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ALFONSO R GENNARO

*Editor, and Chairman
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CHAPTER 21

Particle Phenomena and Coarse Dispersions

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Understanding particle phenomena and concepts of dispersion techniques is important in many areas of pharmaceuticals and biopharmaceuticals. In the formulation and manufacture of dosage forms such as powders, capsules, tablets, suspensions, emulsions, and aerosols, knowledge of particle technology is essential. Also, it is becoming increasingly important to consider such factors as particle size and degree of deaggregation in drug utilization by the patient.

This chapter will discuss the formation of suspensions and emulsions, and the time behavior involving flocculation, coalescence, crystal growth, and caking. The "theory" is intended to give readers qualitative or semiquantitative guidelines, rather than quantitative directions for manufacturing procedures. Many of the equations and concepts presented cannot be used directly for the purpose of formulation; rather they are meant to provide understanding of the interactions involved in the preparation of, for example, an emulsion or a suspension.

For the purposes of the present discussion, a dispersed system will be regarded as a two-phase system in which one phase is distributed as particles or droplets in the second, or continuous, phase. Since each phase can exist in solid, liquid, or gaseous state, there are nine possible combinations. However, since gases are miscible in all proportions, there are in reality only eight combinations. The treatment will be restricted to a discussion of those solid-liquid and liquid-liquid dispersions that are of pharmaceutical significance, namely, suspensions and emulsions. In these systems the dispersed phase is frequently referred to as the discontinuous or internal phase, and the continuous phase is called the external phase or dispersion medium.

All dispersions may be classified into three groups on the basis of the size of the dispersed particles. Chapter 20 deals with one such group—colloidal dispersions—in which the size of the dispersed particles is in the range of approximately 10 Å to 0.5 μm. Molecular dispersions, the second group in this classification, are discussed in Chapters 16 and 17. The third group, consisting of *coarse dispersions* in which the particle size exceeds 0.5 μm, 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 primarily concerned with producing a smooth, uniform, easily flowing (pouring or spreading) suspension or emulsion, one in which dispersion of particles can be effected with minimum expenditure of energy.

In preparing suspensions, particle-particle attractive forces among powder particles present a problem. These forces may 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 a similar situation exists. Frequently high shear rates are 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 or a water-in-oil emulsion preferentially survives the shearing action.

For thermodynamic reasons, 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.

Wetting

Wetting of a solid by a liquid is best illustrated by the behavior of a small droplet of liquid placed on a flat surface of a solid. If the droplet spreads over the solid, the liquid is said to wet the solid completely, and the contact angle, θ , measured through the liquid is zero (see Fig 21-1). The term nonwetting is somewhat arbitrary but may be applied to a liquid when θ

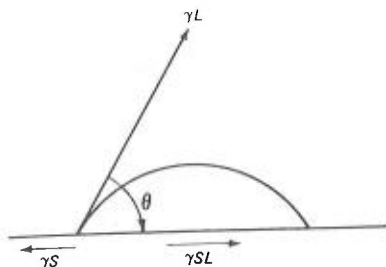


Fig 21-1. A drop of liquid on a flat solid surface. Forces and the contact angle, θ , are shown.

$> 90^\circ$. For the nonspreading region, $0 < \theta < 90^\circ$, the term partial wetting may be applied.

For a better understanding of the wetting process, the Young equation

$$\gamma_S = \gamma_{SL} + \gamma_L \cos \theta \quad (1)$$

deduced from analysis of the force vectors (see Fig 21-1) at equilibrium may be instructive. Here γ_S , γ_{SL} , and γ_L are the surface tension of the solid, the interfacial tension of the solid liquid, and the surface tension of the liquid, respectively. Rearranging Eq 1 gives

$$\cos \theta = \frac{\gamma_S - \gamma_{SL}}{\gamma_L} \quad (2)$$

which states the dependence of θ on γ_S , γ_{SL} , and γ_L . From this equation it is obvious that wetting is favored if γ_S is large, γ_L is small, and γ_{SL} is small. Complete wetting results if the right-hand side of Eq 2 equals one.

The practical significance of wetting may be illustrated by the preparation of methylprednisolone suspensions. Micronized methylprednisolone is not wetted ($\theta > 90^\circ$) by water in the absence of a surfactant, but if a small amount of polysorbate 80 is added the contact angle is reduced to nearly zero and a fine dispersion may be prepared.

Low-Energy Solids—The particle surface of many organic substances is hydrophobic because there are few polar functional groups in the molecules of the substances. For such low-energy solids the surface tension may be relatively small, in the range of 20 to 40 ergs/cm². From Eq 2 it is evident that such surfaces will be poorly wetted by highly polar liquids (of relatively large surface tension) such as water or glycerin. Less polar liquids wet the surfaces more readily. Table I shows that as γ_L decreases, θ decreases in accordance with Eq 2.

Wetting agents are surface-active substances used to reduce contact angle and thus improve wetting. They function by adsorbing at air/liquid and solid/liquid interfaces, reducing both γ_L and γ_{SL} . Eq 2 shows that for wetting of low-energy solids by water, reduction of γ_L is necessary even when γ_{SL} is small.

High-Energy Solids—Metals, silica, clay minerals, and water-insoluble salts are among the substances with γ_S values ranging from several hundred to thousands of ergs/cm².

Table I—Contact Angles of Various Liquids at 20° on Low-Energy Solids

	Paraffin	Polyethylene
Water ($\gamma_L = 73$)	108	94
Glycerol ($\gamma_L = 63$)	96	79
Formamide ($\gamma_L = 58$)	91	77
Bis(2-ethylhexyl) phthalate ($\gamma_L = 31$)	36	5
Benzene ($\gamma_L = 29$)	24	spreads
<i>n</i> -Hexadecane ($\gamma_L = 28$)	28	spreads
Di(<i>n</i> -octyl)ether ($\gamma_L = 28$)	23	spreads
<i>n</i> -Decane ($\gamma_L = 24$)	7	spreads

Hence, clean surfaces of such solids are generally much more wettable by solvents listed in Table I. As Zisman has pointed out, however, there are instances when a relatively low-energy liquid does not spread on a high-energy solid.¹ This behavior occurs when molecules of the liquid or a constituent in it adsorb on the high-energy surface. Sometimes surface contamination of high-energy surfaces by hydrophobic materials significantly lowers γ_S , with the result that wetting does not occur; for example, very low concentrations of cationic surface-active agents render glass nonwetting toward water.

Intermolecular Forces

All interactions involving molecules and ions, and aggregates of molecules and ions include both attractive and repulsive forces. These forces depend on the nature of species, the distance of separation, the orientation of the molecules, and the nature of the medium.

Ion-Ion Electrostatic Interactions—The interionic interaction of two polarizable ions (see Fig 21-2) obeys the following laws:

$$\text{Energy} = E = \frac{q_1 q_2}{\epsilon r} \quad (3)$$

and

$$\text{Force} = F = -\frac{q_1 q_2}{\epsilon r^2} \quad (4)$$

where q_1 and q_2 are the charges on ions 1 and 2, respectively, r is the distance of separation of the ions, and ϵ is the dielectric constant of the medium. As can be seen, if q_1 and q_2 are of the same sign, the force, F , is negative and therefore repulsive in nature. On the other hand, if the charges are of opposite sign, the interaction is attractive. It should be noted that the distance dependence for this situation is inversely proportional to the first power in r for E and second power for F . This difference in the distance dependence results from the fact that

$$E = \int_{-\infty}^r F dr \quad (5)$$

which states that the energy is equal to the work, W , of bringing together the two ions from infinity to a distance r from each other.

An example calculation for sodium chloride can be used to illustrate the magnitude of the ion-ion interaction. For the sodium chloride molecule in the vapor state, r is about 2.5×10^{-8} cm, $q_{\text{Na}^+} = -q_{\text{Cl}^-}$ = electronic charge = 4.8×10^{-10} esu (electrostatic units), and the dielectric constant may be assumed to be unity. Therefore,

$$W = \frac{(4.8 \times 10^{-10})^2}{2.5 \times 10^{-8}} \approx 10^{-11} \text{ erg/ion pair}$$

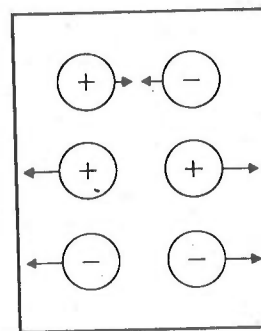


Fig 21-2. Interionic interactions of two polarizable ions. Like charges repel and unlike charges attract.

or

$$W = 120,000 \text{ cal/mole}$$

since

$$\text{cal/mole} = \frac{(\text{erg/molecule})N_0}{4.18 \times 10^7 \text{ ergs/cal}}$$

The value for the work, W , represents the amount of work required to separate one mole of sodium chloride molecules in the vapor state into one mole of sodium and one mole of chloride ions.

Other Electrostatic Interactions—In addition to the ion-ion interaction other electrostatic interactions may be possible involving ions, dipoles, and induced dipoles.

A permanent dipole moment exists in a molecule when the "center of gravity" of the negative charges does not coincide with that for the positive charges.

The field of an ion or permanent dipole temporarily may polarize molecules which may not have a permanent dipole. When this occurs, the resulting polarization leads to an induced dipole in the molecule.

Various pair combinations of ions, permanent dipoles, and induced dipoles give rise to higher order electrostatic interactions such as the ion-dipole, the ion-induced dipole, the dipole-dipole, and dipole-induced dipole. These interactions are weaker and generally more short-range than the ion-ion interaction, the distance dependence for the energies ranging from r^{-2} to r^{-6} (see Table II). Furthermore, all of these interactions usually are directionally dependent.

Hydrogen-Bonding—A hydrogen atom attached to an electronegative atom such as oxygen or nitrogen effectively produces a dipole with a highly exposed positive end. As a result, the proton end can participate in unusually strong dipole-dipole interactions with other strongly electronegative centers. Each water molecule has two such hydrogen-bonding protons and therefore water molecules in liquid water and ice are highly associated. The hydrogen-bonding capabilities of water also partially explain its unusually good solvating ability for other polar molecules.

London Dispersion Forces—These attractive forces arise from the fact that at any given instant the electron distribution around an atomic nucleus may not be symmetrical and consequently this leads to the formation of a temporary dipole moment. Such temporary dipoles in neighboring atoms are correlated so as to produce an effective induced dipole-induced dipole interaction.

The characteristics of the dispersion forces are that they are approximately additive, they are not directionally dependent, and they follow the $1/r^6$ dependence in energy. As will be seen later, the London Forces, along with hydrogen-bonding forces, are generally the most important in describing the intermolecular and the interparticulate behavior of non-ionic compounds in solutions and dispersions.

Born Repulsive Forces—If molecules or ions are brought very close together, the outer electron clouds of the atoms will begin to overlap. This gives rise to a mutual repulsive force that increases very rapidly ($\sim 1/r^{12}$) as the atoms are brought

Table II—Distance Dependence of Various Electrostatic Interactions

Type interaction	Distance dependence	
	Force	Energy
Ion-ion	$1/r^2$	$1/r$
Ion-dipole	$1/r^3$	$1/r^2$
Dipole-dipole	$1/r^4$	$1/r^3$
Dipole-induced dipole	$1/r^7$	$1/r^6$
London dispersion forces	$1/r^7$	$1/r^6$

closer together such as one might expect when two hard rubber balls touch and are pressed together.

Particle-Particle Interactions

The interaction between particles may be analyzed by the same type of forces responsible for interatomic and intermolecular interactions. Let us consider first the interaction of two arbitrary particles as shown in Fig 21-3.

The kinds of interactions contributing to the particle-particle binding energies are:

1. The various electrostatic contributions (attractive and repulsive).
2. The London dispersion forces between the atoms of one particle with those in the other (attractive).
3. The covalent bonds (attractive).
4. The Born repulsion forces.

The latter two can contribute only when the two particles are touching.

A rigorous quantitative treatment of the above contributions to particle-particle binding is beyond the scope of this text. However, considerable insight into the magnitude, nature, and the applications of these forces can be gained by "order of magnitude" theoretical calculations using approximate theories and simplified models.

Charge-Charge Interactions—Let us examine the possibility of electrostatic interactions between two particles, A and B (see Fig 21-3). While contributions from charge-dipole, charge-induced dipole, and dipole-dipole interactions between an atom, ion, or molecule of one particle and that in the other may occur, generally these are probably of much less importance than the charge-charge interactions. Therefore, as a first approximation let us consider only the charge-charge forces between the two particles.

The energy of coulombic interaction may be written as the summation of Eq 3 (assuming $\epsilon = 1$) over all possible ion-pair combinations between the two particles; ie,

$$E = \sum_{i=1}^M \sum_{j=1}^N \frac{q_i q_j}{r_{ij}} \quad (6)$$

where q_i is the charge on the i th ion in Particle A which contains M ions, q_j is the charge on the j th ion in Particle B which contains N ions, and r_{ij} is the distance between ions i and j . If it is assumed that the particles are spheres and that charges on each sphere are uniformly distributed, Eq 6 simply reduces

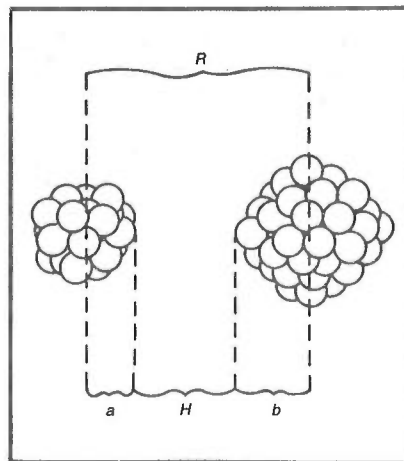


Fig 21-3. Parameters used to describe the interactions between particles where a and b are the particle radii of the particles involved, R is the intercenter distance of separation of the two particles, and H is the distance of separation between the two surfaces of the interacting particles.

to

$$E = \frac{Q_A Q_B}{R} \quad (7)$$

where Q_A and Q_B are the net charges on Particles A and B and R is the intercenter distance between the two spheres (see Fig 21-4). The corresponding equation for the force is

$$F = \frac{-Q_A Q_B}{R^2} \quad (8)$$

It is both instructive and useful at this point to examine the magnitude of maximum energies and forces that might arise from purely electrostatic contributions and compare them to the gravitational forces on the particles. The maximum charge on a given particle in air is limited by the electric breakdown field of about 60 esu, which corresponds to a charge of

$$Q = 60a^2 \quad (9)$$

where a is the radius of the sphere.

Table III tabulates the results of calculations for E and F based on Eqs 7-9 for different-sized particles. It must be kept in mind that these values represent the *maximum* electrostatic interaction limited by surface electrical discharge in air.

It can be noted that for small particles, electrostatic effects may be important. For example, two 1- μm particles with the same maximum charge may repel each other with a force that is 20,000 times greater than the gravitational force, D . These calculations explain why certain dry powders that become charged during trituration in the mortar defy the laws of gravity. Interestingly, as the particle size is reduced, this phenomenon increases in accordance with the predictions of Table III, which shows that the relative importance of the electrostatic force as compared to the gravitational force should increase with decreasing particle size.

London Dispersion Forces—The London dispersion force contribution to the particle-particle interaction may be estimated by summing the attraction over all possible atom pair combinations between the two particles (see Fig 21-5). Thus, we may write

$$E = \sum_{i=1}^M \sum_{j=1}^N \epsilon_{ij} \quad (10)$$

or

$$E = \sum_{i=1}^M \sum_{j=1}^N \frac{k_{ij}}{r_{ij}} \quad (11)$$

where k_{ij} , the London constant, is characteristic of the atom pair involved and is a function of the polarizabilities and the ionization energies of the atoms.

Table III—Maximum Electrostatic Energy and Force of Interaction between Uniformly Charged Spheres Near Contact^a ($R \approx 2a$ and Field = 60 esu) as a Function of Particle Size^b

Radius (cm)	Electrostatic		Gravitational force (dynes)
	Energy (ergs)	Force (dynes)	
10^{-4} (1 μm)	1.8×10^{-9}	9×10^{-6}	4.1×10^{-9}
10^{-3}	1.8×10^{-6}	9×10^{-4}	4.1×10^{-6}
10^{-2}	1.8×10^{-3}	9×10^{-2}	4.1×10^{-3}
10^{-1} (1 mm)	1.8	9	4.1
1	1.8×10^3	9×10^2	4.1×10^3

^a For these calculations the particles are assumed to be touching. These values approximately apply for particles not touching if distances of separation are not comparable to the particle radius.

^b Density of 1 is assumed.

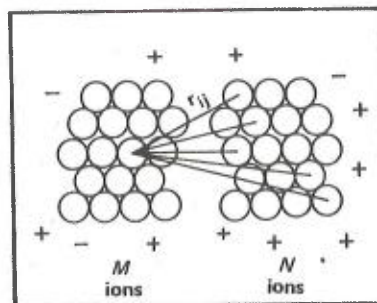


Fig 21-4. Electrostatic interactions between two particles containing M_i and N_j ions, respectively. The distance r_{ij} is the distance between the i th ion of one particle and the j th ion of the other particle.

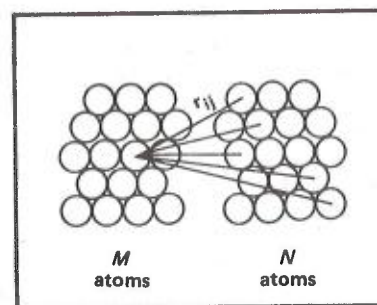


Fig 21-5. The London dispersion force contribution to the particle-particle interaction. This may be estimated by summing the attraction over all possible atom-pair combinations between the two particles, containing M and N atoms, respectively. The above illustrates the interaction of the i th atom of one particle with j atoms of the other particles where i and j are 1, 2, 3, 4, 5, etc.

In the case of two equal-sized spheres of the same substance the summations in Eq 11 may be transformed to double integrals and the following equation is obtained for energy:

$$E = \frac{-A}{6} \left[\frac{2a^2}{R^2 - 4a^2} + \frac{2a^2}{R^2} + \ln \left(\frac{R^2 - 4a^2}{R^2} \right) \right] \quad (12)$$

where $A = \pi^2 n^2 k$, n is the number of atoms/cm³, k is the London dispersion force constant, R is the particle-particle intercenter distance, and a is the radius of the sphere. A more rigorous equation may be deduced which takes into account the so-called "retardation effect," but it would not significantly contribute to the present discussion.

It is worthwhile to present the limiting forms of Eq 12. First, when R is much greater than $2a$ (ie, when the intercenter distance is large compared to the sphere diameter), one can show that the energy and force would be inversely proportional to the 6th and 7th power of R , respectively. On the other hand, when the closest distance, H , between the surfaces of the two spheres is much smaller than the sphere radius, one can show that

$$E = \frac{-Aa}{12H} \quad (13)$$

and

$$F = \frac{Aa}{12H^2} \quad (14)$$

where $H = R - 2a$ and $H \ll a$ (see Fig 21-3).

In order to gain an appreciation for the magnitude of the London attraction between two particles one can compute the energies and forces using Eqs 13 and 14 employing the appropriate values for A . Table IV gives a list of A values. These may be used in the present calculations. As can be seen from the A values, the London forces do not differ too greatly among materials with widely differing properties. The results

Table IV—Tabulation of A Values

Material	$A \times 10^{12}$ ergs
H ₂ O	0.31
Paraffin	0.35
Polyethylene	0.50
Polystyrene	0.63
Fe	1.4
Graphite	1.6
Silica	1.8
Rutile	2.1
Mercury	2.9

of using Eqs 13 and 14 and an A value of 10^{-12} erg are presented in Table V for two distances of separation, 5×10^{-8} and 5×10^{-7} cm. For other A values the reader may make the appropriate adjustments using Table IV information. The H value of 5×10^{-8} should be a reasonable limiting distance of closest approach (within a factor of two) for two atoms involved in the contact of the two macroscopic spheres.

An examination of the results presented in Tables III and V reveals several important relationships. First, as was the case with electrostatic interactions, London forces decrease much more slowly than the gravitational forces with decreasing particle size. Thus, as can be seen at a distance of separation of 5 Å, 1- μ m particles exhibit London attractive forces that are approximately one million times stronger than gravity, but 1-mm particles have approximately the same forces. For this reason fine particles tend to be "stickier" than coarse particles.

Secondly, the London attractive forces decrease more slowly than the electrostatic forces with decreasing particle size. Thus, a 10-fold decrease in particle size corresponds to only a 10-fold decrease in the London forces but to a 100-fold decrease in electrostatic forces. Thus, for 1- μ m particles or smaller, it is likely that London forces are always more important than electrostatic forces when the particles are near contact. However, as the distance of separation is increased, the electrostatic forces remain relatively constant while the London forces decrease rapidly. For example, as the distance of separation is changed from 5 to 50 Å, the London forces are decreased by a factor of a hundred while the electrostatic forces for all particles in Table III essentially remain constant. Thus, electrostatics may play an important role in the flow behavior of powders in which the particles are separated sufficiently during handling; eg, during mixing operations. However, once the powder particles are sufficiently packed, London forces should dominate.

It appears that the above relationships have not always been adequately emphasized in the literature. Texts which discuss electrostatic and London forces limit their discussion to molecular interactions in solutions and in solid crystals and do not apply them to solid particulate interactions. This leaves the impression that London forces are only important in the absence of electrostatic forces, which is obviously not true in solid particle-particle interactions.

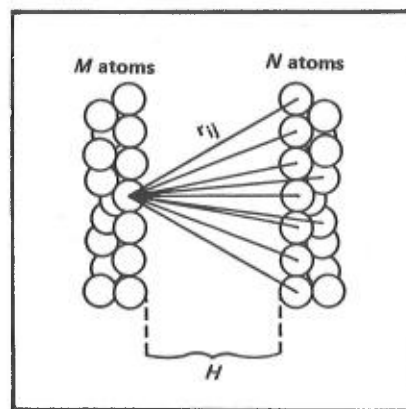


Fig 21-6. The interaction of two particles based on the flat-plate model. For symbolism, see Figs 3 and 5.

Nonspherical Particles—The above discussion was restricted to uniform spheres which do not generally represent real powders. Real powder particles are also subject to both plastic and elastic deformation which would provide larger areas of contact between them. The actual situation for powders would be expected to lie somewhere between the interaction between uniform spheres and that for parallel plates and is much more complicated than either of the above cases. Thus, for example, the interaction of two contacting cubes in contrast to that for two spheres, also depends upon their relative orientation (face to face, face to edge, corner to face, edge to edge, etc). In addition to the mutual orientation and shape effects for real powders, one must consider the particle-size distribution and the important factor of whether or not the particle is deformable (plastic and/or elastic) under the prevailing conditions.

It would be beyond the scope of this text to attempt detailed considerations of the above factors. However, in order to gain an appreciation for the magnitudes of the possible London force interactions between real powder particles it is helpful to examine the limiting case of two interacting flat plates (see Fig 21-6).

For two parallel flat surfaces separated by a distance, H , the equations for the London Force interacting energy and force/unit area are

$$E = \frac{-A}{12\pi H^2} \quad (15)$$

and

$$F = \frac{+A}{6\pi H^3} \quad (16)$$

Table VI tabulates the results of calculations for the same two distances of separation used in Table V for comparison purposes.

Tables V and VI show that suitably oriented flat plates or

Table V—London-van der Waals' Energies and Forces for Spheres as a Function of Particle Size (assuming $A = 10^{-12}$)^a

Radius (cm)	Energy (ergs)		Force (dynes)		Gravity
	$H = 5 \text{ \AA}$	$H = 50 \text{ \AA}$	$H = 5 \text{ \AA}$	$H = 50 \text{ \AA}$	
10^{-5}	1.7×10^{-11}	1.7×10^{-12}	3.3×10^{-4}	3.3×10^{-6}	4.1×10^{-12}
10^{-4}	1.7×10^{-10}	1.7×10^{-11}	3.3×10^{-3}	3.3×10^{-5}	4.1×10^{-9}
10^{-3}	1.7×10^{-9}	1.7×10^{-10}	3.3×10^{-2}	3.3×10^{-4}	4.1×10^{-6}
10^{-2}	1.7×10^{-8}	1.7×10^{-9}	3.3×10^{-1}	3.3×10^{-3}	4.1×10^{-3}
10^{-1}	1.7×10^{-7}	1.7×10^{-8}	3.3	3.3×10^{-2}	4.1

^a Average thermal energy = $kT = 4 \times 10^{-14}$ erg.

Table VI—London–van der Waals' Energies and Forces for Parallel Plates^a as a Function of Contact Area (assuming $A = 10^{-12}$)

Area (cm ²)	Energy (ergs)		Force (dynes)	
	$H = 5 \text{ \AA}$	$H = 50 \text{ \AA}$	$H = 5 \text{ \AA}$	$H = 50 \text{ \AA}$
10^{-12}	1×10^{-11}	1×10^{-13}	5×10^{-4}	5×10^{-7}
10^{-10}	1×10^{-9}	1×10^{-11}	5×10^{-2}	5×10^{-5}
10^{-8}	1×10^{-7}	1×10^{-9}	5	5×10^{-3}

^a Forces and energies are applicable to cubes with a linear dimension of the square root of the area listed.

cubical particles may exhibit interactions several orders of magnitude greater than those for rigid spheres of the same size.

Adsorption and Interfacial Energetics

Because there are unsatisfied intermolecular forces at interfaces, adsorption of molecules can occur there; when it does the free energy of the system is lowered. Consider the unfavorable situation of a system involving a paraffin oil/water interface. Paraffin/paraffin interactions and water/water interactions are such that the molecules of the two phases prefer to remain with their own kind (Fig 21-7A). At the interface between the phases there is a shortage of both water molecules and paraffin molecules; however, if surfactant molecules, for example of sodium dodecyl sulfate, are present a more favorable situation develops. Some of the surfactant molecules move to the interface, their polar portions reaching toward and into the water phase and their hydrophobic tails orienting toward the paraffin oil phase (Fig 21-7B). Maximum free-energy lowering, the best compromise for all components of the system, results.

Gibbs Adsorption Equation—The relationship between interfacial tension and adsorption is important and should be examined (see also Chapter 19, page 263).

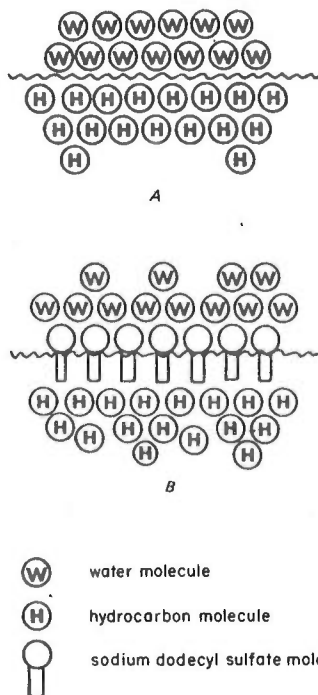


Fig 21-7. Addition of a surface-active agent such as sodium dodecyl sulfate (SDS) lowers the energy of the oil-water interface by adsorption of the SDS molecules as shown. A, Energetically unfavorable without SDS; B, energetically favorable with SDS.

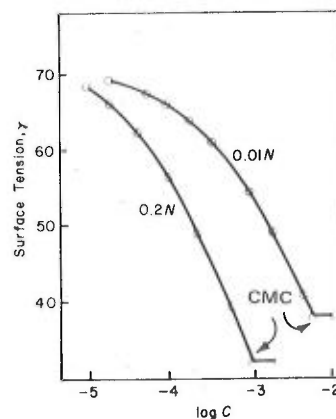


Fig 21-8. Surface tension of sodium lauryl sulfate solutions at 40° in 0.01 and 0.2 N NaCl.

Consider a two-component system containing a solvent and a nonionic solute, with the latter adsorbing at an interface between the solvent phase and another phase. The Gibbs equation for this system may be written

$$\Gamma = -\frac{a}{RT} \left(\frac{d\gamma}{da} \right)_{T} = -\frac{1}{RT} \left(\frac{d\gamma}{d \ln a} \right)_{T} \quad (17)$$

In this equation Γ is the surface excess of solute, in moles/cm², γ is the interfacial tension, a is the activity of the solute in moles/liter, R is the universal gas constant (8.3143×10^7 erg/deg/mole), and T is the absolute temperature. For practical purposes involving surface-active solutes, Γ is essentially equal to moles of solute adsorbed per cm².

Eq 17 shows that the amount of solute adsorbed is simply related to the negative slope of the γ versus $\ln a$ curve. Thus, by measurements of γ , if an air/liquid or liquid/liquid interface is involved, Γ may be determined. This experimental approach is not suitable for a solid/liquid interface. Fig 21-8 depicts plots of γ versus $\log C$ for the aqueous sodium lauryl sulfate/air system at 40°. According to Eq 17, as the concentration of surfactant increases, γ decreases. If it may be assumed that the activity coefficient is constant, then $d \ln a = d \ln C = 2.303 d \log C$. This assumption is probably reasonable, especially in the presence of excess electrolyte, up to the critical micelle concentration (CMC) (see Chapter 20) if pre-micellar association does not occur. Beyond the CMC the curve levels off because with micelle formation the activity, a , of the surfactant changes very little with increasing C .

To calculate Γ , at 40°, (the moles of solute per unit area) near the CMC one may take the limiting slope, $d\gamma/d \log C$ just before the CMC. For the 0.2N sodium chloride solution in Fig 21-8 the slope is approximately -30 , and

$$\Gamma = \frac{30}{2.303 RT} = 5 \times 10^{-10} \text{ moles/cm}^2$$

and the area per molecule = $30 \times 10^{-16} \text{ cm}^2$. As this corresponds to a diameter of 6 to 7 Å for the adsorbed molecule, these results show that at the solution/air interface there is probably a relatively compact monolayer of sodium lauryl sulfate molecules near the CMC.

Eq 17 may also be written in an integral form that expresses γ as a function of Γ and a , thus

$$\gamma = \gamma_0 - \int_0^{\Gamma} \frac{RT\Gamma}{a} da \quad (18)$$

where γ_0 is the interfacial tension in the absence of the solute ($a = 0$). This alternative representation of the Gibbs equation states that γ may be obtained by means of Eq 18 through a determination of the area under the curve $RT\Gamma/a$ versus a . A highly active surfactant would begin to adsorb appreciably

at a low concentration (activity). Hence $RT\Gamma/a$ would be large even when a is small. Therefore the integral $\int_0^a RT\Gamma da/a = \int_0^a RT\Gamma d \ln a$ would be appreciable, and a large reduction, $\gamma_0 - \gamma$, would be achieved even at low concentrations of the surfactant. Thus (see Fig 21-8) it can be said that in 0.2N sodium chloride, excluding the regions beyond the CMC, sodium lauryl sulfate is about ten times more surface-active than in 0.01N sodium chloride, ie, for the 0.2N sodium chloride the same $\gamma_a - \gamma$ and the same extent of adsorption (Γ) are observed at one-tenth the concentration of the surfactant.

Adsorption of a Surfactant—Surface-active substances (surfactants) are those that adsorb or tend to concentrate at interfaces. Conventional soaps, detergents (ionic and non-ionic), gums, and finely divided solids belong in this category. These materials adsorb at interfaces, the amount of adsorption generally increasing with increasing solution activity, a .

Fig 21-9 shows an adsorption isotherm that is similar to the one found for adsorption of a surfactant at the air/liquid or solid/liquid interface. Here C (moles/liter), rather than a , has been plotted on the x-axis. The initial slope of the Γ versus C curve is usually a measure of the inherent affinity of single molecules of surfactant for the adsorption site. Therefore, the greater the affinity the sooner (at low C or a) the adsorption begins. Maximum adsorption (plateau in Fig 21-9) usually occurs for one of two reasons: (1) all adsorption sites have become occupied by surfactant molecules, or (2) owing to micelle formation at the critical micelle concentration (CMC) the activity, a , becomes almost constant even while C continues to increase.

Experimental determinations of adsorption isotherms are easily carried out for solid/liquid systems when the solid is sparingly soluble in the solvent. Generally a given weight of adsorbent is equilibrated with a given volume of solution containing the surface-active agent. Analysis of the solution before and after equilibration gives the amount adsorbed. If the surface area of the adsorbent is known from an independent experiment, then Γ and the area per molecule may be calculated. For monolayers of low-molecular-weight (<500) surfactants, the area per molecule at maximum coverage is usually in the range of 20 to 50 \AA^2 , which is consistent with molecular geometrics.

Table VII gives the results of adsorption experiments carried out by Roseman² in which 100-mg portions of hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] were equilibrated with 100 mL of dodecylammonium chloride (DAC) solutions of different concentrations. Fig 21-10 is a plot of the data. The plateau portion of this figure indicates that 0.6 millimole of DAC was adsorbed per gram of hydroxyapatite. The surface area of the sample was found to be 60 m^2/g , and it was calculated that each adsorbed DAC molecule occupied 16 \AA^2 .

As noted previously, the Gibbs equation may be used to

Table VII—Adsorption of Dodecylammonium Chloride on 100 mg of Hydroxyapatite in Water at 30°. Solution volume = 100 mL.

Initial Conc. (millimolar)	Equil. Conc. (millimolar)	Millimoles Adsorbed/100 Mg
1.52	1.34	0.0018
3.76	2.77	0.0099
4.98	3.50	0.0148
7.33	4.81	0.0252
9.07	5.68	0.0339
11.3	6.73	0.046
13.3	7.77	0.055
15.2	9.36	0.058
18.3	12.3	0.060

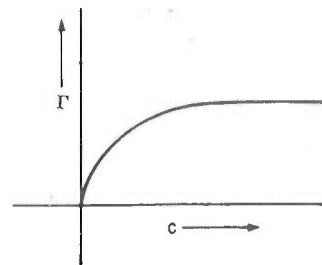


Fig 21-9. A typical adsorption isotherm. Γ is moles adsorbed/ cm^2 and C is moles/liter in the bulk solution.

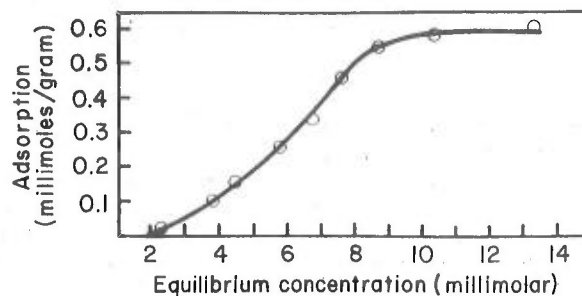


Fig 21-10. Adsorption of dodecylammonium chloride on hydroxyapatite at 30°.

determine Γ and the area per molecule for the liquid/air interface. This approach may be used also for adsorption at liquid/liquid interfaces, except that interfacial tension, rather than surface tension, must be measured as a function of surfactant concentration.

When the plateau in the adsorption isotherm is the result of saturation of adsorption sites, a relatively compact monolayer of surfactant is formed. In some instances, however, multilayer adsorption occurs. Such adsorption is generally assumed when the area per molecule, calculated from Γ , is appreciably less than 20 \AA^2 , the lower limit for a single molecular layer. Also, when multilayer adsorption occurs, isotherms are usually more complex than that shown in Fig 21-9. For example, sodium lauryl sulfate and dodecylammonium chloride appear to pack as monolayers on barium sulfate and calcium fluoride surfaces in water. On aluminum oxide and titanium oxide, however, these agents appear to adsorb by a multilayer mechanism at certain pH values. A multilayer mechanism can describe adsorption of cationic agents on glass. At low concentrations these surfactants adsorb with their hydrophobic tails extending into the water phase; a second layer forms at higher concentrations, with the ionic portions in the aqueous phase.

Fig 21-11 shows the adsorption isotherm for dodecylammonium chloride on alumina. The complex curve suggests that at least two layers are formed near the CMC; the first inflection point in the curve probably represents the beginning of the second layer.

The CMC phenomenon is very important because it limits the "ultimate surface activity" of surfactants; the greater the CMC the better the surfactant. The CMC prevents most surfactants from providing zero or negative interfacial tensions (and therefore spontaneous emulsification), as evident in Eq 18. If sufficiently high activity could be attained, γ would become zero or negative. Aerosol OT is a good wetting agent, probably because its irregular shape makes micelle formation difficult. Hence, its CMC in water is relatively high, and low γ_L and γ_{SL} values are obtained with it.

The CMC of many surfactants is lowered by mixed micelle formation with other molecules (Fig 21-12). Long-chain al-

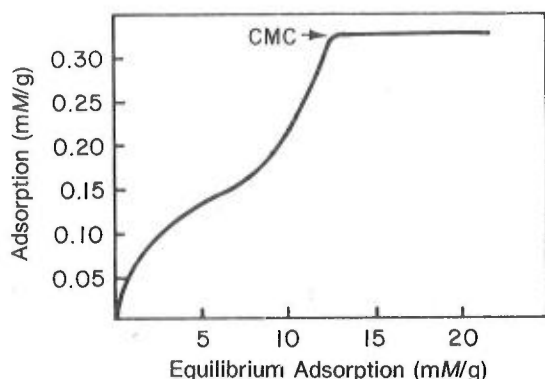


Fig 21-11. Adsorption isotherm for dodecylammonium chloride on alumina at 20°.

cohols, amines, and esters may participate in mixed micelle formation with ionic and nonionic surfactants. The lowering of the CMC may be considerable. A consequence of this may be reduced surface activity unless these additives are equally proficient in enhancing surface activity by mixed surface-film formation. Thus, in the preparation of emulsions, either impurities in the oil or the oil itself may lower the CMC of the surfactant by incorporation into the micelles, and the surface activity of the agent may then be quite different from what it is in water alone.

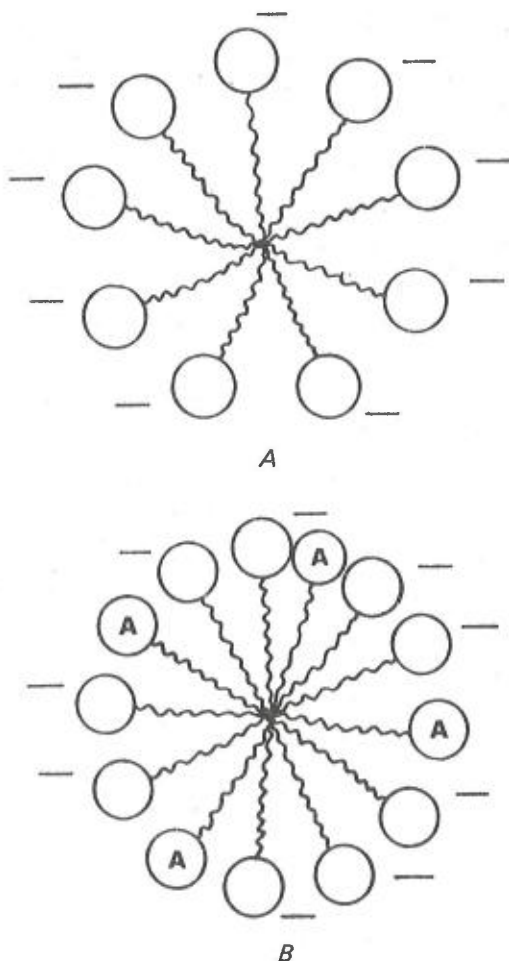


Fig 21-12. Incorporation of long-chain alcohol molecules can lower the energy of a micelle, thus lowering the critical micelle concentration. A, Micelle of anionic molecules (higher energy); B, mixed micelle: anion + alcohol (A) molecules (lower energy).

Adsorption of surfactants at interfaces may be greatly influenced by the chain length, branching, and nature of the polar head group(s) in the surfactant molecule; the pH; the temperature; added salt in solution; and the nature of the interface-forming phases.

Adsorption of Polymers—Polymeric materials, such as suspending agents, are used in most dispersed pharmaceutical products. Several unique features characterize adsorption of polymers. The polymer consists of a skeleton molecular structure to which is attached, periodically along the skeleton, functional groups of different activity than the rest of the molecule; these groups adsorb at the interface. Neighboring segments may be adsorbed to form a “train” in the interface, or “loops” may form that extend into the solution. The adsorbed anchor groups at the two ends of the loop bind the loop to the interface. The interaction energy between the anchor group and the adsorbent need not be large to produce very extensive adsorption. This is a consequence of the multiple anchor groups. It is not probable that random thermally induced fluctuations would remove all anchor groups simultaneously, even if the individual anchor group interacts with only 4 or 5 kT energy. Many anchor groups may be attached to the loop section of the molecule and cannot adsorb at the same interface. However, they have the potential of adsorbing at the interface of a neighboring solid particle.

The nature of the train-loop configuration of adsorbed polymers causes the amount of polymer adsorbed per unit of surface area to increase extremely rapidly with increase in polymer concentration until the surface coverage of the solid is nearly complete. Above this plateau level further adsorption may be negligible. The adsorption often is nearly irreversible, very little being removed by repeated washing.

As polymer adsorbs, the free energy of interaction between neighboring loops becomes strong enough to arrest adsorption. In a good solvent this interaction is stronger than in a poor solvent; therefore, the adsorbed layer will contain more polymer when the adsorption is from a poor solvent. Conversely, in a good solvent long loops tend to cause the polymer to desorb because of the large free energy of interaction of polymer loops in close proximity. Similarly, the configuration of the molecule and the extension of the loops are dependent on solvent quality. Loops in a poor solvent tend to coil and to extend less distance from the interface than those in a good solvent. Again the controlling factor is the magnitude of the interaction of neighboring loops.

Particles in Liquid Systems

The behavior of particles dispersed in a liquid medium is subject to essentially the same forces as those described for powders although the results can be different due to the presence of the liquid. For example, as will be seen, the electrical forces in aqueous media between particles can play a more important role than in powders under certain conditions.

Effect of Charges—A solid particle or a droplet of an immiscible liquid may be electrically charged because an excess of ions of one sign may be present at the interface. The charge-conferring ions may be a constituent of the particle itself, impurity ions from the external-phase liquid, or surfactant ions preferentially adsorbed at the interface.

The particle charge gives rise to a surface potential, ψ_0 , at the surface of the particle (see Fig 21-13). The potential will drop to zero at some distance away from the surface depending on the concentration of the counter-ions in the external-phase bulk. The region in which the influence of the surface charge is appreciable is called the electrical double-layer region.

The double layer may be visualized as being made up of two parts. The specific adsorption of counter-ions in the Stern

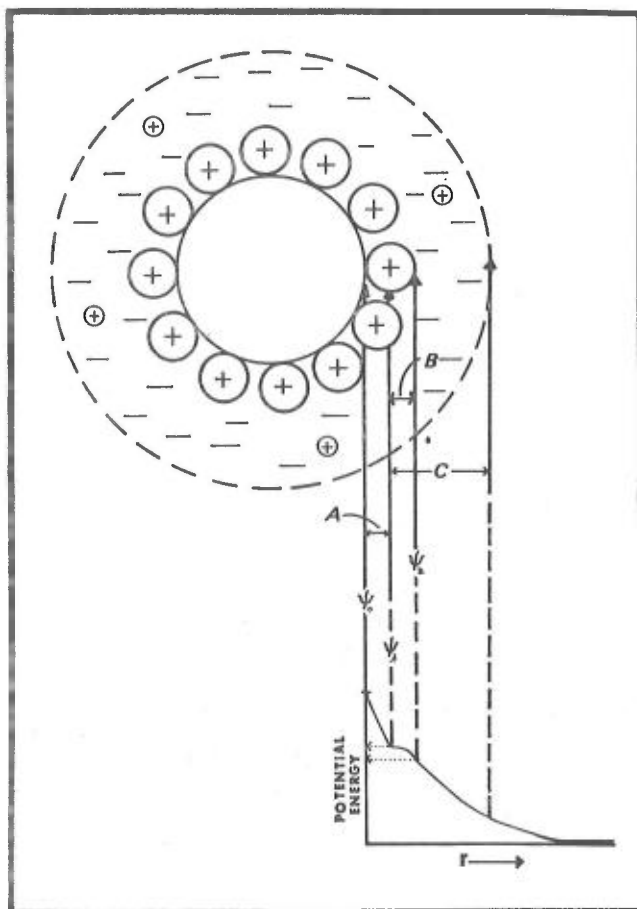


Fig 21-13. The electrical double layer and the symbols used to describe the potential at various points. A: The Stern layer, B: the plane of shear, and C: the sphere of influence of the diffuse double layer.

Layer comprises the first part, the thickness of which is of the order of ionic dimensions. The potential drop across this region is $\psi_0 - \psi_\delta$. The second part is called the diffuse double layer across which the potential drop is ψ_δ . The thickness of the diffuse double layer is given by the Debye-Hückel quantity $1/\kappa$.

$$1/\kappa = \left(\frac{\epsilon k T}{4\pi e^2 \sum n_i z_i^2} \right)^{1/2} \quad (19)$$

where ϵ is the dielectric constant in the diffuse double-layer region, k is the Boltzmann constant, T is the absolute temperature, e is the electronic charge, n_i is the bulk concentration of ion i , and z_i is its valence.

According to Eq 19 a 1% aqueous sodium chloride solution at room temperature gives $1/\kappa = 8 \text{ \AA}$, a 0.01% solution gives $1/\kappa = 80 \text{ \AA}$, a $1 \times 10^{-4}\%$ solution gives $1/\kappa = 800 \text{ \AA}$, etc. These calculations show that the electrical influence among particles in aqueous media is relatively short-range compared to that involving powder particles, which, as predicted by Eqs 3 and 4, extend to distances of the order of particle dimensions.

In nonpolar media n , the bulk ionic concentration, is usually very small. Therefore, $1/\kappa$ values of the order of centimeters are sometimes encountered, and in such cases the distances of electrical influence approach those encountered in powders. This frequently leads to the "electrostatic" problems in such systems. Antistatic agents are helpful in these situations by reducing $1/\kappa$ and by relieving the buildup of charge.

Eq 19 also shows that polyvalent counterions are much more effective than monovalent ions in reducing the double-layer thickness. A 2-2 electrolyte is about four times more

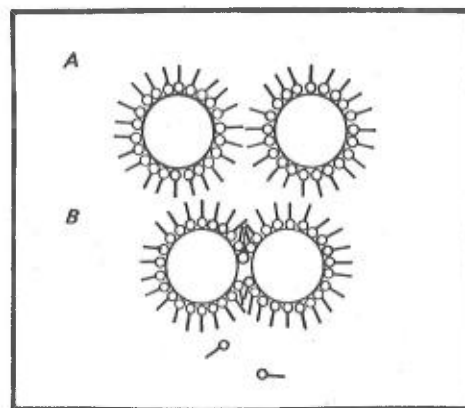


Fig 21-14. The interaction of two particles coated with surfactant molecules. A: Particles separated by a distance which is large as compared to the size of the adsorbed surfactant molecules; B: particles at a close distance where repulsive forces arise when surfactant molecules are squeezed together and/or desorbed.

effective than a 1-1 electrolyte in reducing the diffuse double-layer thickness.

Zeta Potential—When a charged particle suspended in a liquid is placed in an electrical field, it will migrate towards the electrode with the opposite charge. The ions in the Stern Layer and the bound solvent molecules are also carried along with the particle. Thus, the plane of shear (see Fig 21-13) is very close to the Stern Layer but slightly farther away from the particle surface. While the exact relationship between the zeta potential, ψ_z , and ψ_δ is not clear, it is generally supposed that ψ_δ and ψ_z are of the same order of magnitude, the latter being slightly smaller. If, in addition, ψ_0 is small (≈ 50 mV) and there is little special counterion-binding tendency at the interface, the zeta potential will also reflect the ψ_0 value and the changes in it. The surface potential, ψ_0 , is related to the surface charge density, the number of charges per unit area, by the Gouy-Chapman diffuse electrical double layer theory.

As will be seen in the next section, when electrical repulsion is present, the flocculation behavior of suspensions and emulsions strongly depends upon the surface charge on the particles which is reflected in the magnitude of ψ_z . Generally when ψ_z is of the order of 25 mV or less, the system becomes kinetically unstable to flocculation and aggregation or coalescence may take place.

Particle Interactions in Liquids—According to the theory of the stability of lyophobic colloids (particles in liquid media) a number of forces are at play in determining the overall interaction among particles. Consideration of these interaction forces is helpful in understanding the dispersion process as well as aggregation and coalescence behavior of dispersed particles. At relatively large distances of separation ($\approx 10 \text{ \AA}$) the primary forces are the London dispersion forces of attraction and the electrical repulsive forces resulting from the interaction of the diffuse double layers of the particles. The electrolyte flocculation behavior of suspensions and emulsions is frequently attributed to the interplay of the electrical and the dispersion forces.

Other forces of repulsion should also be considered, particularly at close distances of approach between the particles. These are the repulsive contributions due to the surfactant molecules themselves, arising from steric hindrance (see Fig 21-14). Particles at very close distances of approach may be kept apart by this mechanism and by the resistance of the adsorbed agents from being displaced (desorbed) from the interface. When surfactant desorption is involved, work must be done against those same forces that are responsible for the

interfacial-tension lowering. Barriers to particle-particle aggregation and/or droplet coalescence are also set up by adsorption of polymers and finely divided solids. Lyophilic polymers often provide thick films ($\approx 100 \text{ \AA}$) that effectively prevent close approach of the particles.

London Dispersion Forces of Attraction—As previously stated, the London dispersion forces are generally regarded as short-range and relatively weak. However, considering the large number of molecules in a suspension particle or an emulsion droplet, one finds that the aggregate attraction between two particles may be significant even at surface separation distances (H) of the order of 100 \AA .

Eq 20 gives the attraction energy between two spheres according to theory:

$$V_A = -\frac{A'a_1a_2}{6(a_1+a_2)} \left(\frac{\lambda}{\lambda H + 3.54\pi H^2} \right) \quad (20)$$

where a_1 and a_2 are the radii of the spheres, λ is the London wavelength, usually taken as 10^{-5} cm , and A' is the effective Hamaker's constant.

Diffuse Double-Layer Repulsion—When two spherical particles of the same size are close enough so that their electric double layers are appreciably overlapping, a substantial repulsion may arise. Eq 21 may be used to estimate the repulsive potential energy, V_R , as a function of the distance of separation:

$$V_R = \frac{\epsilon a_1 a_2 \psi_0^2}{(a_1 + a_2)} \ln [1 + \exp(-\kappa H)] \quad (21)$$

where ϵ is the dielectric constant of the double-layer region, a_1 and a_2 are the radii of the spheres, ψ_0 is the surface potential, and H is the shortest distance of separation between the surfaces of the spheres. Eq 21 was derived for the case in which the double-layer thickness, $1/\kappa$, is small compared to the radius of the smaller particle. This generally would be a good assumption for most situations in which water is the continuous phase and for particle sizes down to $ca 100 \text{ \AA}$. The equation is only applicable for small ψ_0 values, *viz* $\psi_0 \lesssim 25 \text{ mV}$. If larger ψ_0 values are involved, it may be more appropriate to substitute ψ_δ for ψ_0 in Eq 21.

Interactions between Adsorbed Layers—As two particles with adsorbed polymer approach each other, the loops of polymer extending from neighboring particles interact. The generic term for stabilization produced by these interactions is "steric stabilization." The interactions are essentially the same as would occur with an increase in concentration of the polymer in solution. The conformations available in one loop will be reduced by the presence of another loop; therefore entropy decreases. A decrease in entropy increases the free energy, so a repulsion develops between the two particles. Since the quality of the solvent affects the excluded volume, it also influences the magnitude of the repulsion at a given distance of separation between the particles. Obviously, two loops cannot interpenetrate without "squeezing out" solvent. Thus, as two particles approach, the loops of adsorbed polymers must replace polymer-solvent interactions with polymer-polymer interactions. Again the quality of the solvent determines the enthalpy changes that occur.

The influence of solvent quality has been studied and verified,³ but efforts to distinguish experimentally between enthalpic and entropic stabilization have been less successful. Use of model systems to describe particle-particle interactions has improved, but the models are not adequate to explain all observations. One of the simple models for the potential energy of entropic and enthalpic repulsion V_S ,⁴ which attempts to embody the aforementioned concepts, is expressed by

$$V_S = \frac{4\pi k T \bar{V}_S^2}{3\bar{V}_1} \psi_1 \left(1 - \frac{\theta}{T} \right) \left(\delta - \frac{H}{2} \right)^2 \left(3r + 2\delta + \frac{H}{2} \right) \quad (22)$$

where k is the Boltzmann constant, T is the absolute tem-

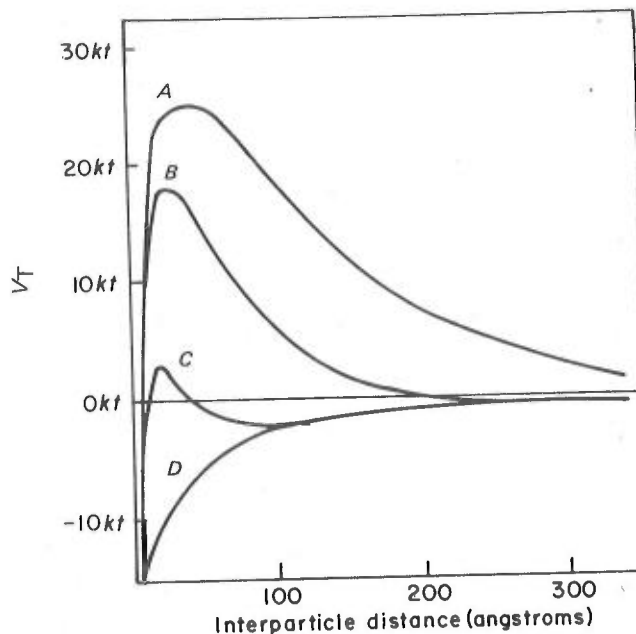


Fig 21-15. The net interaction of two spherical particles considering only the London forces of attraction and electrical repulsion (kt units) as a function of the interparticle distance (\AA) for two equally sized particles of $0.1 \mu\text{m}$. A: $\kappa = 2 \times 10^6$, B: $\kappa = 4 \times 10^6$, C: $\kappa = 10^7$, and D: $\kappa \geq 2 \times 10^7$. The peaks represent the maximum potential, V_{max} . These calculations used the following values: $A = 10^{-13} \text{ ergs}$, $\psi_0 = 25 \text{ mV}$, and $\lambda = 10^{-5} \text{ cm}$.

perature, θ is a temperature parameter (Flory temperature), ψ_1 is an entropy term for solvent-polymer interaction, δ is the thickness of the adsorbed polymer layer, r is the radius of the bare particle, \bar{V}_S is the volume fraction of adsorbed polymer in the overlap region, and \bar{V}_1 is the molecular volume of the solvent molecules. When the interparticle distance, H , is less than 2δ , V_S is greater than 0; for $H \geq 2\delta$, $V_S = 0$. For additional examples and information see references 5 to 14, at the end of this chapter.

Total Interaction—The net interaction of two spherical particles is given by,

$$V_{\text{total}} = V_A + V_R + V_S \quad (23)$$

Considering only the London forces of attraction and the electrical repulsion,* Fig 21-15 shows plots of V_{total} for two particles of equal size ($a_1 = a_2 = 0.1 \mu\text{m}$) at different ionic strengths, in water. At low ionic strengths, where $1/\kappa$ is large (see Eq 19), electrical repulsion dominates at most distances, and V_{total} is positive for all distances beyond the first few angstroms; the maximum potential, V_{max} , is large, $\sim 25 \text{ kt}$. As the salt concentration is increased ($\kappa = 4 \times 10^6$, *ca* 0.10% NaCl), V_{max} decreases and a minimum develops in the potential energy curve at $H \approx 150 \text{ \AA}$. This minimum is called the secondary minimum, V_{min} , which, although small in the present example, could be of substantial depth for larger particles. At high salt concentrations ($\kappa = 10^7$ to 2×10^7 , *ca* 1% NaCl), the repulsion is almost completely eliminated and only attraction persists. The influence of particle size on the total potential energy is shown in Fig 21-16. The energy barrier tends to increase with increasing particle size.

In an aqueous solution at higher concentrations of elec-

*Sample numerical calculations of the potential energy of repulsion, of the potential energy of attraction, and of adsorbed polymer repulsion are given in Appendix B of a communication by Schneider, Stavchansky, and Martin (*Am J Pharm Ed* 42: 280, 1978).

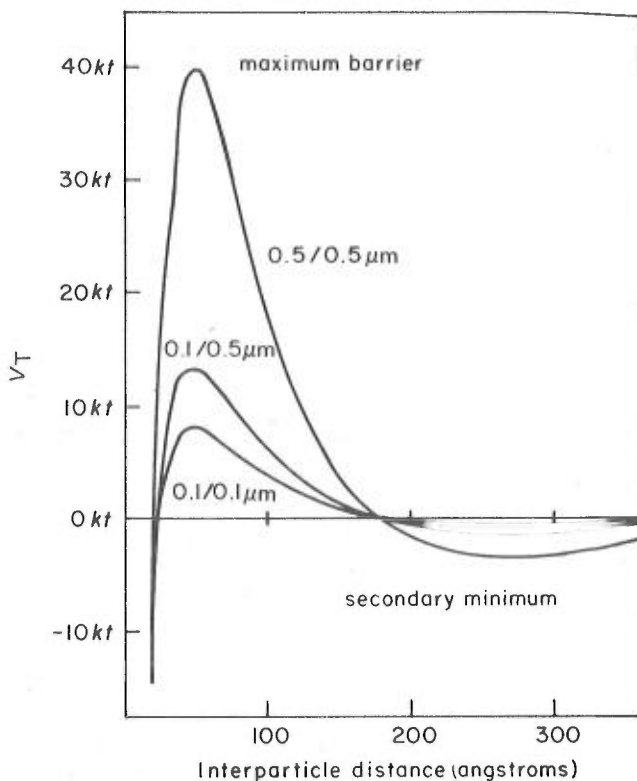


Fig 21-16. Influence of particle size on total potential energy of interaction. $A = 5 \times 10^{-13}$ erg, $\psi = 25$ mV, and $\kappa = 2 \times 10^6$ cm $^{-1}$.

trolytes, the double-layer thickness may be so small that it will have no significant effect on the stability of a sterically stabilized system,⁵ eg, a double layer of a few angstroms thickness would have little influence when the polymer loops extend into the solution 30 or more angstroms, ie, $1/\kappa < \delta$. As suggested earlier, electrolytes may produce flocculation in the presence of adsorbed polymer, but the flocculation may not be the result of their effect on the double layer. The use of electrophoretic mobility to determine the charge on the particle must be viewed with apprehension when adsorbed polymer is present. The extending loops cause the hydrodynamic shear plane to be moved out from the particle surface; thus, a much lower value of the zeta potential will be observed than would be justified for the charge distribution in the double layer. The presence of other solvents may affect the Stern layer.⁶ Also, changes of the dielectric constant of the liquid and of the solvent quality are not independent factors.

An anchor group on the polymer may form a weak bond and be an inefficient anchor.⁵ Such a polymer could desorb during interparticle collisions. This is designated "displacement flocculation." The kinetics of this should depend on the size of the adsorption interaction energy. Also, the addition of smaller molecules that could compete for and displace the polymer from the adsorption sites would be a controlling factor for the effectiveness of the polymer. One should be alert to these possibilities.

A possible mechanism of polymer action is that the polymer could prevent the particles from entering into the deep potential energy well illustrated in Fig 21-16, resulting from the combination of the van der Waals attraction and the double-layer repulsions.⁷ The relative thickness of the double layer and the adsorbed polymer layer would determine whether steric repulsion prevented entry into the primary minimum. If properly balanced, the net effect of the two terms could be to change the primary minimum to a shallow minimum by preventing closer approach of the particles.

Thereby the adsorbed polymer would lead to a condition in which redispersion would be readily accomplished. Definitive work in this area is lacking, but this possibility should be considered.

Charged particles approaching another charged surface must overcome a potential energy barrier before a successful collision is achieved. This mechanism of particle-particle collision has been used to explain a number of phenomena which include the adhesion of cells, flocculation of charged phospholipid vesicles (or liposomes), and the interaction between particles in blood and surfaces of prosthetic materials. The electrical properties of the interfacial barrier are largely responsible for the slow dissolution rates of cholesterol particles (or cholesterol gallstones) in the presence of negatively charged micelles. The dissolution rates are enhanced manyfold in the presence of high electrolyte concentrations, neutralizing amines and quaternary ammonium compounds. Hence, the dissolution of cholesterol gallstones by perfusion of the gallbladder with sodium cholate micellar solutions is interfacial barrier-controlled in the absence of salt and is aqueous diffusion layer-controlled in sodium chloride solutions.

Flocculation Kinetics

Rapid Flocculation—In the absence of any repulsive barrier ($V_{\text{Total}} = 0$) and when it is controlled only by Brownian motion diffusion, the flocculation rate of a monodispersed suspension is given by the Smoluchowski equation:

$$\frac{dN}{dt} = -4\pi DRN^2 \quad (24)$$

where dN/dt is the disappearance rate of particles/cc, 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. Eq 24 shows that the flocculation reaction is bimolecular, the rate being proportional to the square of the particle concentration. If D is replaced by the Einstein relation, $D = kT/6\pi\eta a$, and $R = 2a$, the Smoluchowski rate constant for rapid flocculation is predicted by

$$K = 4\pi DR = \frac{4kT}{3\eta} \quad (25)$$

The time, $t_{1/2}$, required to reduce the total number of particles to one-half the original number is given by

$$t_{1/2} = \frac{3\eta}{4kTN} \quad (26)$$

Here, η is the viscosity of the liquid medium and N is the initial concentration of particles (number of particles per cc).

It is well known that agitation promotes flocculation but appears to have little influence in the initial stages of the flocculation. In the simplest case (see Fig 21-17) consider the particles in a laminar shear field with a velocity gradient, g , so that other particles are swept into the sphere of action of a central particle. The increase in the flocculation rate is evident when the collisions caused by the movement of the liquid and by Brownian motion are added. By comparing the probability of laminar shear collision, J , with the probability of Brownian collision, I ,

$$J/I = \frac{\eta a^3 g}{2kT} \quad (27)$$

the measure of the relative contributions of these types of motions to flocculation is found. Table VIII shows that for small colloidal particles collisions caused by agitation are few compared to those caused by Brownian motion unless the shear gradient is very high. It also shows the transition between the region of colloidal dispersion, where Brownian

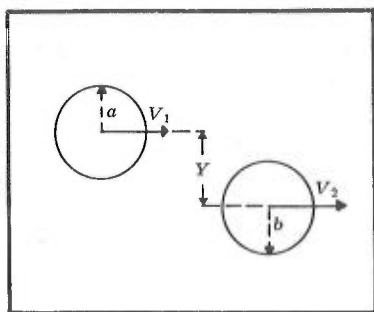


Fig 21-17. The influence of shear upon aggregation rate. If $V_1 > V_2$, collision will occur. Also, any other particle whose center is within the target area $4\pi a^2$ will collide if its velocity is less than Particle 1. The velocity gradient, G , is given by $(V_1 - V_2)/Y$; V_1 is the velocity of Molecule 1 and V_2 is the velocity of Molecule 2.

Table VIII—Relative Contribution of Shear-Induced Flocculation to the Brownian-Motion-Induced Flocculation^a

Radius (μm)	Brownian motion only ^b ($t_{1/2}$)	Brownian and laminar shear motions	
		g (sec^{-1})	J/I^c
0.05	0.95 sec	659	1/1000
		6,590	1/10
		65,900	1
0.5	950 sec	659	10/1
5.0	264 hr	659	1000/1

^a Concentration of particles is 0.1% in water at 25°.

^b Calculated using Eq 26.

^c Calculated using Eq 27.

motion is predominant, and the region of suspensions, where agitation may govern flocculation.

Slow Flocculation (Energy Barrier)—When an energy barrier such as the electrical one discussed in the previous section is present, the flocculation rates may be much smaller than those predicted by Eq 24. When shear effects in the medium are negligible, one may write

$$G_{12} = \frac{2kT}{3\eta W_{12}} \left(\frac{1}{a_1} + \frac{1}{a_2} \right) (a_1 + a_2) N_1 N_2 \quad (28)$$

where G_{12} is the sticking rate of two particles of radii a_1 and a_2 with concentrations of N_1 and N_2 , respectively. The factor W_{12} accounts for the energy barrier and is given by

$$W_{12} = 2 \int_2^\infty \exp(V_{\text{Total}}/kT) \frac{dS}{S^2} \quad (29)$$

where $S = 2R/(a_1 + a_2)$, R is the intercenter distance between the two particles, and V_{Total} is the potential energy function.

When V_{Total} is primarily the result of the diffuse double-layer repulsion and the London attraction, V_{Total} may be expressed by Eqs 20 and 21 for aqueous media.

The above indicates that the sticking rates of particles can be calculated in the following way: Eqs 20, 21 and 22 are used to calculate V_T at all distances of separation. The values of V_T as a function of S can also be obtained from Fig 21-15. The V_T 's obtained by either method are substituted into Eq 29 and numerically integrated between limits to obtain W_{12} . Substituting this value for W_{12} in Eq 28 permits G_{12} to be calculated and G' is obtained from Eq 30.

Fig 21-18 gives the results of calculation with Eqs 20, 21, 22, 28 and 29. The quantity G' is defined by

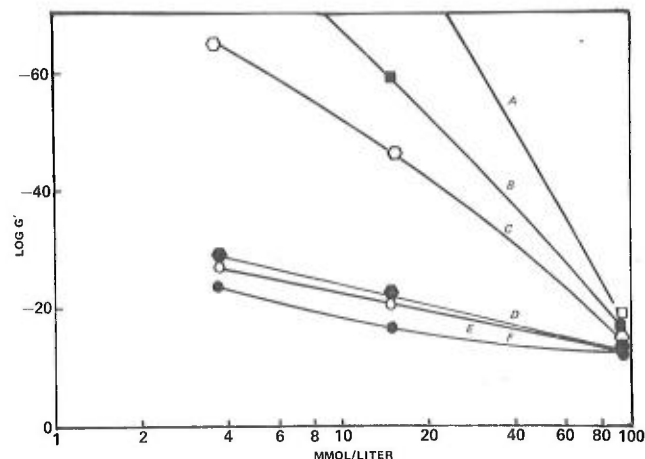


Fig 21-18. The calculated rates of aggregation of 0.1 μm , 0.5 μm , and 1 μm particles with themselves and with larger particles as a function of concentration of a 1-1 electrolyte in solution. ψ_0 is 25 mv and A' is 1×10^{-13} ergs. A: 1.0/1.0 μm ; B: 0.5/1.0 μm ; C: 0.5/0.5 μm ; D: 0.1/1.0 μm ; E: 0.1/0.5 μm ; F: 0.1/0.1 μm .

$$G' = \frac{G_{12}}{N_1 N_2} = \frac{2kT}{3\eta W_{12}} \left(\frac{1}{a_1} + \frac{1}{a_2} \right) (a_1 + a_2) \quad (30)$$

It can be seen how electrolyte concentration may markedly increase the preference for the aggregation (or coalescence) of small particles with each other or with large particles. Thus, when $\kappa \approx 2$ to 4×10^6 for $\psi_0 \approx 25$ mV, it can be seen (Fig 21-18) that the rate of aggregation (or coalescence) of 0.1- μm particles with themselves or larger particles may be 10 to 30 orders of magnitude greater than that for two 0.5- μm particles.

Crystal Growth

Particles in suspensions may undergo dissolution and re-crystallization, in part because of the recognized variation of solubility with particle size, expressed mathematically as

$$S = S_\infty \exp \left(\frac{2\gamma M}{r\rho RT} \right) \quad (31)$$

where S is the solubility of a spherical crystal of radius r , S_∞ is the solubility of an infinitely large crystal ($r = \infty$), M is the molecular weight, ρ is the density, γ is the crystal/solvent interfacial tension, R is the gas constant, and T is the absolute temperature. Only approximations can be obtained with this equation, because the particles are not spheres, and γ values are different for different crystal faces. Table IX shows the magnitude of particle size effects on the solubility for reasonable values of M , γ , and ρ . It is evident that with particles smaller than 1 μm , S values become appreciably greater than that for a coarse crystal, hence the tendency for very fine particles to dissolve and for coarse crystals to grow at the expense of the former. This difference in solubility explains why difficulty is encountered in preparing and stabilizing suspensions of very fine particles of certain substances.

Table IX—Solubility of Small Particles

r (μm)	S
0.01	$7 S_\infty$
0.10	$1.12 S_\infty$
1.0	$1.01 S_\infty$
10	$1.001 S_\infty$

$$M = 500; \gamma = 30 \text{ ergs/cm}^2; \rho = 1$$

Growth rates of drug crystals may be significantly retarded by use of certain agents that appear to function by adsorption at surface steps and kinks. Tweens and Triton X-100 at very low concentrations (0.005%) significantly retard growth of methylprednisolone crystals in aqueous media. Gelatin and polyvinylpyrrolidone, at concentrations <0.10%, retard crystal growth of sulfathiazole in water.⁸

Other reasons may exist for the dissolution and recrystallization phenomenon. Because of the molecular complexity of many drugs, polymorphic forms other than the thermodynamically stable one may crystallize; these are always more soluble than the stable form. Steroids, sulfonamides, bar-

biturates, chloramphenicol palmitate, and many other drugs exhibit polymorphism. Solvate formation is another route by which more energetic crystal forms may develop. Also, during milling of a powder a significant amount of amorphous material may be produced, which would be more soluble than the crystalline material. Crystal habit effects are important only if particle sizes are small. Finally, temperature fluctuations in a dispersed system can create a situation whereby the system may be undersaturated for a period of time, then supersaturated for a period, and so on. These changes favor disappearance of small crystals, with concomitant growth of large ones.

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, applied to the skin in topical preparations, and used ophthalmically in the eye. They are an important class of dosage form. Since some products are occasionally prepared in a dry form, to be placed in suspension at the time of dispensing by the addition of an appropriate 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 occurs, the sediment must not form a hard cake. Rather, it must be capable of redispersion with a minimum effort on the part of the patient. Additionally, the product should be easy to pour, pleasant to take, and resistant to microbial attack.

The three major problem areas associated with suspensions are (1) adequate dispersion of the particles in the vehicle, (2) settling of the dispersed particles, and (3) caking of these particles in the sediment so as to resist redispersion. Much of the following discussion will deal with the factors that influence these processes and the ways in which they can be minimized.

Interfacial Properties

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 in either air or a liquid medium, is an attempt by the particles to reduce the excess surface free energy of the system. The increase in surface free energy is related to the increase in surface area produced when the particle size is decreased. It may be expressed as follows:

$$\Delta F = \gamma \Delta A \quad (32)$$

where ΔF is the increase in surface free energy in ergs, ΔA is the increase in surface area in cm^2 , and γ is the interfacial tension, in dynes/cm, between the dispersed particle or droplet and the dispersion medium. The smaller ΔF is, the more thermodynamically stable is the suspension of particles. A reduction in ΔF often is effected by the addition of a wetting agent which is adsorbed at the interface between the particle and the vehicle, thereby reducing the interfacial tension.

Unfortunately, while the particles remain dispersed, or deflocculated, and settle relatively slowly, they can form a hard cake at the bottom of the container when they eventually settle. Such a sediment can be extremely difficult to redisperse.

Surface Potential—As discussed earlier in this chapter, both attractive and repulsive forces exist between particles in a liquid medium. The balance achieved between these opposing forces determines whether or not two particles approaching each other actually make contact or are repulsed at a certain distance of separation.

While much of the theoretical work on electrical surface potentials in dispersed systems has been carried out on lyophobic colloids, the theories developed in this area have been applied to suspensions and emulsions.⁹

Flocculation and Deflocculation—Zeta potential ψ_z is a measurable indication of the potential existing at the surface of a particle. When ψ_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 ψ_z . At some concentration of the added ion the electrical forces of repulsion are lowered sufficiently that 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 aggregation 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 can eventually 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 X.

Table X—Relative Properties of Flocculated and Deflocculated Particles in Suspension

Deflocculated	Flocculated
<ol style="list-style-type: none"> 1. Particles exist in suspension as separate entities. 2. Rate of sedimentation is slow, since each particle settles separately and particle size is minimal. 3. A sediment is formed slowly. 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 which is difficult, if not impossible, to redisperse. 5. The suspension has a pleasing appearance, since the suspended material remains suspended for a relatively long time. The supernatant also remains cloudy, even when settling is apparent. 	<p>Particles form loose aggregates. Rate of sedimentation is high, since particles settle as a floc, which is a collection of particles. A sediment is formed rapidly. The sediment is loosely packed 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. 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.</p>

Settling and Its Control

In order 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 non-ideal conditions. He must also be aware of 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.

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 follows:

$$v = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta} \quad (33)$$

where v is the terminal velocity in cm/sec, r is the radius of the particles in cm, ρ_1 and ρ_2 are the densities (g/cm^3) of the dispersed phase and the dispersion medium, respectively, g is the acceleration due to gravity (980.7 cm/sec^2) and η 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. Furthermore, an implicit assumption to Stokes' law is that the particle exceeds the critical radius, which is expressed by

$$r_c \geq \left[\frac{40 kT}{\pi g(\rho_1 - \rho_2)} \right]^{1/4} \quad (34)$$

where r_c is the critical radius in cm in which gravity is the dominant force, kT is the thermal energy. For example, the critical radius for latex polymer spheres of $\rho_1 = 1.05 \text{ g/cm}^3$ is $3.2 \mu\text{m}$ in water at 25° , while r_c for gold particles of $\rho_1 = 19.3$ is $0.74 \mu\text{m}$. Most drugs have densities between 1 and 1.5. On the other hand, latex and gold particles which are smaller than their r_c will settle in a more random fashion due to the increasing influence of thermal forces acting upon the particle to impart Brownian movement. It is estimated that, in the limit, when the particles are less than the critical radius, r_c^* , thermal forces will be sufficiently dominant over gravitational forces so that the particles are constantly in Brownian motion. The r_c^* is estimated by use of the expression,

$$\frac{2(r_c^*)^2(\rho_1 - \rho_2)}{9\eta} < 1.16 \times 10^{-6} \text{ cm/sec} \quad (35)$$

Thus, the r_c^* values are $0.33 \mu\text{m}$ for latex particles and $0.017 \mu\text{m}$ for gold particles. 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, Eq 33 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 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 22), since it then becomes difficult to redisperse material which has settled. It also may be inconvenient to remove a viscous suspension from its container.

According to Stokes' law, the rate of sedimentation will be reduced if the difference in the densities (ρ_1 and ρ_2) of the dispersed particles and the continuous phase can be decreased. This is rarely possible in practice, and will not be discussed further.

Brownian Movement—When the size of particles undergoing sedimentation is reduced to approximately $2 \mu\text{m}$, 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. However, at the lower limit of the coarse-size range, the dispersed particles may remain suspended for a prolonged period of time due to this phenomenon.

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 that 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.

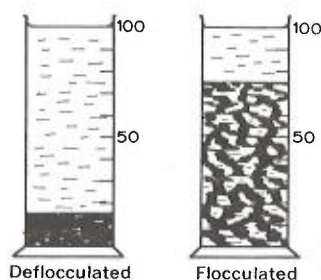


Fig 21-19. Sedimentation parameters of suspensions. Deflocculated suspension: $F_{\infty} = 0.15$. Flocculated suspension: $F = 0.75$; $\beta = 5.0$.

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 to 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_u , to the total volume of the suspension, V_0 . Thus,

$$F = V_u/V_0 \quad (36)$$

As the volume of suspension which 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 Fig 21-19. Obviously, in a particular suspension, if F can be made to approach closer to unity, the product becomes more acceptable, since the volume of supernatant (undoubtedly regarded as unsightly) is being progressively reduced. 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*, β , which relates the sedimentation volume of the flocculated suspension, F , to the sedimentation volume of the suspension when deflocculated, F_{∞} . It is expressed as

$$\beta = F/F_{\infty} \quad (37)$$

The degree of flocculation is, therefore, an expression of the increased sediment volume resulting from flocculation. If, for example, β has a value of 5.0 (Fig 21-19), this means that the volume of sediment in the flocculated system is five times that in the deflocculated state. The flocs are quite porous and the desirable scaffold-like structure is present. If a second flocculated formulation results in a value for β 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, β 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,

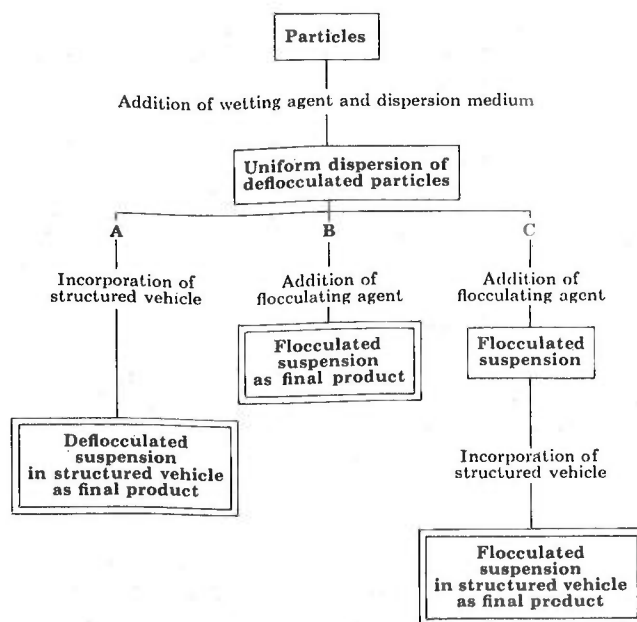


Fig 21-20. Alternative approaches to the formulation of suspensions.

a combination of the two previous methods, results in a product with optimum stability. The various schemes are illustrated in Fig 21-20.

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 7–9. 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 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, which are usually negatively charged in aqueous solution. Typical examples are methylcellulose, carboxymethylcellulose, acacia, bentonite, and Carbopol. The concentration employed will depend on the consistency desired for the suspension which, 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, in accordance with Stokes' law. It should be noted, however, that Stokes' law applies strictly only to Newtonian fluids; the majority of suspending agents used in practice are non-Newtonian.

The rheological properties of suspending agents are considered elsewhere (Chapter 22). Ideally, these form pseudoplastic or plastic systems which 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 this approach (see Fig 21-20, B 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 either electrolytes, polymers, or surfactants. The aim is to control flocculation by adding that amount of flocculating agent which results in the maximum sedimentation volume.

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. Since 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.¹⁰ 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 $AlCl_3$ is continued.

If sedimentation studies are run simultaneously on suspensions containing the same range of $AlCl_3$ concentrations, a relationship is observed (Fig 21-21) between the sedimentation volume, F , the presence or absence of caking, and the zeta potential of the particles. In order 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 PO_4^{3-} is added to a suspension of positively charged particles such as bismuth subnitrate. Ionic and nonionic surfactants and lyophilic polymers also have been used to flocculate particles in suspension. Polymers, which act by forming a "bridge" between particles, may be the most effi-

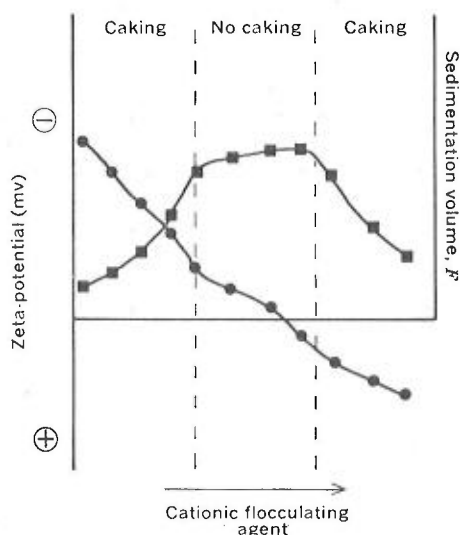


Fig 21-21. Typical relationship between caking, zeta potential, and sedimentation volume, as a positively charged flocculating agent is added to a suspension of negatively charged particles. ●: zeta potential; ■: sedimentation volume.

cient additives for inducing flocculation. Thus, it has been shown that the sedimentation volume is higher in suspensions flocculated with an anionic heteropolysaccharide than when electrolytes were used.

Work by Matthews and Rhodes,¹¹⁻¹³ 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 page 315) 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 mV 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 Fig 21-21.

Matthews and Rhodes then went on to show, by computer analysis, that the DLVO theory (see page 284) 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 \AA , and led Matthews and Rhodes to conclude that coagulation had taken place in the primary minimum.

Schneider *et al*¹⁴ 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 in Structured Vehicles—The ideal formulation for a suspension would seem to be when flocculated particles are supported in a structured vehicle. The advantages of such a combination, in view of the previous discussion, should be obvious to the reader.

As shown in Fig 21-20 (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 introduced here, in that virtually all the structured vehicles in common use are hydrophilic colloids, and these 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 suspendibility. This situation does not arise with particles that bear a positive charge, as the negative flocculating agent which the formulator must employ is compatible with the similarly charged suspending agent.

One approach, outlined in Fig 21-22, has universal utility. Here, regardless of the sign of the initial charge on the particle, a positively charged agent is adsorbed onto the particles. Flocculation is then brought about by means of an anionic flocculant which is compatible with the hydrophilic colloid used to keep the flocs in suspension.

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 mL.

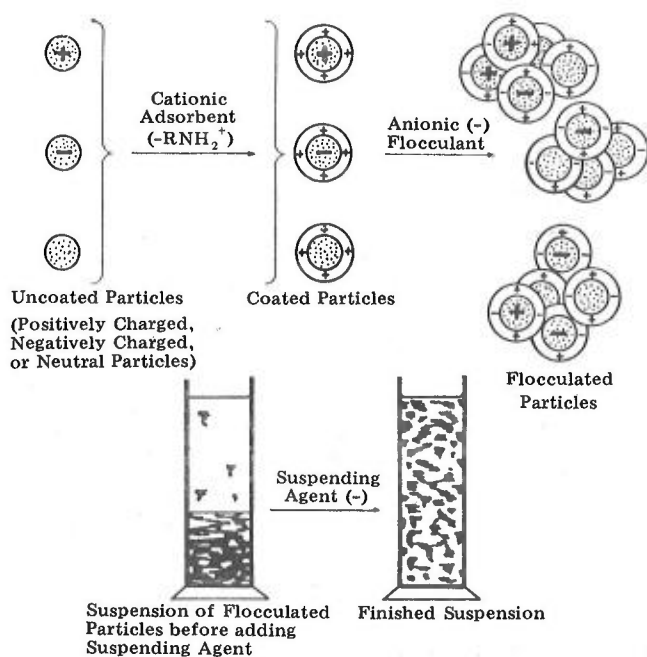


Fig 21-22. Sequence of steps involved in the preparation of a stable suspension, regardless of the initial charge on the particles.²¹

As a result, the material in solution may be susceptible to degradation. Little work has been performed to quantitate and predict the chemical stability of suspended materials.

However, Tingstad and co-workers¹⁶ 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, and (3) dissolution is not rate-limiting on degradation.

Preparation of Suspensions—The small-scale preparation of suspensions may be readily undertaken by the practicing pharmacist with the minimum of equipment. It is probably true to say that any suspension will only be as good as the initial dispersion of the particles. This preliminary step is best carried out, therefore, 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 Fig 21-20 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.

If the structured vehicle has a high consistency, it may be advisable to leave the slurry in the mortar and add the suspending agent there. Gentle trituration ensures complete dispersion of the powder throughout the vehicle. The final product is then transferred to the container.

For a detailed discussion of the methods used in the large-scale production of suspensions, see the relevant section in Chapter 83.

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 0.1–100 μm . 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. In order 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 which are stable for many months and even years, even though they are thermodynamically unstable.

Emulsions are widely used in pharmacy and medicine, and emulsified materials can possess advantages not observed when formulated in other dosage forms. Thus, certain medicinal agents having 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 offer potential in the design of systems capable of giving controlled rates of drug release and of affording protection to drugs susceptible to oxidation or hydrolysis. There is still a need for well-characterized dermatological products with reproducible properties, regardless of whether these products are antibacterial, sustained-release, protective, or emollient lotions, creams, or ointments. The principle of emulsification is 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 84.

Emulsion Type and Means of Detection

A stable emulsion must contain at least three components; namely, the dispersed phase, the dispersion medium, and the emulsifying agent. Invariably, one of the two immiscible liquids is aqueous while 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.

Recently, 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, ie, 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.

On theoretical grounds the volume of the dispersed phase can constitute up to approximately 75% of the total volume of the emulsion. However, the assumptions on which this figure is based (namely, that the droplets are rigid spheres of uniform size) are not realized in practice. Accordingly, the volume of the dispersed phase can exceed this value. There comes a point, however, at which the volume of continuous phase is insufficient to contain the dispersed phase. Either the emulsion breaks, or it inverts, whereupon the internal phase now becomes the continuous phase, and *vice versa*. This change in type with increasing phase volume is frequently accompanied by a marked change in viscosity.

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

Dilution Test—This 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 due to 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, namely, 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; ie, 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

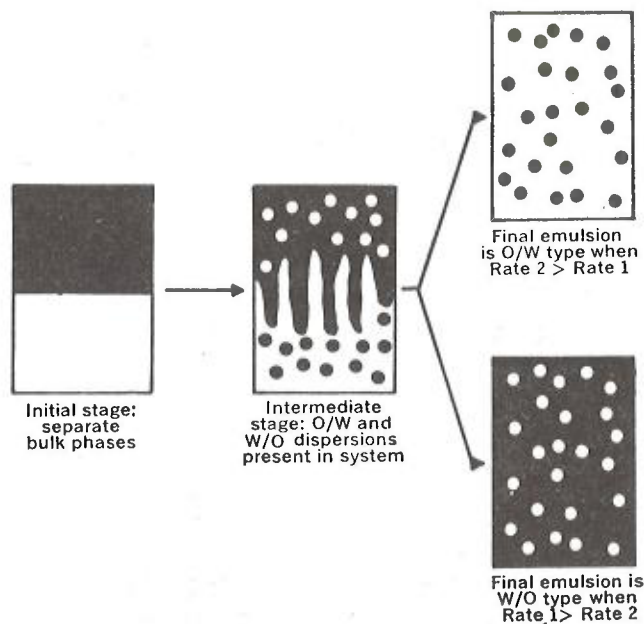


Fig 21-23. Effect of rate of coalescence on emulsion type. Rate 1: O/W coalescence rate; Rate 2: W/O coalescence rate. ●: oil; ○: water. For an explanation of Rates 1 and 2, refer to the discussion of Davies on p 323.

and well-operated machinery, capable of producing droplets in a relatively short period of time. Such equipment is discussed in Chapter 84. The reversal back to the bulk phases is minimized by utilizing those parameters which influence the stability of the emulsion once it is formed.

Dispersion Process To Form Droplets—Consider two immiscible liquid phases in a test tube. The heavier phase lies below the second liquid and the system is thermodynamically stable. In order 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 varicose or beaded. The beads separate and become spherical, as illustrated in Fig 21-23. 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. Under normal conditions, 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 commonly employed, 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 which is forced across the interface time to break down into drops which 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 and homogenizers. Ultrasonic techniques also have been employed and are described in Chapter 84.

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 (*Bibliography*).

Coalescence of Droplets—Coalescence is a process distinct from flocculation (aggregation), which commonly precedes it. While flocculation is the clumping together of particles, coalescence is the fusing of the agglomerates into a larger drop, or drops. Coalescence is usually rapid when two immiscible liquids are shaken together, since 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 which 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.

Davies¹⁷ showed the importance of coalescence rates in determining emulsion type; this work is discussed in more detail on page 323.

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 (1) the desirable properties of emulsifying agents, (2) how different emulsifiers act to optimize emulsion stability, and (3) 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 which will prevent coalescence, (3) impart to the droplets an adequate electrical potential so that mutual repulsion occurs, (4) increase the viscosity of the emulsion, and (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 (Eq 32). Assuming the droplets to be spherical, it can be shown that

$$\Delta F = \frac{6\gamma V}{d} \quad (38)$$

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

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

The system attempts to lose this excess surface free energy

to its surroundings by coalescence of the droplets. These grow in size and decrease in number until one large drop (the original bulk phase) is formed. This has minimum surface area in contact with the second phase and the surface free energy is now at a minimum. However, an emulsifying agent which is adsorbed as a monolayer at an interface lowers surface tension in accordance with the Gibbs' equation (Eq 17).

In the above example the addition of an emulsifier that will reduce γ 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 dyne/cm, a common occurrence, the original surface free energy is reduced a hundredfold.

While the above calculations are an oversimplification of the total energies involved in emulsification, they do show that a reduction of interfacial tension by the addition of an emulsifying agent 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 which 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.

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.

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. Apart from a possible increase in viscosity, there is little advantage in having a large excess present; indeed, it may produce such undesirable effects as foaming. 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 μm . Thus,

$$\text{Particle diameter} = 1 \mu\text{m} = 1 \times 10^{-4} \text{ cm}$$

$$\text{Volume of particle} = \frac{\pi d^3}{6} = 0.524 \times 10^{-12} \text{ cm}^3$$

$$\text{Total number of particles in 50 g}$$

$$= \frac{50}{0.524 \times 10^{-12}} = 95.5 \times 10^{12}$$

$$\text{Surface area of each particle} = \pi d^2 = 3.142 \times 10^{-8} \text{ cm}^2$$

$$\text{Total surface area} = 3.142 \times 10^{-8}$$

$$\times 95.5 \times 10^{12} = 300 \times 10^4 \text{ cm}^2$$

If the area each molecule occupies at the oil/water interface is 30 \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

Table XI—Factors Influencing Emulsion Viscosity¹⁸

1. Internal phase
 - a. Volume concentration (ϕ); hydrodynamic interaction between globules; flocculation, leading to formation of globule aggregates.
 - b. Viscosity (η_1); 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 (η_0), 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

Pigments, hydrocolloids, hydrous oxides; effect on rheologic properties of liquid phases, and interfacial boundary region.

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, etc. 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 and these are summarized in Table XI. 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.¹⁹

Mechanism of Action

Emulsifying agents may be classified in accordance with the type of film they form at the interface between the two phases. Such a classification is summarized in Table XII.

Table XII—Mechanism of Action of Emulsifying Agents

Type of film	Example	Mechanism
Monomolecular	Potassium laurate Polyoxyethylene sorbitan monooleate	Coherent, flexible film formed by surface-active agents. These agents also lower interfacial tension markedly, and this contributes to stability of emulsion. Are widely used, especially the nonionic type. Depending on the particular agent(s) chosen, can prepare O/W or W/O emulsions.
Multimolecular	Acacia Gelatin	Strong, rigid film formed, mostly by hydrocolloids which produce O/W emulsions. Interfacial tension is not reduced to any degree; stability due mainly to strength of interfacial film.
Solid Particle	Bentonite Graphite Magnesium hydroxide	Film formed by solid particles that are small in size compared to the droplet of dispersed phase. Particles must be wetted by both phases to some extent in order to remain at the interface and form a stable film. From either O/W or W/O emulsions, depending on method of preparation.

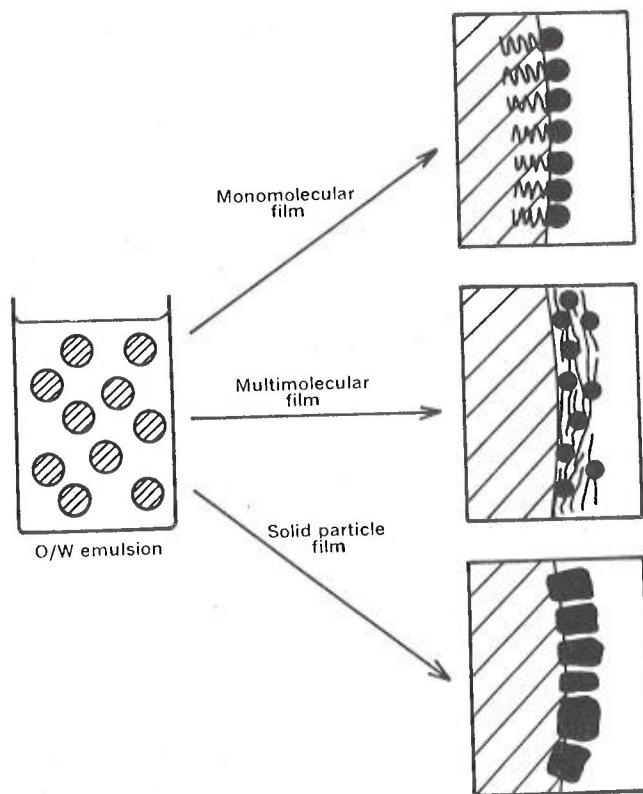


Fig 21-24. Types of films formed by emulsifying agents at the oil/water interface. Orientations are shown for O/W emulsions. ▨: oil; □: water.

Monomolecular Films—Those surface-active agents which are capable of stabilizing an emulsion do so by forming a monolayer of adsorbed molecules or ions at the oil/water interface (Fig 21-24). In accordance with Gibbs' law (Eq 17) 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 which 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 particles 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 (Fig 21-24). The use of these agents has declined in recent years

Table XIII—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
Natural	Multimolecular	<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
	Monomolecular	<i>Hydrophilic colloids:</i> Acacia Gelatin Lecithin Cholesterol
Finely divided solids	Solid particle	<i>Colloidal clays:</i> Bentonite Veegum <i>Metallic hydroxides:</i> Magnesium hydroxide

because of the large number of synthetic surface-active agents available which possess well-marked emulsifying properties. While 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 (Fig 21-24).

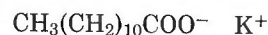
Chemical Types

Emulsifying agents may also be classified in terms of their chemical structure; there is some correlation between this classification 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 XIII). A fourth group, the *auxiliary materials* (Table XIV), are weak emulsifiers. The agents listed are designed to illustrate the various types available; they are not meant to be exhaustive.

Synthetic Emulsifying Agents—This group of surface-active agents which act as emulsifiers may be subdivided into anionic, cationic, and nonionic, depending on the charge possessed by the surfactant.

Anionics—In this 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 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 emulsifier and 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. While these O/W emulsifiers are also limited to external preparations, 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. Probably the most frequently used compound is sodium lauryl sulfate:



Table XIV—Auxiliary Emulsifying Agents¹⁵

Product	Source and composition	Principal use
Bentonite	Colloidal hydrated aluminum silicate	Hydrophilic thickening agent and stabilizer for O/W and W/O lotions and creams
Cetyl alcohol	Chiefly C ₁₆ H ₃₃ OH	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Glyceryl monostearate	C ₁₇ H ₃₅ COOCH ₂ CHOHCH ₂ OH	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Magnesium hydroxide	Mg(OH) ₂	Hydrophilic stabilizer for O/W emulsions
Methylcellulose	Series of methyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Silica gel	Hydrous oxide of silica	Hydrophilic stabilizer used in the preparation of ointments
Sodium alginate	The sodium salt of alginic acid, a purified carbohydrate extracted from giant kelp	Hydrophilic thickening agent and stabilizer for O/W emulsions
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
Stearyl alcohol	Chiefly C ₁₈ H ₃₇ OH	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Tragacanth	Dried gummy exudation from species of <i>Astragalus</i> , containing a soluble portion and an insoluble portion that swells in water	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Veegum	Colloidal magnesium aluminum silicate	Hydrophilic thickening agent and stabilizer for O/W lotions and creams

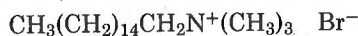
Sulfonates are a class of compounds in which the sulfur atom is connected directly to the carbon atom, giving the general formula



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 this 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 4–6 range. Since this includes the normal pH of the skin, cationic emulsifiers are advantageous in this regard also.

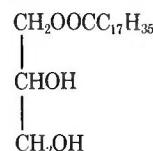
Cationic agents are weak emulsifiers and are generally formulated with a stabilizing or auxiliary emulsifying agent such as cetostearyl alcohol. The only group of cationic agents used extensively as emulsifying agents are the quaternary ammonium compounds. An example is cetyltrimethylammonium bromide:



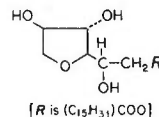
Cationic emulsifiers should not be used in the same formulation with anionic emulsifiers as they will interact. While the incompatibility may not be immediately apparent as a precipitate, virtually all of the desired antibacterial activity will generally have been lost.

Nonionics—These 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.

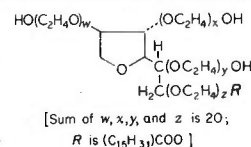
A glyceryl ester, such as glyceryl monostearate, is too lipophilic to serve as a good emulsifier; it is widely used as an auxiliary agent (Table XIV) and has the structure



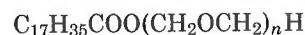
Sorbitan fatty acid esters, such as sorbitan monopalmitate (Span 40, Atlas Division of ICI Americas, Inc),



are nonionic oil-soluble emulsifiers that promote W/O emulsions. The polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monopalmitate (Tween 40, Atlas Division of ICI (Americas) Inc), are hydrophilic water-soluble derivatives that favor O/W emulsions.



Polyoxyethylene glycol esters, such as the monostearate,



are widely used also.

Very frequently, the best results are obtained from blends of nonionic emulsifiers. Thus, an O/W emulsifier such as Tween 40 customarily will be used in an emulsion with a W/O emulsifier such as Span 40. 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. The gum can be precipitated from aqueous solution by the addition of high concentrations of electrolytes or solvents less polar than water, such as alcohol.

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. In order to avoid an incompatibility, all emulsifying agents should carry the same sign. Thus, if gums (such as tragacanth, acacia, and agar) which are negatively charged are to be used with gelatin, Type B material should be used at an alkaline pH. Under these conditions the gelatin is similarly negatively charged.

Lecithin is a phospholipid which, because of its strongly hydrophilic nature, produces O/W emulsions. It is liable to microbial attack and tends to darken on storage.

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—This group of emulsifiers forms particulate films around the dispersed droplets and produces emulsions which, while coarse-grained, 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.

Several colloidal clays find application in pharmaceutical emulsions; the most frequently used are bentonite, a colloidal aluminum silicate, and Veegum (*Vanderbilt*), a colloidal magnesium aluminum silicate.

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 trituration. Since 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.

While 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—Included under this heading are those compounds which 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. Thus, tragacanth is sometimes combined with acacia to increase the consistency of the aqueous phase of an O/W emulsion. Agents in common use are listed in Table XIV.

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 mono- and multilayer films the emulsifier is in solution and, therefore, 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. The present discussion, therefore, 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.

As described in Chapter 19, surface-active agents are *amphiphiles* in which the molecule or ion contains both hydrophilic and lipophilic portions. Griffin²⁰ 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), while 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 since they concentrate at the oil/water interface. The relationship between HLB values and the application of the surface-active agent is shown in Table XV. Some commonly used emulsifiers and their HLB numbers are listed in Table XVI. 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—Davies¹⁷ 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 which contains oil dispersed in water and water dispersed in oil (Fig 21-23). The type of the final emulsion which 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 since 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, the rate at which oil globules coalesce when dispersed in water is given by the expression

Table XV—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 XVI—Approximate HLB Values for a Number of Surfactants

Generic or chemical name	Trademark	HLB
Sorbitan trioleate	Span 85, ^a Arlacel 85 ^a	1.8
Sorbitan tristearate	Span 65 ^a	2.1
Propylene glycol monostearate (pure)		3.4
Sorbitan sesquioleate	Arlacel C ^a	3.7
Glycerol monostearate		3.8
Sorbitan monooleate	Span 80 ^a	4.3
Propylene glycol monolaurate	Atlas G-917, ^a Atlas G-3851 ^a	4.5
Sorbitan monostearate	Arlacel 60 ^a	4.7
Glyceryl monostearate (self-emulsifying)	Aldo 28, Tegin ^b	5.5
Sorbitan monopalmitate	Span 40, ^a Arlacel 40 ^a	6.7
Sorbitan monolaurate	Span 20, ^a Arlacel 20 ^a	8.6
Polyoxyethylene lauryl ether	Brij 30 ^a	9.5
Gelatin		9.8
Methocel 15		10.5
Polyoxyethylene monostearate	Myrj 45 ^a	11.1
Polyethylene glycol 400 monostearate	S-5411 ^c	11.6
Triethanolamine oleate (Trolamine)		12.0
Polyoxyethylene alkyl phenol	Igepal CA-630 ^d	12.8
Tragacanth		13.2
Polyoxyethylene sorbitan monolaurate	Tween 21 ^a	13.3
Polyoxyethylene castor oil	Atlas G-1794 ^a	13.3
Polyoxyethylene sorbitan monooleate	Tween 80 ^a	15.0
Polyoxyethylene sorbitan monopalmitate	Tween 40 ^a	15.6
Polyoxyethylene sorbitan monolaurate	Tween 20 ^a	16.7
Polyoxyethylene lauryl ether	Brij 35 ^a	16.9
Polyoxyethylene monostearate	Myrj 52 ^a	16.9
Sodium oleate		18.0
Sodium lauryl sulfate		40.0

^a Atlas, Division of ICI Americas, Inc.

^b Goldschmidt.

^c Glycol.

^d General Aniline.

$$\text{Rate 1} = C_1 e^{-W_1/RT} \quad (39)$$

The term C_1 is a collision factor which 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, since 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 10 Å thick with a consistency of butter. Finally, the total energy barrier depends on the fraction of the interface covered by the emulsifying agent.

Eq 40 describes the rate of coalescence of water globules dispersed in oil, namely

$$\text{Rate 2} = C_2 e^{-W_2/RT} \quad (40)$$

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.

Davies¹⁷ 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. With experience, he should be able to select an effective emulsifier with the minimum of experimentation. At the same time, he has to take steps to ensure that no incompatibilities occur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the pharmacist must be able to prepare the product in such a way as not to prejudice his formulation. This requires not only a knowledge of the available methods of small-scale preparation, but a possession of the necessary practical skills.

Selection of Emulsifying Agents

The selection of the emulsifying agent, or agents, is of prime importance in the successful formulation of an emulsion. In addition to its emulsifying properties, the pharmacist must ensure that the material chosen is nontoxic and that the taste, odor, and chemical stability are compatible with the product. Thus, an emulsifying agent which 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^{20,21} provided a

Table XVII—Required HLB Values for Some Common Emulsion Ingredients

Substance	W/O	O/W
Acid, stearic	...	17
Alcohol, cetyl	...	13
Lanolin, anhydrous	8	15
Oil, cottonseed	...	7.5
mineral oil, light	4	10-12
mineral oil, heavy	4	10.5
Wax, beeswax	5	10-16
microcrystalline	...	9.5
paraffin	...	9

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

Another factor is the presence or absence of any polarity in the material being emulsified, since this will affect the polarity required in the emulsifier. Again, as a result of extensive experimentation, Griffin evolved a series of "required HLB" values; ie, 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 XVII. 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. Naturally, one should not use emulsifiers that are incompatible. The following formula should serve as an example.

O/W Emulsion	
Liquid petrolatum (Required HLB 10.5)	50 g
Emulsifying agents	5 g
Span 80 (HLB 4.3)	
Tween 80 (HLB 15.0)	
Water, qs	100 g

By simple algebra it can be shown that 4.5 parts by weight of Span 80 blended with 6.2 parts by weight of Tween 80 will result in a mixed emulsifying agent having the required HLB of 10.5. Since the formula calls for 5 g, the required weights are 2.1 g Span 80 and 2.9 g Tween 80. The oil-soluble Span is dissolved in the oil and heated to 75°; the water-soluble Tween is added to the aqueous phase which is heated to 70°. At this point the oil phase is mixed with the aqueous phase and the whole stirred continuously until cool.

The formulator is not restricted to Span 80 and Tween 80 to produce a blend with an HLB of 10.5. Table XVIII shows the various proportions required, using four 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 standard-

Table XVIII—Nonionic Blends having HLB Values of 10.5

Surfactant blend ^a	HLB	Required amounts (%) to give HLB = 10.5
Span 65	2.1	34.4
Tween 60	14.9	65.6
Arlacel 60	4.7	43.2
Tween 60	14.9	56.8
Span 40	6.7	57.3
Tween 40	15.6	42.7
Arlacel C	3.7	48.5
Brij 35	16.9	51.5

^a Atlas.

ized 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, ±1 HLB unit.

There are methods for finding the HLB value of a new surface-active agent. Griffin²¹ developed simple equations which 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 has been developed by Davies¹⁷ and is related to his studies on the relative rates of coalescence of O/W and W/O emulsions (page 323). 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 XIX). Provided the molecular structure of the surfactant is known, one simply adds the various group numbers in accordance with the following formula:

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

where *m* is the number of $-\text{CH}_2-$ groups present in the surfactant. Poor agreement is found between the HLB values calculated in this manner and the experimental values obtained by Griffin.

Later, Davies and Rideal²² attempted to relate HLB to the $C_{\text{water}}/C_{\text{oil}}$ partition coefficient and found good agreement for a series of sorbitan surfactants. Schott²³ showed, however,

Table XIX—HLB Group Numbers²²

	Group number
Hydrophilic groups	
$-\text{SO}_4^- \text{Na}^+$	38.7
$-\text{COO}^- \text{K}^+$	21.1
$-\text{COO}^- \text{Na}^+$	19.1
N (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	
$-\text{CH}-$	
$-\text{CH}_2-$	
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

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 which could be determined more readily than HLB has not been successful." Lowenthal²⁴ carried out a statistical multiregression analysis of HLB for a series of polyoxyethylene polyoxypropylene surfactants. He obtained an equation describing the relationship between HLB, percent polyoxyethylene, and the molecular weight of the polyoxypropylene part of the molecule.

The observant reader will have already realized that 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.

Mixed Emulsifying Agents—Emulsifying agents are frequently used in combination since a better emulsion is usually 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, and (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.

Finally, some materials are added primarily to increase the consistency of the emulsion. This may be done to increase stability or improve emolliency and feel. Tragacanth is frequently added to thicken the external phase of emulsions prepared with acacia. Cetyl alcohol, stearic acid, and beeswax are also added to formulations to improve the consistency of the oil 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.

Small-Scale Preparation

Traditionally, emulsions have been prepared by the pharmacist using a mortar and pestle. Today, this tool is being replaced by the use of electric mixers and hand homogenizers which, rightly so, are recognized now as normal equipment in a contemporary pharmacy.

Mortar and Pestle—This approach is invariably used only for those emulsions that are stabilized by the presence of a

multimolecular film (eg, acacia, tragacanth, agar, chondrus) at the interface. There are two basic methods for preparing emulsions with the mortar and pestle. These are the *Wet Gum* (or so-called *English*) *Method* and the *Dry Gum* (or so-called *Continental*) *Method*.

The Wet Gum Method—In this method the emulsifying agent is placed in the mortar and dispersed in water to form a mucilage. The oil is added in small amounts with continuous trituration, each portion of the oil being emulsified before adding the next increment. Acacia is the most frequently used emulsifying agent when preparing emulsions with the mortar and pestle. When emulsifying a fixed oil, the optimum ratio of oil:water:acacia to prepare the initial emulsion is 4:2:1. Thus, the preparation of 60 mL of a 40% cod liver oil emulsion requires the following:

Cod liver oil	24 g
Acacia	6 g
Water, qs	60 mL

The acacia mucilage is formed by adding 12 mL of water to the 6 g of acacia in the mortar and triturating. The 24 g of oil is added in increments of 1–2 g and dispersed. The product at this stage is known as the *primary emulsion*, or *nucleus*. The primary emulsion should be triturated for at least 5 min, after which sufficient water is added to produce a final volume of 60 mL.

The Dry Gum Method—In this method, preferred by most pharmacists, the gum is added to the oil, rather than the water as with the wet gum method. Again, the approach is to prepare a primary emulsion from which the final product can be obtained by dilution with the continuous phase. If the emulsifier is acacia and a fixed oil is to be emulsified, the ratio of oil:water:gum is again 4:2:1.

Provided dispersion of the acacia in the oil is adequate, the dry gum method can almost be guaranteed to produce an acceptable emulsion. Because there is no incremental addition of one of the components, the preparation of an emulsion by this method is rapid.

With both methods the oil:water:gum ratio may vary, depending on the type of oil to be emulsified and the emulsifying agent used. The usual ratios for tragacanth and acacia are shown in Table XX.

The preparation of emulsions by both the wet and dry gum methods can be carried out in a bottle rather than a mortar and pestle.

Other Methods—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 70–75°. 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

Table XX—Usual Ratios of Oil, Water, and Gum Used to Produce Emulsions

System	Acacia	Tragacanth
Fixed oils (excluding liquid petrolatum and linseed oil)	4	40
Water	2	20
Gum	1	1
Volatile oils, plus liquid petrolatum and linseed oil	2–3	20–30
Water	2	20
Gum	1	1

be dispersed in the emulsion. The relatively simple methodology involved in the use of synthetic surfactant-type emulsifiers is one factor which 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.

Hand homogenizers and blenders are being used more widely by practicing pharmacists for preparing emulsions. With hand homogenizers an initial rough emulsion is formed by trituration in a mortar or shaking in a bottle. The rough emulsion is then 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 84.

Stability of Emulsions

There are several criteria which 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, since 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 Garrett²⁵ and Kitchener and Mussellwhite.²⁶ For information on the effect that emulsification can have on the biologic activity and chemical stability of materials in emulsions, see Wedderburn,²⁷ Burt,²⁸ and Swarbrick.²⁹

The physical stability of an emulsion depends on many factors, some of which have been discussed. Thus, the various properties of an emulsifying agent (see page 319) are all considered desirable because each makes a contribution to the physical stability of the emulsion.

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; and (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, while 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 dispersed 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 (Eq 33). While other equations have been developed for bulk systems, Stokes' equation is still useful since 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, although a few successful attempts have been made to equalize the densities of the oil and aqueous phases, to reduce the rate of movement to zero. Reduction of particle size contributes greatly towards overcoming or minimizing creaming, since 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 μm . 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, since 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 (flocculation) 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. While not as serious as coalescence, it will accelerate creaming or sedimentation, since the aggregate behaves as a single drop.

While aggregation is related to the electrical potential on the droplets, coalescence depends on the structural properties of the interfacial film. In an emulsion stabilized with surfactant-type emulsifiers forming monomolecular films, coalescence is opposed by the elasticity and cohesiveness of the films sandwiched between the two droplets. In spite of the fact that two droplets may be touching, they will not fuse until the interposed films thin out and eventually rupture. Multilayer and solid-particle films confer on the emulsion a high degree of resistance to coalescence, due to their mechanical strength.

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.³⁰

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.

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.

Bioavailability from Coarse Dispersions

In recent years, considerable interest has focused on the ability of a dosage form to release drug 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 37, 38 and 39. While 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 is important and so will be considered in some detail.

Bioavailability from Suspensions—On theoretical grounds, one would expect orally administered dispersion-type dosage forms to be at least as bioavailable as the same drug formulated as a tablet or capsule. Frequently suspensions may be expected to demonstrate improved bioavailability. 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.*³¹ 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; these workers were 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 and co-workers³² in a study of the bioavailability of several doxycycline products, including a suspension and hard gelatin capsules. Meyer *et al.*³³ studied sulfadiazine bioavailability in 16 male volunteers, using the drug in solution, suspension and two different tablets to determine whether there was any statistical difference in the rate and level of absorption. It was concluded that the suspension showed neither better nor worse bioavailability characteristics, and was equivalent to the solution and tablet dosage forms. Sansom and coworkers³⁴ found mean plasma phenytoin levels 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.*³⁵ 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 subjects and taking blood samples at predetermined times over a period of 10 hours, the workers 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 in *in vivo* tests half an hour after administration. The results showed that 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^{36,37} have shown the need to determine the dissolution rate of suspensions in order 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 were able to maintain a clinically acceptable urinary nitrofurantoin concentration for an additional two hours by increasing the viscosity of the vehicle³⁸.

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 study appears to have been made in direct comparison of 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 gastrointestinal tract. For example, with an oil-in-water 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 and co-workers³⁹ found that indoxole, a nonsteroidal anti-inflammatory agent, was significantly more bioavailable in an oil-in-water emulsion than in either a suspension or a hard gelatin capsule. Bates and Sequeira⁴⁰ found significant increases in maximum plasma levels and total bioavailability of micronized griseofulvin when formulated in a corn oil/water 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 gastrointestinal motility.

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