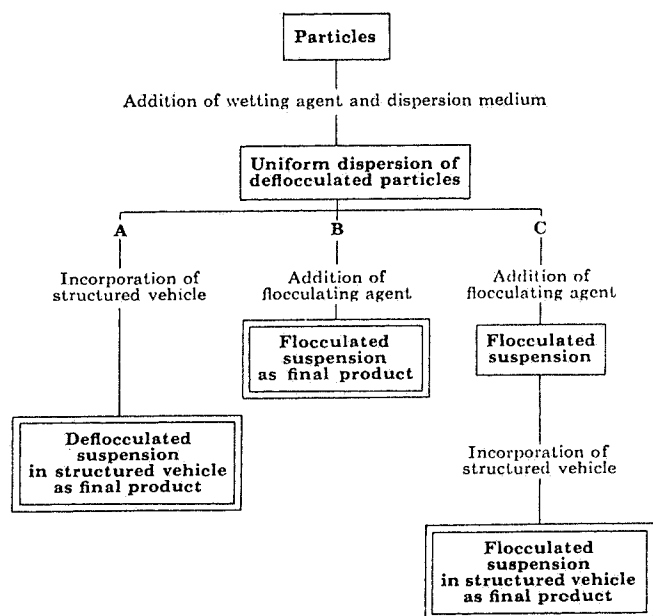


Figure 22-2. Alternative approaches to the formulation of suspensions.

an undesirable taste or odor to the product. Invariably, as a result of wetting, the dispersed particles in the vehicle are deflocculated.

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

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

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

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

This principle is illustrated by reference to the following example, taken from the work of Haines and Martin.<sup>2</sup> Particles of sulfamerazine in water bear a negative charge. The serial addition of a suitable electrolyte, such as aluminum chloride, causes a progressive reduction in the zeta potential of the particles. This is due to the preferential adsorption of the trivalent aluminum cation. Eventually, the zeta potential will reach zero and then become positive as the addition of  $\text{AlCl}_3$  is continued.

If sedimentation studies are run simultaneously on suspensions containing the same range of  $\text{AlCl}_3$  concentrations, a relationship is observed (Fig 22-3) between the sedimentation volume  $F$ , the presence or absence of caking, and the zeta potential of the particles. To obtain a flocculated, noncaking suspension with the maximum sedimentation volume, the zeta potential must be controlled so as to lie within a certain range (generally less than 25 mV). This is achieved by the judicious use of an electrolyte. A comparable situation is observed when a negative ion such as  $\text{PO}_4^{3-}$  is added to a suspension of positively charged particles such as bismuth subnitrate.

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

Matthews and Rhodes then went on to show, by computer analysis, that the DLVO theory (see Chapter 21) predicted the results obtained—namely, that the griseofulvin suspensions under investigation would remain deflocculated when the concentration of aluminum chloride was  $10^{-4}$  molar or less. Only at concentrations in the range of  $10^{-3}$  to  $10^{-2}$  molar aluminum chloride did the theoretical plots show deep primary minima, indicative of flocculation. These occurred at a distance of separation between particles of approximately 50 Å, which led

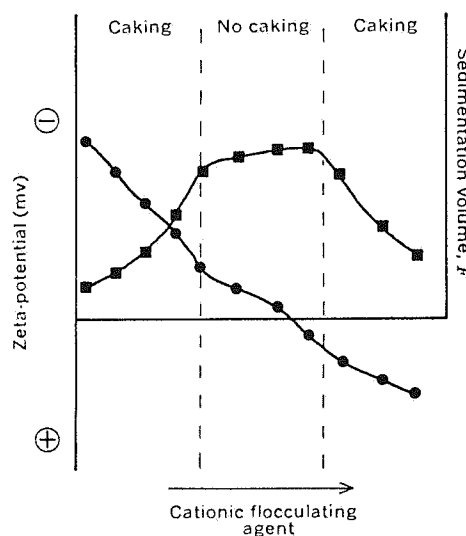


Figure 22-3. Typical relationship between caking, zeta potential, and sedimentation volume, as a positively charged flocculating agent is added to a suspension of negatively charged particles. ●: zeta potential. ■: sedimentation volume.



Matthews and Rhodes to conclude that coagulation had taken place in the primary minimum.

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

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

The effectiveness of a polymer as a stabilizing agent for suspensions primarily depends on the affinity of the polymer for the particle surface as well as the charge, size, and orientation of the polymer molecule in the continuous phase. Many pharmaceutically useful polymers contain polar functional groups that are separated by a hydrocarbon backbone. As a result of this structure, many active centers exist on a given polymer molecule that are capable of interacting with a particle surface. If one considers that each of these active centers is reversibly adsorbed to the surface of the particle, then numerous equilibria are established between each of the active centers of a given polymer molecule and a particle. At any particular time, some active centers will be adsorbed and others will be desorbed, but due to the large numbers of active centers, it is highly unlikely that all sites will be desorbed at the same time. This model may account for the strong attraction of many pharmaceutically useful polymers for dispersed solids.

Although DLVO theory provides the most successful description of suspension stability in general, it does not always predict the behavior of suspensions that are formulated with polymeric stabilizing agents. This is because factors other than electrostatic interactions are responsible for flocculation and other interparticle interactions in suspensions. As observed with ionic flocculating agents, polymers can produce both flocculated and deflocculated suspensions. It is believed that the primary mechanism by which polymers act as flocculants is due to the bridging of the polymer between the surfaces of two different particles. The effect can be highly concentration dependent as illustrated in Figure 22-4. The effect has been interpreted as follows.

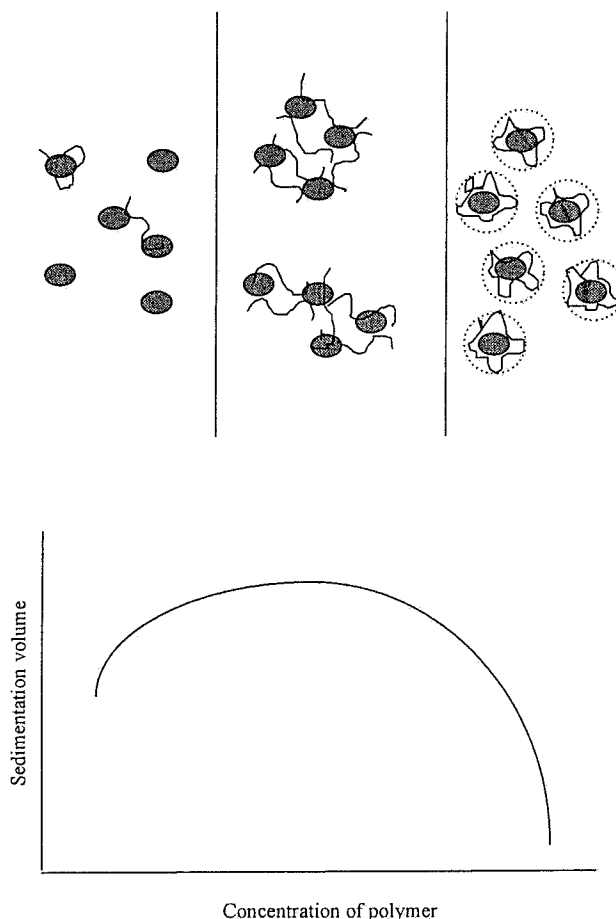
At very low concentrations of polymer, a large number of sites on the surface of the dispersed solid are available for adsorption of polymer. Bridging between particles occurs as a result of the simultaneous adsorption of a polymer molecule onto the surfaces of different particles. At low polymer concentrations, the number of particle-particle bridges is relatively low. At somewhat higher concentrations of polymer, sufficient binding sites are still available on the particles, permitting additional interparticle attachments to form. It is these intermediate concentrations that result in optimum flocculation and sedimentation volume. At high concentrations of polymer, complete coverage of the particle surface with polymer occurs and insufficient binding sites remain on the particles to permit interparticle bridging. In this instance, the polymer can lead to the formation of a deflocculated or peptized system because adsorbed layers of polymer on separate particles will prevent close attraction of the particles via the phenomenon of steric stabilization (discussed further in the section on emulsions). In general, *steric stabilization* refers to the ability of adsorbed polymers to prevent close approach and cohesion of dispersed particles due to the fact that the mixing of polymers adsorbed at the particle surfaces is energetically unfavorable. Suspensions formulated with relatively high concentrations of polymer would be deflocculated and therefore tend to have small sedimentation volumes.

A potential complicating factor in the above analysis is that the degree of flocculation may depend upon the length of time and magnitude of mixing during formulation. In some cases,

gentle mixing could result in a flocculated suspension; however, continued or more vigorous mixing could result in reorientation of the polymer at the particle surface with fewer interparticle bridges formed. It must also be remembered that high concentrations of polymer may result in the formation of a structured vehicle, the advantage of which must be weighed against possible effects of deflocculation. Practical considerations in the formulation of suspensions using polymers have been presented by Scheer.<sup>7</sup>

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

The conformation of the polymers in the continuous phase may also have an effect on the degree of flocculation. At concentrations where flocculation occurs, polymers that have a



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

linear conformation in the continuous phase will generally be more effective flocculants than polymers that are coiled in the continuous phase.

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

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

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

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

negative flocculating agent that the formulator must employ is compatible with the similarly charged suspending agent.

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

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

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

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

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

container, such as suspensions for oral use. Additional information on the bioavailability of drug from suspensions is presented at the end of this chapter.

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

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

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

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

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

$$f = \frac{q_1 q_2}{x} \quad (6)$$

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

In general, most nonaqueous pharmaceutical liquids have a dielectric constant that is lower than water. This would result in a greater attraction between ions or particles of opposite

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

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

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

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

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

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

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

## EMULSIONS

An *emulsion* is a dispersed system containing at least two immiscible liquid phases. The majority of conventional emulsions in pharmaceutical use have dispersed particles ranging

in diameter from 0.1 to 100  $\mu\text{m}$ . As with suspensions, emulsions are thermodynamically unstable as a result of the excess free energy associated with the surface of the droplets. The

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

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

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

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

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

## EMULSION TYPE AND MEANS OF DETECTION

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

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

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

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

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

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

## FORMATION AND BREAKDOWN OF DISPERSED LIQUID DROPLETS

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

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

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



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

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

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

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

phase between particles clumped together. Davies<sup>13</sup> showed the importance of coalescence rates in determining emulsion type; this work is discussed in more detail on page 329.

## EMULSIFYING AGENT

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

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

## Desirable Properties

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

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

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

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

$$\Delta F = \frac{6\gamma V}{d} \quad (7)$$

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

$$\begin{aligned} \Delta F &= \frac{6 \times 50 \times 100}{1 \times 10^{-4}} = 30 \times 10^7 \text{ ergs} \\ &= 30 \text{ joules or } 30/4.184 = 7.2 \text{ cal} \end{aligned}$$

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

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

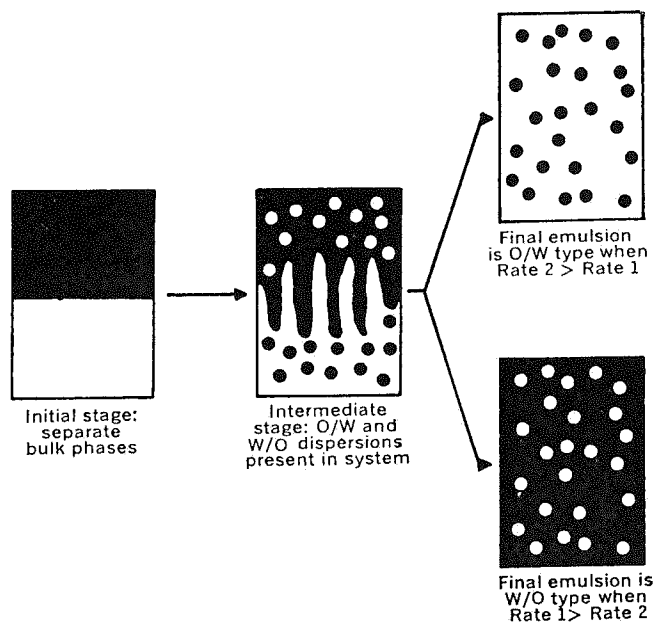


Figure 22-5. Effect of rate of coalescence on emulsion type. Rate 1: O/W coalescence rate. Rate 2: W/O coalescence rate. ●: oil. ○: water. For an explanation of Rates 1 and 2, refer to the discussion of Davies on page 329<sup>13</sup>.

**Table 22-3. Factors Influencing Emulsion Viscosity**

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

Source: Davies, Rideal 1961.<sup>14</sup>

**ELECTRICAL POTENTIAL**—The origin of an electrical potential at the surface of a droplet has been discussed earlier in the chapter. Insofar as emulsions are concerned, the presence of a well-developed charge on the droplet surface is significant in promoting stability by causing repulsion between approaching drops. This potential is likely to be greater when an ionized emulsifying agent is employed. Electrical potential has been shown to be a significant factor for maintaining the stability of intravenous fat emulsions that are stabilized with lecithin.

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

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

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

If the area each molecule occupies at the oil–water interface is 30  $\text{\AA}^2$  ( $30 \times 10^{-16} \text{ cm}^2$ ), we require

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

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

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

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

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

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

## Mechanism of Action

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

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

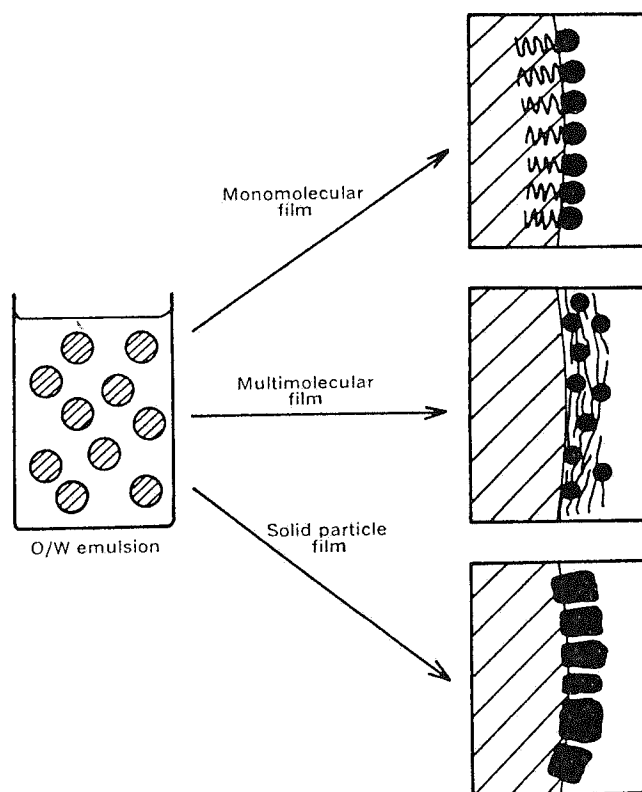


Figure 22-6. Types of films formed by emulsifying agents at the oil–water interface. Orientations are shown for O/W emulsions. ▨: oil. □: water.

**Table 22-4. Classification of Emulsifying Agents**

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

ticles may still carry a charge; this arises from adsorption of a specific ion or ions from solution.

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

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

## Chemical Types

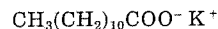
Emulsifying agents also may be classified in terms of their chemical structure; there is some correlation between this clas-

sification and that based on the mechanism of action. For example, the majority of emulsifiers forming monomolecular films are synthetic, organic materials. Most of the emulsifiers that form multimolecular films are obtained from natural sources and are organic. A third group is composed of solid particles, invariably inorganic, that form films composed of finely divided solid particles.

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

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

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



Solutions of *alkali soaps* have a high pH; they start to precipitate out of solution below pH 10 because the unionized fatty acid is now formed, and this has a low aqueous solubility. Further, the free fatty acid is ineffective as an emul-

**Table 22-5. Auxiliary Emulsifying Agents**

PRODUCT	SOURCE AND COMPOSITION	PRINCIPAL USE
Cetyl alcohol	Chiefly $\text{C}_{16}\text{H}_{33}\text{OH}$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Glyceryl monostearate	$\text{C}_{17}\text{H}_{35}\text{COOCH}_2\text{CHOHCH}_2\text{OH}$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Methylcellulose	Series of methyl ethers of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Sodium carboxymethylcellulose	Sodium salt of the carboxymethyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions
Stearic acid	A mixture of solid acids from fats, chiefly stearic and palmitic	Lipophilic thickening agent and stabilizer for O/W lotions and ointments. Forms a true emulsifier when reacted with an alkali

sifier, so emulsions formed from alkali soaps are not stable at pH values less than about 10.

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

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

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

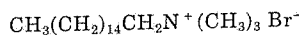
**Sulfonates** are a class of compounds in which the sulfur atom is connected directly to the carbon atom, giving the general formula



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

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

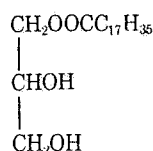
Cationic agents are weak emulsifiers and generally are formulated with a stabilizing or auxiliary emulsifying agent such as cetostearyl alcohol. The only group of cationic agents used extensively as emulsifying agents are the quaternary ammonium compounds. An example is cetyltrimethyl-ammonium bromide.



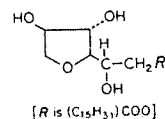
Cationic emulsifiers should not be used in the same formulation with anionic emulsifiers because they will interact. The incompatibility may not be immediately apparent as a precipitate, but virtually all of the desired antibacterial activity will generally have been lost.

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

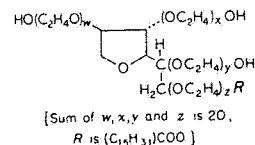
A glyceryl ester, such as glyceryl monostearate, is too lipophilic to serve as a good emulsifier; it is used widely as an auxiliary agent (see Table 22-5) and has the structure



Sorbitan fatty acid esters, such as sorbitan monopalmitate

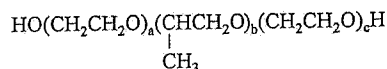


are nonionic oil-soluble emulsifiers that promote W/O emulsions. The polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monopalmitate



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

Polyoxyethylene glycol esters, such as the monostearate, C<sub>17</sub>H<sub>35</sub>COO(CH<sub>2</sub>OCH<sub>2</sub>)<sub>n</sub>H, also are used widely. Poxoxyethylene/poxoxypropylene block copolymers



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

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

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

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

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



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

Lecithin can be an excellent emulsifier for naturally occurring oils such as soy, corn, or safflower. Highly stable O/W emulsions can be formed with these oils. Purified lecithins from soy or egg yolk are the principal emulsifiers for intravenous fat emulsions. Lecithin provides stable emulsions with droplet sizes of less than 1  $\mu\text{m}$  in diameter. It is critical that a small, uniform particle size be maintained in these emulsions to eliminate the risks of fat embolism after intravenous injection. The excellent stability observed with these emulsions may be a result of the large negative zeta potential that results from the small quantity of charged lipids present in lecithin as well as the ability of the lecithin to form mesophases resembling liposomes. During manufacture of the emulsions, homogenization produces small droplets that are surrounded by concentric layers of phospholipids. The latter may form a protective layer that prevents coalescence of the droplets. As an emulsifier, lecithin produces the best results at a pH of around 8.

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

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

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

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

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

**AUXILIARY EMULSIFYING AGENTS**—Auxiliary emulsifying agents include those compounds that are normally incapable themselves of forming stable emulsions. Their main value lies in their ability to function as thickening agents and thereby help stabilize the emulsion. Agents in common use are listed in Table 22-5.

## Emulsifying Agents and Emulsion Type

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

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

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

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

**RATE OF COALESCENCE AND EMULSION TYPE**—Davies<sup>13</sup> indicated that the type of emulsion produced in systems prepared by shaking is controlled by the relative coalescence rates of oil droplets dispersed in the oil. Thus, when a mixture of oil and water is shaken together with an emulsifying agent, a multiple dispersion is produced initially that contains oil dispersed in water and water dispersed in oil (see Fig 22-5). The type of the final emulsion that results depends on whether the water or the oil droplets coalesce more rapidly. If the O/W coalescence rate (Rate 1) is much greater than W/O coalescence rate (Rate 2), a W/O emulsion is formed because the dispersed water droplets are more stable than the dispersed oil droplets. Conversely, if Rate 2 is significantly faster than Rate 1, the final emulsion is an O/W dispersion because the oil droplets are more stable.

According to Davies,<sup>13</sup> the rate at which oil globules coalesce when dispersed in water is given by the expression

$$\text{Rate 1} = C_1 e^{-W_1/RT} \quad (8)$$

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

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

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

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

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

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

$$\text{Rate 2} = C_2 e^{-W_2/RT} \quad (9)$$

Here, the collision factor  $C_2$  is a function of the water-oil phase volume ratio divided by the viscosity of the oil phase. The energy barrier  $W_2$  is, as before, related to the fraction of the interface covered by the surface-active agent. Another contributing factor is the number of  $-\text{CH}_2-$  groups in the emulsifying agent; the longer the alkyl chain of the emulsifier, the greater the gap that has to be bridged if one water droplet is to combine with a second drop.

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

## PREPARATION OF EMULSIONS

Several factors must be taken into account in the successful preparation and formulation of emulsified products. Usually, the type of emulsion (ie, O/W or W/O) is specified; if not, it probably will be implied from the anticipated use of the product. The formulator's attention is focused primarily on the selection of the emulsifying agent, or agents, necessary to achieve a satisfactory product. No incompatibilities should oc-

cur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the product should be prepared in such a way as not to prejudice the formulation.

## Selection of Emulsifying Agents

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

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

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

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

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

### O/W Emulsion

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

By simple algebra it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of

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

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

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

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. Table 22-9 shows the various proportions required, using other pairs of emulsifying agents, to form a blend of HLB 10.5. When carrying out preliminary investigations with a particular material to be emulsified, it is advisable to try several pairs of emulsifying agents. Based on an evaluation of the emulsions produced, it becomes possible to choose the best combination.

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

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

An interesting approach, developed by Davies,<sup>13</sup> is related to his studies on the relative rates of coalescence of O/W and W/O emulsions (page 329). According to Davies, hydrophilic groups on the surfactant molecule make a positive contribution to the HLB number, whereas lipophilic groups exert a negative effect. Davies calculated these contributions and termed them HLB Group Numbers (Table 22-10). Provided the molecular structure of the surfactant is known, one simply adds the various group numbers in accordance with the following formula:

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

where  $m$  is the number of  $-\text{CH}_2-$  groups present in the surfactant. Poor agreement is found between the HLB values calculated by the use of group numbers and the HLB values obtained using the simple equations developed by Griffin. However, the student should realize that the absolute HLB values per se are of limited significance. The utility of the HLB approach (using values calculated by either Griffin's or Davies' equations) is to

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

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

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

**Table 22-10. HLB Group Numbers**

	GROUP NUMBER
Hydrophilic groups	
$-\text{SO}_4^-\text{Na}^+$	38.7
$-\text{COO}^-\text{K}^+$	21.1
$-\text{COO}^-\text{Na}^+$	19.1
<i>N</i> (tertiary amine)	9.4
Ester (sorbitan ring)	6.8
Ester (free)	2.4
$-\text{COOH}$	2.1
Hydroxyl (free)	1.9
$-\text{O}-$	1.3
Hydroxyl (sorbitan ring)	0.5
Lipophilic groups	
$-\text{CH}-$	
$-\text{CH}_2-$	
$\text{CH}_3-$	-0.475
$=\text{CH}-$	
Derived groups	
$-(\text{CH}_2-\text{CH}_2-\text{O})-$	+0.33
$-(\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O})-$	-0.15

Source: Wedderburn 1964.<sup>18</sup>

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

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

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

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

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

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

With regard to the second point, Schulman and Cockbain in 1940 showed that combinations of certain amphiphiles formed stable films at the air-water interface. It was postulated that the complex formed by these two materials (one, oil-soluble; the other, water-soluble) at the air-water interface was also

present at the O/W interface. This interfacial complex was held to be responsible for the improved stability. For example, sodium cetyl sulfate, a moderately good O/W emulsifier, and elaidyl alcohol or cholesterol, both stabilizers for W/O emulsions, show evidence of an interaction at the air-water interface. Furthermore, an O/W emulsion prepared with sodium cetyl sulfate and elaidyl alcohol is much more stable than an emulsion prepared with sodium cetyl sulfate alone.

Elaidyl alcohol is the *trans* isomer. When oleyl alcohol, the *cis* isomer, is used with sodium cetyl sulfate, there is no evidence of complex formation at the air-water interface. Significantly, this combination does not produce a stable O/W emulsion either. Such a finding strongly suggests that a high degree of molecular alignment is necessary at the O/W interface to form a stable emulsion. This high degree of molecular alignment may be a prerequisite event for the formation of lamellar liquid crystalline phases. As illustrated in Figure 22-7, the combination of certain long chain acids and alcohols with water can result in the formation of micelles and liquid crystals. If the correct ratios of water, acid and alcohol are maintained at an oil-water interface, enhanced stability can result from the presence of the liquid crystalline phase.

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

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

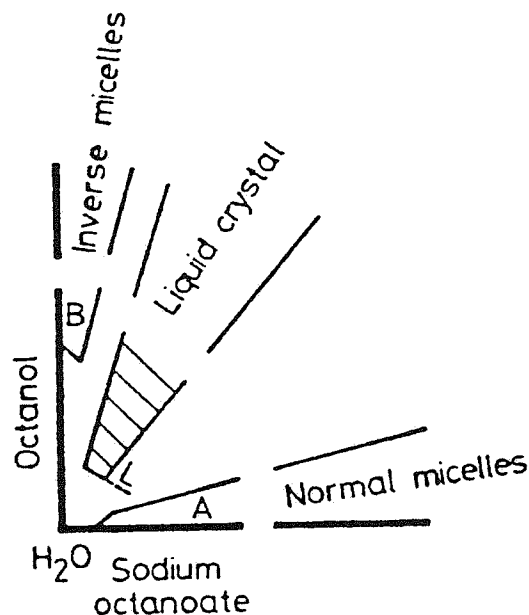


Figure 22-7. Phase diagram illustrating the formation of micellar and liquid crystalline phases in mixtures of a long-chain alcohol, long-chain acid, and water. Compositions that form the lamellar liquid crystalline phase can provide enhanced emulsion stability. (Reprinted with permission<sup>26</sup>).

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

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

## Method of Preparation

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

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

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

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



## STABILITY OF EMULSIONS

Several criteria must be met in a well-formulated emulsion. Probably the most important and most readily apparent requirement is that the emulsion possess adequate physical stability; without this, any emulsion soon will revert back to two separate bulk phases. In addition, if the emulsified product is to have some antimicrobial activity (eg, a medicated lotion), care must be taken to ensure that the formulation possesses the required degree of activity. Frequently, a compound exhibits a lower antimicrobial activity in an emulsion than, say, in a solution. Generally, this is because of partitioning effects between the oil and water phases, which cause a lowering of the effective concentration of the active agent. Partitioning has also to be taken into account when considering preservatives to prevent microbiological spoilage of emulsions. Finally, the chemical stability of the various components of the emulsion should receive some attention, as such materials may be more prone to degradation in the emulsified state than when they exist as a bulk phase.

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

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

The three major phenomena associated with physical stability are

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

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

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

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

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

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

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

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

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

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

Inversion often can be seen when an emulsion, prepared by heating and mixing the two phases, is being cooled. This

takes place presumably because of the temperature-dependent changes in the solubilities of the emulsifying agents. The phase inversion temperature (PIT) of nonionic surfactants has been shown by Shinoda and Kunieda<sup>28</sup> to be influenced by the HLB number of the surfactant—the higher the PIT value, the greater the resistance to inversion.

## BIOAVAILABILITY FROM COARSE DISPERSIONS

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

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

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

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

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

the rate of absorption of sulfamethiazole from a suspension depended on the rate of dissolution of the suspended particles, which in turn was related to particle size. Previous studies<sup>33,34</sup> had shown the need to determine the dissolution rate of suspensions to gain information as to the bioavailability of drugs from this type of dosage form.

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

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

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

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