—————Review Article—————

Theory of Coarse Suspension Formulation

By EVERETT N. HIESTAND

INTRODUCTION

A COMPLETE REVIEW of the theory of the physical stability of suspensions would include a survey of a large part of colloid science. However, by limiting the discussion to a descriptive treatment of coarse (particles larger than 0.1-μ diameter) suspensions,[1] a reasonably comprehensive outline of the basic concepts may be considered in this brief review.

The primary objective is to present information useful to the formulator. Current theories of suspension stability will be examined and the experimental evidence considered. Shelf-life[2] stability usually requires the use of flocculated particles when suspensions are formulated; therefore, most of this discussion will describe flocculated suspensions. The objective in most discussions of dispersions is to produce the stable (peptized) condition; hence, textbooks of colloid chemistry provide a much more thorough treatment of the deflocculated state.

FUNDAMENTALS

Wetting

The introduction of the particle into the vehicle is a critical step in the preparation of an elegant suspension. Usually, slightly lyophobic[3] (sol-

vent fearing) powders present no difficulty. Strongly lyophobic powders may float because of the high interfacial energy of the vehicle-powder interface. Forced deaggregation of a nonwet powder may create some difficult problems because microscopic quantities of air stick to the particle surface. The particles tend to clump and float to the surface of the suspension. Usually, the objectionable air may be removed by high shearing action such as that obtained in a colloid mill; the presence of a wetting agent facilitates this operation. Either detergents or polyelectrolytes may be used as the surfactants. Detergents are superior in penetration because of their lower molecular weight.

If a good penetrating surfactant is present when the powder is added, the penetration of the liquid phase into the powder will be sufficiently rapid to displace the air from the particles. Also, the particles will separate at low shear forces and an elegant preparation is made more readily.

Contact Angle.—Equation 1 can be used in some cases to describe the thermodynamics of wetting in terms of the interfacial tension and the contact angle at the point of contact of the three phases.

$$\gamma_{SA} = \gamma_{LS} + \gamma_{LA} \cos \theta \qquad \text{(Eq. 1)}$$

γ_{SA}, γ_{LA}, and γ_{LS} are interfacial tensions at the air-solid, liquid-air, and liquid-solid interfaces, respectively. θ is the contact angle measured through the liquid.

For a discussion of this equation, nearly any general book on colloid chemistry may be con-

sulted, (*e.g.*, *References* 1, 2, and 3). Equation 1 describes an equilibrium situation and says nothing about the rate of the penetration. Of course, it does indicate when spontaneous spreading will not occur, *i.e.*, when $\theta > 0°$. At the other extreme of good wetting, the contact angle becomes zero at relatively low energies (4). The equation's primary value to the formulator is in helping him understand the wetting process. One seldom has the necessary data to use the equation; and obtaining the data is more time consuming than just trying a few surfactants.

Penetration Rate.—With the same objective, it is interesting to examine some of the kinetic studies that have been reported. Eley and Pepper (5) studied the displacement of one fluid by another from a capillary and also for displacement from a powder. They obtained the equation

$$\gamma_{12} \cos \theta_{12} \frac{rt}{4k^2} = \frac{(\eta_1 - \eta_2)x^2}{2} - \eta_2/x \quad \text{(Eq. 2)}$$

where r is the average radius of the equivalent capillaries, k is the tortuosity factor and is obtained from bulk density and gas permeability data, γ_{12} is the interfacial tension between the two fluids, l is the length of the equivalent capillaries, x is the distance through which the meniscus has advanced in time, t, η_1 and η_2 are the viscosities of the two fluids, and θ_{12} is the contact angle. Equation 2 confirms one's intuitive expectations, however, these investigators found reproducibility only when the surfaces had been previously wet by the advancing liquid. Furthermore, the work of Kling and Lange (6) did not fit Eq. 2. Kawasaki (7) discussed some other factors considered in wetting, such as penetration of water molecules, change in orientation of polar groups in the solid surface, and the migration of polar groups of impurity molecules from the interior of the solid toward the surface. Bristow (8) reviews the theory of wetting and penetration in more detail. Obviously, much more work must be done before the rate of penetration of a fluid into a powder bed can be described quantitatively.

Supplemental reports of theoretical interest may be found in a group of papers on the "Interaction of Water and Porous Materials" (9) and on "Contact Angles, Spreading and Wetting" (10). Zisman and co-workers (11) have demonstrated the existence of a critical surface tension which may be considered as that value of the surface tension of a liquid below which liquids spread on the solid surface.

Selecting Surfactants.—In a more practical interest, a simple method can be used to screen wetting agents when penetration is a problem

to the formulator. The author has used a narrow, very lyophobic trough several inches long (either paraffin coated or made of Teflon for aqueous systems). Powder is placed at one end of the trough; the other end is filled with a solution of the wetting agent. The relative rates of penetration of various agents may be observed directly. A more elaborate method of determining dispersibility is described by Zacek (12). He observes the fraction of the powder that passes through a standard gauze, which is wet by the solution, when a given amount of the dispersant solution is dropped onto it from a fixed point.

Based on the above procedure and knowledge, it shall be assumed that the formulator has found a satisfactory wetting agent and now has the powder immersed in the liquid phase.

Settling

If particles immersed in a liquid are not in true solution, usually the thermodynamic conditions favor aggregation. Lowering of the interfacial tension will reduce the associated free energy change, but will not remove it entirely. However, it is possible to shield particles from each other by surrounding them with an energy barrier, and thereby reduce the rate of aggregation to a negligible value.

Peptized Particles.—For peptized particles of colloidal size, ambient convection currents arising from slight thermal gradients will produce adequate mixing to overcome the very slow sedimentation. Consequently, colloidal particles may remain uniformly dispersed indefinitely. The significance of the very small size in producing a small sedimentation velocity is evident from Stokes'[1] law for the free fall of a sphere in a very large body of fluid

$$v = \frac{2 r^2 (\Delta\rho) g}{9 \eta} \quad \text{(Eq. 3)}$$

where v is the velocity, r the radius, $\Delta\rho$ the density difference between fluid and sphere, g the gravitational constant, and η is the viscosity of the Newtonian liquid.

Sometimes the concentration equalizing process of diffusion is combined with Eq. 3 to estimate how much settling must occur before the sedimentation rate becomes equal to the opposing diffusion rate. Perrin's equation includes these factors

$$\ln \frac{n_1}{n_2} = \frac{N}{RT} v (\Delta\rho) gh \quad \text{(Eq. 4)}$$

where n_1 and n_2 are the number of particles in each of the two layers spaced h distance apart, v is the volume of the particle, N is Avagadro's number, T is the absolute temperature, and R is the

gas constant. However, one should remember that a net transfer by diffusion occurs only when there is a concentration gradient—something one would like to avoid.

Sample calculations often are used to provide perspective for the appreciation of these equations (*Reference* 1, Chapter 3). When they are made, one is forced to conclude that single large particles in suspensions will sediment in the usually accepted shelf-life requirement of pharmaceutical products.

Flocculated Particles.—Subsidence is a term often used to describe the settling of flocculated suspensions. The subsidence rate usually refers to the settling rate measured by following the boundary between the sediment and the clear liquid overhead. This could not apply to peptized polydispersed suspensions because the boundary is not well defined. The large particles settle downward past the smaller ones; the smallest ones may fall very slowly. In a concentrated peptized suspension the particles do not fall completely independent of each other; the largest are said to undergo hindered settling and the smallest are accelerated over the Stokes' law value (13). In flocculated suspensions the particles are linked together into flocs and they settle initially at a rate determined by the floc size and the porosity of the aggregated mass. Later the rate is a compaction and rearrangement process. Because the smallest particles are a part of the flocs, they do not remain behind to form the cloudy layer on top. Probably intermediate cases are possible in which the particles are not all associated into flocs.

Both subsidence and hindered settling have been studied by various investigators. Oden (14) has summarized the early work. Better known are the works of Robinson (15), Egolf and McCabe (16), and Ward and Kammermeyer (17). Kynch (18) gave a very detailed theoretical treatment. Steinour (19) considered the settling of nonflocculated suspensions of spheres of uniform size under conditions that made Stokes' law applicable at infinite dilution. He found the empirical Eq. 5 represented all of his data for the settling rate, Q, of the top surface

$$Q = v_s \, \epsilon^2 \, 10^{-1.82(1-\epsilon)} \qquad \text{(Eq. 5)}$$

where $10^{-1.82(1-\epsilon)}$ is the empirical term which represents both size and shape of flow space; v_s is the Stokes' velocity, and ϵ is the volume fraction of the liquid. Steinour modified this equation by using the hydraulic radius as a spacing factor and obtained an equation similar to those obtained by Higuchi (20) and others (21, 22), who have based their equations either on the Kozeny equation for permeability or on correction terms to Stokes' equation.

Steinour (23) considered concentrated flocculated suspensions in another communication. His equation (Eq. 6.) fits most of the data and includes an empirical dimensionless constant, w_i, and the specific surface, σ, calculated on an equivalent sedimenting sphere basis. The other terms in Eq. 6 have the same significance as before.

$$Q = \frac{0.246}{\sigma^2 (1 - w_i)^2} \cdot \frac{g \Delta \rho (\epsilon - w_i)^3}{n(1 - \epsilon)} \qquad \text{(Eq. 6)}$$

Starting with the equation of Richardson and Zaki (21), Michaels and Bolger (24) describe the settling rate and the sediment volume of aqueous flocculated suspensions as a function of concentration and container dimensions. Their model assumes that small flocs form and become the primary fundamental structural unit moving at the low shear of gravitational settling. Aggregates grow by collision of the flocs but may be broken by the shear force resulting from the weight of the particles above. This compacts the bottom layers. The settling rate, the sediment volume, and the aggregate size are expressed in terms of the floc volume concentration and the attractive force between the flocs.

Forces Between Particles

Even when the surface is covered with a good wetting agent, the interfacial tension may be finite. Therefore, two particles that make contact reduce the interfacial area and produce a lowering of the total free energy of the system. If this energy is small, comparable to the thermal energy, some spontaneous dispersion will result. However, van der Waals' forces of attraction must be considered also. Therefore, flocculation would be expected to occur. The deflocculated condition is a thermodynamically unstable one. However, it can be made to appear stable by surrounding the particles with ions so that the particles repel each other. This may reduce the rate of combination to a negligible rate. The stability of unprotected lyophobic colloid sols may be assigned to this mechanism.

Before proceeding further, a preferred definition of the terms lyophobic and lyophilic should be given. These terms are used ambiguously by some investigators. Sometimes they are considered to be synonomous with nonwetting and wetting. As noted in an earlier paragraph, the process of wetting involves the relative magnitude of three interfacial layers. Usually, the air-liquid and the air-solid interfaces as well as the liquid-solid interface are considered. The terms are more useful in the discussion of the stability of sus-

pensions or dispersions if lyophobic and lyophilic are considered as properties of only the liquid-solid interaction. A consequence of this definition is that some lyophobic particles are wet by the liquid—hence, the use of *slightly* and *strongly* lyophobic in the discussion of wetting.

Rebinder (25, 26) considers lyophilic materials to be those whose interfacial tension is less than some critical value, γ_m, which is fixed by the temperature, *i.e.*, γ_m is proportional to kT. A lyophobic material has an interfacial tension larger than γ_m. Lyophilic materials tend to disperse spontaneously because of the entropy factor. Glazman (27) disagrees and says that some materials that have interfacial tensions larger than γ_m are lyophilic. He distinguishes between the two by observing their behavior at various electrolyte concentrations. Lyophobic sols are very sensitive to the addition of electrolytes, and lyophilic sols are not. The test of sensitivity to electrolytes is used by Kruyt and Overbeek (28) also, but with the added test of reversibility. A lyophilic material that has been precipitated by electrolytes will redisperse upon dilution with the vehicle; a lyophobic substance will not. It is unnecessary to choose among these definitions in this discussion. By any of these standards, the subject discussed here is the theory of the formulation of suspensions of *lyophobic* materials.

The shelf-life stability of suspensions ideally requires that no settling occurs; but if some settling is allowed, it requires that the sediment be readily redispersed by mild shaking. Also, after shaking it must remain uniformly dispersed long enough for the withdrawal and administration of an accurately measured dose. Obviously, a peptized suspension that settles to form a clay does not meet these requirements. However, it is necessary to understand the theory of lyophobic colloid stability, which produces the peptized condition, in order to understand the unstable or flocculated condition. A brief review of these factors will be given.

Forces of Attraction.—van der Waals' equation for gases is well known. The constant for the attraction between molecules is usually given the symbol "a" in his equation. This constant does not designate the origin or the nature of the attractive forces. After Margenau (29) and de Boer (30), the definition of van der Waals' forces used here will include forces from dipolar and quadrupolar molecules as well as nonpolar forces. London (30, 31) discovered the close connection between nonpolar van der Waals' forces and optical dispersion. Consequently, these nonpolar forces are often called dispersion forces; they are also

called London–van der Waals' forces to distinguish them from the other van der Waals' forces. London deduced on a theoretical basis that even for apolar atoms an attraction exists. This attraction arises because even neutral atoms consist of charged particles which form oscillating fields. These oscillating charges mutually interact to produce a net force of attraction. For atoms, the potential energy of interaction is inversely proportional to the sixth power of the distance, r, between the atoms. Deryagin, Abricosova, and Lifshitz (32) state that the interaction is through the magnetic fields. Because of the time required to transmit an electromagnetic wave, the inverse sixth power law does not hold at all distances. A detailed analysis of this subject is beyond the scope of this review.

Obviously, any interactions that depend on the inverse sixth power of the distance cannot act over a very long range. However, for colloids and larger particles, one is not considering isolated atoms, in which case an estimate of the London–van der Waals' energy may be obtained by summing the interactions between the atoms of the particles; the London energies are to a first approximation independent of the interaction with other atoms.

These calculations have been conducted by assuming that, except for close neighbors, the summation sign may be replaced by the integral. In this case, for flat plates, the interaction *energy* varies inversely as the third power of r, but for perfectly conducting plates it is as the fourth power. For two spheres this complex problem has been solved by Hamaker (33) to give, at small distances, a variation inversely proportional to r. One must again emphasize that these conclusions hold only for close distances compared to the size of the particle and the wavelength associated with the interaction; but, at least the forces may be considered active for distances approximating the particle radius. Overbeek points out that the ratio of the radius to the distance between the particles is the important factor, not the absolute size.

Deryagin and Abricosova (32, 34) were the first to measure accurately the London–van der Waals' forces by using an extremely well designed negative feed back balance. They measured the attraction between a quartz plane and a convex surface. They claim closer correlation to a theory they assign to Lifshitz (32) than to the earlier theories. Lifshitz's theory permits calculations without some of the assumptions in the method described above. However, most important, Deryagin and Abricosova obtained a correlation with the theoretical prediction of the power of the

term for distance between particles. They measured these forces at distances of 10^{-5} and 10^{-4} cm.; therefore, long range forces are observed. The quantitative aspects are beyond the scope of this review. The reader is referred to original references (32, 34–38) that pursue this subject.

The Diffuse Double Layer.—The theory of the double layer which is a primary factor in the stability of hydrophobic dispersions is equally as complicated as the London–van der Waals' force theory. However, in a qualitative sense it is easily understood. One's familiarity with the Debye-Huckel theory of electrolytes provides additional background.

As a result of either the preferential adsorption of ions from the surrounding liquid or the preferential loss of ions from the crystal surface, a net charge exists at the surface of most solids immersed in a liquid. Only by careful adjustment does one neutralize this charge. In the absence of thermal motion this charge would be neutralized by intimately associated ions of opposite charge. However, the ions of opposite charge have Brownian motion and tend to diffuse away from the surface. Consequently, they distribute themselves in the vicinity of the particle; the largest concentration of these counter ions is near the particle surface, and the concentration diminishes at greater distances because of the shielding effect of the ions nearer the surface.

Ions of the same charge as the particle will be repelled from the region near the particle, but thermal motion will tend to redistribute these ions also. Their concentration profile would be the mirror image of that of the counter ions, except that the screening effect is more limited by the solution concentration. The total result of the distribution of charges about the particle is to produce a diffuse region called the double layer that surrounds the particle. (*Reference* 1 develops these concepts in this way but in much more detail.)

Because the potential in this double layer diminishes gradually, the double layer cannot be assigned an absolute thickness that includes all of it. However, a reference thickness has been chosen as that thickness in which the potential decreases by a factor of $1/e$. An additional complication arises because the actual charge of the particle surface cannot be determined experimentally. A part of the double layer is immobilized and moves with the particle. Therefore, the charge determined by electrokinetic methods such as electrophoresis is the charge at this shear plane and is not the true charge at the particle surface. This charge is called the zeta potential and is often used as the best available estimate of the particle charge.

Combined Attraction and Repulsion Forces. —Deryagin (32) and independently Verwey and Overbeek (35) combined the potential energy resulting from the diffuse double layer with the London–van der Waals' energy of attraction to obtain the potential energy curves for model cases. They concluded that for sufficiently small or sufficiently large separation the potential energy is always negative, *i.e.*, attractive forces predominate. However, at intermediate distances the potential energy may become positive because of the repulsion from the double layers of the two surfaces. It is this positive potential energy region that provides in effect the "activation energy" to the process of the combining of two particles. Always, the probability is finite that the kinetic energy of two particles may exceed this barrier and the particles combine; but the rate of flocculation may be extremely small. The particles that do combine usually cannot be separated by thermal energy, for the potential energy minimum that exists when two particles are in contact is deep when compared to kT.

In calculating the potential energy curves for the interactions of particles, a smaller minimum, usually called the secondary minimum, is found at much greater distances from the particle surface than the larger minimum. The secondary minimum has significant magnitude only for particles larger than colloidal size. Schenkel and Kitchener (38) described a case of flocculation in this secondary minimum. They used surface sulfonated polystyrene beads of 10-μ diameter. Adding electrolytes, they observed flocculation when the energy barrier at close approach was estimated to be greater than $24\ kT$. They concluded that the flocculation must be in the secondary minimum. Flocculation in the secondary minimum should be readily reversed because the energy well is not deep. However, one should not conclude that whenever easily reversible flocculation is observed, it necessarily is a case of flocculation in the secondary minimum.

Because the repulsion between particles results from the diffuse double layer, the ionic strength and the kinds of ions on the surface and in the double layer will influence the total charge and/or the thickness of the double layer. Also, the effectiveness of the double layer in preventing the flocculation of particles will be related to both the total charge and the thickness of the double layer. It often has been demonstrated that particles may be flocculated by increasing the ionic strength and thereby reducing the thickness of the double

layer. Also, specific adsorption of a charged ion such as a detergent ion may, on the first addition, reduce the charge to the extent that it allows flocculation, while further additions reduce the charge to zero, reverse the charge, and finally, produce a large enough charge of opposite sign to form a peptized dispersion of opposite charge. Detergents are believed to adsorb in micellar or hemimicellar form when the concentration exceeds the critical micelle concentration (39, 40). This is easily detected by a discontinuity in the adsorption isotherm.

Pharmaceutical suspensions predominately are in aqueous vehicles. However, some products use lipophilic vehicles. Because of the large difference in the dielectric constant, there are significant differences in the stability characteristics of particles in the two types of vehicles. The potential between two charges is inversely proportional to the dielectric constant of the medium between them. Therefore, the distribution of ions in the double layer will depend on the dielectric constant of the vehicle. In low dielectric liquids such as oils, the double layer will be many times thicker than in liquids with a high dielectric constant such as water. Also, only a few ions in an oil will produce the same potential produced by many ions in water.

Albers and Overbeek (41) have concluded that for water-in-oil emulsions, except in extremely dilute systems, the thickness of the double layer is large compared to the distance between two particles. The potential energy of the particles is larger than when the particles are at infinite distance, *i.e.*, located outside each other's double layer regions. Therefore, the potential energy that must be overcome to bring two particles together is reduced by this amount. Consequently, in an oil vehicle the double layer around the particles often will not protect the particles against flocculation.

The only repulsion force usually considered to be acting between particles is based on the electric layer as described above. However, Voropaeva, Deryagin, and Kabanov (42) have obtained evidence of a repulsion force of undetermined origin. They measure the forces acting between two crossed platinum wires as they are brought closer and closer together. The wires have external electrical connections through which charges on the wires may be controlled. Present knowledge does not justify speculating on the possible role this nonelectrical repulsion force may play in suspension formulation.

Adsorbed Layers.—In the early literature, part of the stability of sols was assigned to the formation of lyospheres, *i.e.*, a thick layer of adsorbed vehicle covering the surface of the particle. These layers were considered somewhat diffuse. They provided protection against flocculation by reducing the interfacial tension to a negligible value and by preventing the particles from approaching sufficiently close to undergo strong interaction from the London–van der Waals' attraction. Proof of such thick films is lacking, although their existence has been invoked to explain numerous observations.

The confusion existing at the present time is illustrated in three papers that discuss the preferred contents of a course in colloid chemistry (25, 43, 44). Because only the Deryagin-Verwey-Overbeek theory of stability has yielded to quantitative interpretation, the relative importance of other factors has been a point of disagreement among various investigators. Deryagin has described the phenomena in term of a disjoining pressure consisting of two components: the electrical (P_e) and nonelectrical (P_o). Glazman (27) refers to this classification and concludes that for ideal lyophobic sols, P_o is much smaller than P_e. For lyophilic sols, P_e is nearly zero and P_o dominates. He concludes that in real cases, lyophobic sols are nearly always solvated so that P_o is a factor in nearly all stable systems.

Yampolskii and Shu-Chiu (45) studied the electrical conductivity of carbon-black suspensions in oil. They found that the conductivity increased with increase in temperature of their flocculated suspensions. This and other observations were consistent with the view that a very thin solvent layer is left between the dispersed particles. Rebinder (26) discusses these thin interlayers of the medium in his review article.

These concepts and the Deryagin-Verwey-Overbeek theory of lyophobic colloid stability will aid us in discussing qualitatively the theory of suspension formulations. The thick solvation layer concept does not appear to be valid or necessary to account for the shelf-life stability of suspensions.

The influence of adsorbed layers of nonsolvent molecules on the particle interactions has been considered in a theoretical treatment by Vold (46). She has derived a general formula for the interaction of spherical particles surrounded by adsorbed layers. Her calculations show that the London–van der Waals' attraction might be reduced by as much as 20% which is less than the possible reduction calculated for bound solvent layers. In both cases it is concluded that flocculation can be inhibited significantly only for very small particles or for very thick adsorbed layers.

Her calculations were not extended to layers more than 20 Å. thick. Mackor and van der Waals (47) treated the adsorption of rod-shaped molecules. They concluded that the free energy rises due to the interaction of two adsorbed layers and they give an expression for the free energy of repulsion.

More will be said about various factors in flocculation when it will be possible to show their function in influencing the shelf-life stability of a suspension. First, the kinetics of flocculation will be discussed.

Flocculation Rate

The rate of disappearance of primary particles has been treated by von Smoluchowski (48) as a collision rate calculation that is diffusion controlled. Every collision is assumed to result in the combination of two primary particles, and no repulsion forces are present. Many books discuss this subject in a reasonably concise manner (1, 49). The rate is given by

$$- \frac{dn}{dt} = 4\pi DRn^2 \qquad \text{(Eq. 7)}$$

where n is the total number of particles, t is the time, D is the diffusion coefficient, and R is the collision radius usually assumed to be equal to the particle diameter. If the diffusion coefficient is replaced by Einsteins's equation $D = kT/3\pi\eta R$, where k is the Boltzman constant, η is the viscosity, and T is the absolute temperature, it may be shown that the time, $t_{1/2}$, required to reduce the total number of particles to one-half their original number is

$$t_{1/2} = \frac{3\eta}{4\,kTn} \qquad \text{(Eq. 8)}$$

Any reasonable value for n and η substituted into this equation results in a small value for $t_{1/2}$.

If every collision does not result in a combination, then some protection exists. If the particle is assumed to be protected by an energy barrier, V, a rough approximation of the rate of disappearance of primary particles is obtained by multiplying Eq. 7 by $\exp(V/nkT)$. Obviously, the larger the protective energy barrier, the slower the rate of combination. The initial rate of coagulation has been observed experimentally and used to estimate the magnitude of V (50, 51). When V is very large, possibly 25 kT, the rate of flocculation is going to be negligible. von Smoluchowski's equations have been extended to describe other cases than spherical particles (52).

Gillespie (53) studied the flocculation of latex by methylcellulose and found that in this case

there seemed to be a deflocculation rate also. An equilibrium existed between the rates of flocculation and of deflocculation. This is not expected in the usual case for electrolyte flocculation where the deflocculation rate will be negligible because of the deep potential energy minimum for two particles in contact. Flocculation produced by polymers forming "molecular bridges" between particles must be considered as a special case. They will be discussed in a later section.

When slow coagulation by electrolytes is considered, Bhattacharya and Bhattacharya (54) have demonstrated that in many cases the following relation holds

$$\frac{1}{c - a} = \frac{n}{m}\,t + \frac{1}{m} \qquad \text{(Eq. 9)}$$

where c is the electrolyte concentration, t is time of coagulation—or more accurately—the time required to reach a preselected degree of flocculation, and m, n, and a are constants. In this equation, plots of c *versus* $1/t$ have an intercept on the c axis at $1/t = 0$ or $t \rightarrow \infty$, so a is the concentration of electrolyte up to which the stability of the sol remains unaffected. When $1/t$ is very large, compared to n, *i.e.*, as $t \rightarrow 0$, n may be neglected so that $c - a \rightarrow m$ in the rapid coagulation zone; therefore, m represents the concentration of electrolyte in excess of a that will produce very rapid coagulation. It can be shown that n has the dimensions of $1/(\text{time})$. Note that n appears in the slope term of the linear equation. It can be shown that n represents the sensitivity of the sol to the electrolyte; this must be a cumulative effect of such things as shape, charge, dielectric constant, etc. Obviously, this type of information helps one to compare the flocculation of any systems to which it applies.

Another factor of interest in coarse suspensions is the comparison of the rate of collision produced by thermal energy and by mild laminar flow. Reich and Vold (55) discuss the analogy between temperature in a chemical reaction rate study and agitation in the flocculation rate of large particles. This analogy is possible because Brownian motion may be relatively ineffective in producing collisions of large particles when compared to the collision rate produced by agitation (48, 55). The collision of uniform spheres in sheared suspensions have been treated theoretically by von Smoluchowski (48) and by Manley and Mason (56). Reich and Vold give sample calculations for different diameter particles using a shear rate of 100 sec.$^{-1}$ They assumed the weight fractions of solids constant; therefore, the total number of particles change. For 0.1-μ particles the probability of collision from Brownian motion is 100

times greater than from the agitation. However, for a 1-μ particle, the agitation-produced collision rate is ten times the Brownian motion rate. While these are calculated for a specific case, they illustrate the importance of particle size in determining which factor is significant as one goes from the colloidal size range to the microscopic size.

Reich and Vold conclude for unstabilized systems that even though the rate may be very small, the floc size will continue to grow in the absence of agitation. However, when they become large enough, they may be broken by the mild shearing forces produced by ambient thermal convection. Most important, however, is their observation that large particle systems deflocculated by agitation may appear nearly frozen in this deflocculated state for several hours. Since R appears in Eq. 8 indirectly because it determines n (when weight per cent is constant), either the floc size must be large or the volume fraction must be small before this apparent frozen state would be possible. Reich and Vold used low concentrations of solids in their studies.

Voet (57) has combined the methods of rheology, conductivity, and dielectric constant measurements to observe the flocculation breakdown during shear and also reformation of structure on the cessation of shear. In some cases, flocculation continued over a very long period of time. Both temperature and concentration effects were observed. For example, in a 2% dispersion the conductivity remained constant for about 1000 seconds after shearing was stopped; then the conductivity increased rapidly. This apparent induction period probably was the period of small agglomerate formation; it was followed by the formation of aggregates of sufficient size to bridge between the electrodes. Both higher temperatures and higher concentrations of solids reduced this induction period No induction period was observed at 8% or higher concentrations.

The probability of flocculation of large particles of different size during sedimentation has been considered by Andersson (13, 58). His theoretical treatment applies to very dilute systems. He concluded that hydrodynamic effects decrease the flocculation rate.

Hubley, Robertson, and Mason (59) used light scattering to observe flocculated suspensions subjected to laminar shear. Their apparatus resembled a Couette viscometer. Controlled shear rate was possible during the observations. They observed plug flow at very low shear rates. Frisch (60) studied coagulation in a turbulent flow system. He found that at low coagulation rates the

von Smoluchowski equation could be used by replacing the normal diffusion coefficient with an eddy diffusivity constant.

Michaels and Bolger (61) considered the equilibrium between shear flocculation and deflocculation in a detailed mechanistic interpretation of the plastic flow behavior of kaolin suspensions. Smellie and LaMer (62) have developed a mathematical treatment of the competing flocculation and deflocculation processes produced in a polymer bridging process. Healy and LaMer (63) have extended the earlier model. The importance of agitation is indicated in their statement that if polymers are used to insure complete dispersion of a colloidal material, intense agitation should be used so that macro-flocs will be destroyed and complete adsorption, *i.e.*, total surface coverage, attained. This important work will be discussed in a later section.

Another important observation is that mild agitation may increase markedly the flocculation rate (64, 65). Freundlich and Juliusburger (66) discovered the analogous process in gels and gave the phenomenon the name *rheopexy*. The nature of flocculated suspension that seems to develop from all of these studies is not grossly different from that pictured by rheologists, previously. Specifically, it is one of the formation of small flocs which aggregate to form larger particle clusters. These aggregates form loose networks that extend throughout the suspension. These are broken by agitation—first into the aggregate at low shear, then into the flocs, and finally at high shear may be deflocculated. It is the problem of the formulator to control the nature of the flocculation in a manner that will produce a large sedimentation volume. Ideally, the individual flocs and aggregate size should be sufficiently small to produce a smooth appearance to the eye and to produce the large sedimentation volume, Neither the agitation in large tanks nor the filling of bottles provide sufficient shear to break the smallest flocs. Therefore, in practice, the flocculation and sedimentation processes do not start from the completely deflocculated state.

PREVENTING SEDIMENTATION AND CAKING

So far in this discussion, several major steps have been taken toward a basic understanding of the shelf-life stability of a suspension:

It has been recognized that for peptized suspensions, gravitational forces on large particles are sufficient to produce sedimentation.

A relatively low interfacial energy is preferred to

produce proper wetting when the particles go into the vehicle.

Flocculation of the suspension is possible, but the nature of the flocs may vary.

The initial flocculation rate may be fast, but the attainment of equilibrium may be very slow.

Therefore, to prevent sedimentation, one must either learn to control the flocculation process to produce the desired characteristics or find some other way of supporting the particles. One attractive concept is to trap the particles into a structure built of other materials. This will be called a structured vehicle since the structure is to be a part of the vehicle. Presumably, the particles will remain effectively deflocculated because they will be trapped into individual cells. It may help to peptize the particles so that they will stay apart long enough to permit the cells to form about them.

Structured Vehicles

Obviously, it will be necessary to construct the cells so that their holes are smaller than the particle to be trapped; otherwise, the particle will slip through. Therefore, the structure-former must have a smaller particle size than the particles to be suspended. One group of materials that might meet the requirements is soluble polymers. Thermal setting gels are not ideal because the suspensions might have to be heated before a dose could be withdrawn. Linear polymers usually do not form linkages of long durations, so they would permit the particles to drift downward as the Brownian motion of the polymer molecules released them. Of course, at very high concentrations they might function satisfactorily; but this forms a high apparent viscosity medium. It already has been concluded that acceptable fluidity is not compatible with the high viscosity needed to retard the sedimentation of the particles sufficiently.

McVean and Mattocks (67) report that Carbopol 934 solutions behave as an elastic body and do not relax when a small applied force is used. They conclude that this should be the ideal suspending agent. The author must agree with this conclusion but is unaware of definitive experiments that have been conducted to demonstrate that in the completed pharmaceutical suspension, Carbopol 934 produces a pure example of a structured vehicle. It would be necessary to demonstrate the absence of flocculation in the same system to do this. However, Meyer and Cohen (68) report the ability to suspend permanently marbles, golf balls, and sand. Certainly this is convincing evidence that structured

vehicles are a possible approach to supporting large particles in a suspension.

Belugina, Zakieva, Konstantinova, and Rebinder (69) studied structured vehicles for suspending aluminum powder in a hydrocarbon medium. Aluminum soaps of oleic acid and naphthenic acids were used as typical surface-active structure producing agents, and polyisobutylene (mol. wt. 200,000) as an example of a surface-inactive structure producing agent. They did not obtain complete retardation of sedimentation in some of their suspensions. Consequently, they recommended that both adsorptional (protective colloid effect) and volume structuralization be used in the same system. Steiger-Trippi (70) has worked with aqueous systems and has concluded that structure in the vehicle supplemented by structure produced by flocculation of the suspended particles produces optimum results. Because the materials used to produce structure also adsorb on the particles, it will be advantageous to reconsider the combined effect after polymer flocculation has been discussed in more detail. Probably some suspending agents produce both structure in the vehicle and flocculation of the particles. The author has examined numerous elegant suspensions, some produced in our own laboratories and some by other pharmaceutical companies. The viscoelastic properties of the suspensions were observed; then the solids were removed by either filtration or centrifugation; the vehicle was reexamined. Usually no structure was detected in the vehicle. While the sensitivity of the method might not have been adequate to detect very weak structures, the evidence was sufficient to justify the conclusion that for these suspensions much of the structure was associated with the particles, *i.e.*, they were flocculated. Therefore, it appears that many elegant suspensions can be prepared in which structured vehicles are not the major "force" supporting the particles. This possibility will be explored in following sections.

Flocculated Suspensions

Let us consider the evidence that flocculation can produce the desired characteristics in a suspension. Later, possible mechanisms will be considered. One important aspect is the sedimentation volume which sometimes is defined as the final apparent volume the sediment occupies. Superior definitions will be considered also.

Sedimentation Volume.—By itself, the sedimentation volume is a meaningless number for lack of a reference value. To avoid this difficulty, Robinson (15) and Ward and Kammermeyer (17) used the ratio of the ultimate

settled height to the original height, $F = H_u/H_o$. H_u is the apparent height of solids after sedimentation, and H_o is the total height of the original suspension before settling. Dintenfass (71) used the same ratio in terms of volumes to describe sedimentation volume, $F = V_u/V_o$, but extends its usefulness to describe degree of flocculation designated as β.

A completely peptized suspension sediments to a close-packed structure of very small volume which he calls V_∞. $F_\infty = V_\infty/V_o$, so the ratio $\beta = F/F_\infty$ is the degree of flocculation. Dintenfass identifies three classes of sediments, *viz.*, cases where $F<1$, $F>1$, or $F = 1$. At first this is hard to accept since for $F>1$ (he claims values as high as 4 or 5), the settled volume must be larger than the total original volume. However, he points out that by dilution with the vehicle these suspensions will settle to occupy more than the original volume before dilution. These he calls compressed sediments when confined to the original suspension volume. The values for $F<1$ are obviously the usual ones, and he calls these expanded sediments. When $F = 1$, he says the system is in true equilibrium.

Dintenfass determines F_∞ either by observing a completely peptized suspension or by estimating it from rheological data. He states that log $\eta_\infty/\eta = F_\infty/1\text{-}F_\infty$, where η = viscosity of liquid vehicle, and η_∞ is viscosity of suspension at infinite shear-rate, *i.e.*, when all flocs are broken by the shearing action.

If sedimentation in the suspension is acceptable, a large sedimentation volume still is desirable because the particles are much less likely to form a hard cake. Therefore, the flocculated suspension is considered the preferred form and has sedi-

mentational stability, especially when the sedimentation volume equals the total volume, *i.e.*, $F \geq 1$. Note that this is not a stable suspension in the usual colloid science sense. Chwala (72) described this situation as the "sedimentation paradox" (see Fig. 1).

Vold (73) has conducted some interesting theoretical studies that indicate how porous a sediment may be. She used a computer generated statistical model in which the probability of cohesion of two spherical particles upon contact varies from 0 to 1. According to these results, when the probability of cohesion is less than about 0.35, the sediment volume depends critically upon this probability. For higher probabilities of cohesion the sediment volume is not a sensitive measure of particle interactions. Also, when the probability equalled 1, her results indicated that for polydispersed systems the number of particle contacts may average 2 (74). While this model has some deficiencies in predicting lower volumes than may be observed, it emphasizes the point that a flocculated suspension may reasonably have a very porous structure. She concludes that the model needs to include both sedimentation and flocculation to give more representative results. In real cases still other factors may be important.

Nakagaki and Sunada (75) calculated the sedimentation volume of spherical particles attracted by cohesional forces. A simple relationship was found between the sedimentation volume and the ratio of range of attractive force to the radius of the sphere.

Another important consideration in any real suspension is the distribution of particle sizes. Vold (74) concluded that for the case she considered, the sediment structure was more sensi-
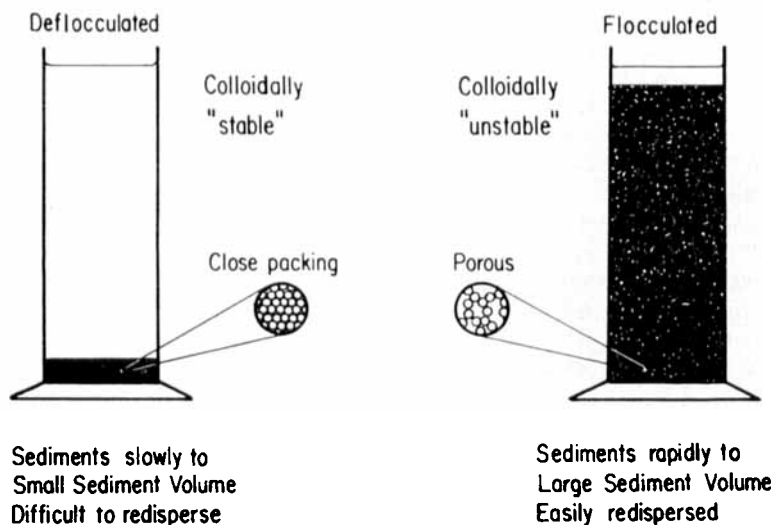

Fig. 1.—Most suspensions undergo sedimentation in the absence of structural support. Peptized suspensions (on left) form clays that are difficult to redisperse. Controlled flocculation can produce a large sediment volume. (From *Reference* 86).

tive to size distribution than to the model used for interaction. There seems to have been no detailed experimental evaluation of this factor; however, Wolf and Kurtz (76, 77) observed that the smaller the particles, the greater the sediment volume. Wolf and Wolff (78) observed the effect of temperature on the sedimentation volume. Kuno (79) has determined the influence of vehicle viscosity and density. Except for the choice of vehicle, these factors are relatively unimportant, and are not variables that the formulator may use to control the sedimentation volume. Instead, the problem is to control the flocculation in a manner to obtain the desired characteristics in the vehicle when using particle sizes chosen on therapeutic criteria.

Figure 2 illustrates how much the sedimentation volume may vary. Note the gradual increase in sedimentation volume with increase in surfactant addition. Each graduate contains exactly the same weight of solid medicament. Often one adds a surfactant to produce deflocculation. But in this example the surfactant is producing the opposite effect. It is so effective that the sedimentation volume exceeded the total volume of the suspension. When enough surfactant was added, it became a rigid gel if confined in volume.

Redispersion.—When a flocculated suspension settles to occupy less than the total vehicle volume, there is an inherent benefit in the use of large particle size. Everyone is aware of the "Shake Well Before Using" label. Overbeek (80) considers the influence of particle size on the effectiveness of shaking in repeptizing a coarse suspension. He states, "Qualitatively this easy repeptization can be explained in the following way: By agitation a shearing motion of the liquid is excited. This causes a force trying to tear two neighboring particles apart, which force is proportional to the radius of the particles (Stokes' law) and to the distance between their centres (difference in the velocity of the liquid). So the separating force is proportional to the square of the radius of the particles. On the other hand, the attractive force is, at best, proportional to the first power of the radius of the particles (London force for spherical particles), and if the particles are not very regularly formed, the attractive force will soon be independent of the overall dimensions. . . . It may be remarked here that although a flocculated suspension is easily repeptized it is very difficult to redisperse the compact sediment of a stable suspension. . . . The sediment is so compact that the particles can only be attacked by hydrodynamic motions layer by layer which evidently is a very slow process."

The difference between a peptized suspension and a flocculated one is shown diagrammatically in Fig. 1.

So far, this discussion has been presenting evidence that a flocculated suspension may be a preferred condition in avoiding caking in a suspension. The long history of the use of flocculation to produce a desirable suspension and the methods by which it has been obtained should be a convincing and interesting argument for it. Kinsman and Bowles (81) have reviewed the use of flocculation in pigment suspensions; Haines and Martin (82) used the sedimentation volume as a criterion of flocculation in their study of the prevention of caking. They related the flocculation characteristics to the zeta potential of the particles. One problem in discussing the results of studies of this kind is the difficulty of describing the real character of the flocs. Part of this difficulty arises because only a gross property, such as sedimentation volume, usually is observed. Unless this is expressed as a β value, the meaningful reference point is missing. Such phrases as partial flocculation or degree of flocculation are not very specific. They not only lack a quantitative interpretation, but also lack a clear connotation. For this reason, a terminology that seems to offer some advantages will be adopted in this review.

Sediment Structure.—When an interaction between two particles results in sufficient attraction to hold them together for a significant time, the interaction will be considered to have produced a *link* between the particles.

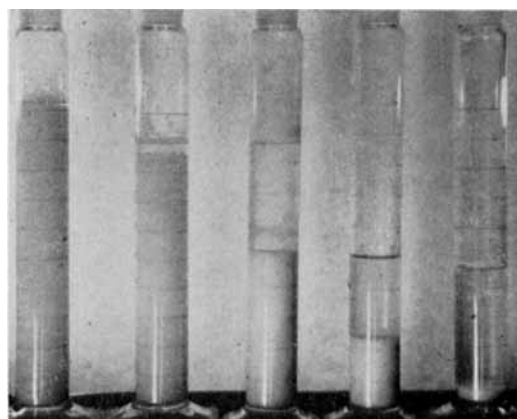F>2   F = 1.7   F = 1.06   F = .52   F∞ = .1

Fig. 2.—The sedimentation volume of this suspension increased with increased surfactant concentration. Equilibrium vehicle was added to three containers on the left to provide space in which to sediment. Twenty-five mg./ml is normal dosage level. Center suspension would be a satisfactory product since at $F = 1$ sediment volume is equal to total volume desired. (From *Reference* 86).

Link is chosen in preference to bond to eliminate confusion between primary chemical bonds and the interactions producing flocculation. A particle may form links to more than one neighboring particle. The number of particles to which links are formed will be called the coordination number of the particle. This terminology would permit a reasonably clear description of the flocculated state if sufficient information were available; but it never is. However, it avoids possible confusion between the completeness of the process, the strength of the links, and the structure of the flocculated particles.

Two extreme cases are observed repeatedly (see Fig. 3). A compact floc consists of particles of very high coordination number. A loose floc has an open, scaffold-like, three-dimensional structure with many large void spaces, almost cellular in character. The average coordination number will be smaller in the loose flocs than in the compact ones. However, some of the scaffold building units may be small aggregates instead of individual particles. In this case a broad range of coordination numbers would exist. An adequate description of the structure would require a knowledge of the distribution of coordination numbers. Qualitatively, one would expect the high coordination number case to correspond to a low value of β, a broad distribution of coordination numbers to an intermediate value of β, and a low coordination number to a large value of β. For uniform spheres, the maximum number of nearest neighbors is 12, and the corresponding coordination number would be 12. For polydispersed systems, values larger than 12 would be possible for the large particles, but certainly the sediment containing particles whose average coordination number approaches 12 would not produce the large sediment volume of interest to the formulator. As previously mentioned, Vold (74) and also Nakagaki and Sunada (75) have explored the relationship between coordination number and sediment volume for idealized cases.

Rebinder (83) describes a most interesting case in which, apparently, the coordination number was controlled by the number of coagulation centers. This influenced the character of the flocculation produced. He states that where the area of these regions is a considerable fraction of the total particle surface, compact aggregates form. However, when the coagulation centers are localized at a few points, a network structure with thixotropic properties is formed. He adsorbed surfactants onto calcium stearate to control the number of coagulation centers. If one may generalize his observations, the procedure for preparing elegant suspensions is given direction. Perhaps this is a part of the explanation of the success of the flocculation study reported by Haines and Martin (82). However, their cationic coating agent did not reduce the coordination number sufficiently, so they added a suspending agent also. They observed that the suspending agent stabilized against sedimentation but did not report whether the suspending agent was acting also as a flocculating agent.

Probably as suggested above, thixotropy occurs only when there is a low coordination number for the particles. Elongated (flat or long) particles often produce thixotropic suspensions. One might expect the ends or edges to have different energies than the bulk of the surface. These could influence the effective number of coagulation centers. It has been demonstrated that the method of producing the flocculation may determine whether a gel is produced. For example, kaolinite flocculated with hydrochloric acid produces the scaffold-like "edge-to-face" flocculation; while sodium chloride flocculation produces "face-to-face" flocculation (84), a much more compact floc. Heller (85) has studied the flocculation of anisometric particles and has concluded that rapid flocculation by electrolytes produces structurally isotropic coagula, while slow flocculation by electrolytes and by stirring produces anisotropic coagula. Of course, his results cannot be extended to isometric particles.

Methods of Producing Flocculation.—The suspension may flocculate without the intentional addition to, or adjustment of, the vehicle to produce flocculation. Of course, the causes of flocculation in this case are identical to the intentionally induced flocculation. However, some points of interest are worth discussing.
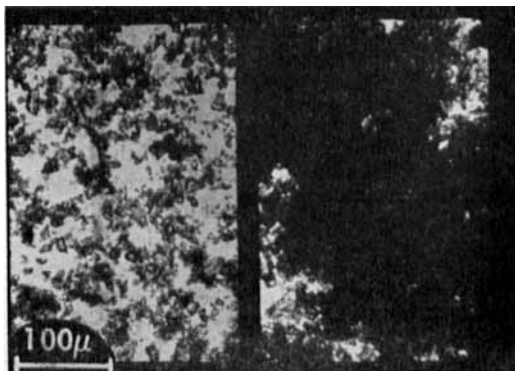

Fig. 3.—Comparison of flocculated sediments that produce a large sediment volume (left) and a small sediment volume (right). Both are aged slides to permit both flocculation and sedimentation to proceed. Initial suspensions had the same solids content.

In theory, any pure lyophobic material should flocculate when put into the pure vehicle unless a protective double layer forms. *Pure* is the important property to be considered here. Very few solids are pure, especially with respect to uncontaminated surfaces, and very few vehicles are pure enough to contain insufficient impurity to adsorb onto the particle surface. Consequently, it is not possible to predict *a priori* whether a flocculated or peptized suspension will result when a powder is put into a simple liquid. If a large sedimentation volume results, and if the particles are isometric, one may suspect that the surface is contaminated either initially or by adsorption from the vehicle. In some cases this can be demonstrated by noting a marked change in sediment volume when powders have been pretreated by placing them under vacuum for several hours or passing helium over them for several hours to remove impurities. Of course, the impurity has to be volatile for this to be effective. The technique is not selective to surface impurities since molecules of solvation might be removed by the same pretreatment. In one case observed in this laboratory, the crystals were extremely difficult to wet with water; most surfactants were ineffective. However, when the residual solvent was removed, the crystals wet readily without a surfactant. A formulation based on the purified material could have been entirely unsatisfactory if made using the contaminated powder. Subtle changes in the trace impurities may result from changes in the purification or crystallization procedure used in manufacturing the raw chemical. These changes may not be detected by usual control procedures; yet, they may produce marked changes in the characteristics of a simple suspension. It is feasible to use a control procedure based on the sedimentation volume in simple liquids to warn of such changes in the raw material.

Electrolyte Flocculation

The basic theory that applies to electrolyte flocculation has been discussed in an earlier section of this paper. The use of electrolyte flocculation does not provide a means of controlling the coordination number of the particles. In the absence of other controls, flocs produced by adding electrolytes would be expected to produce coarse, compact masses with a curdled appearance. Often, this is observed. The floc size probably is determined more by the kinetics of the process than by any other factor. Of course, this conclusion assumes that the flocculation is in the primary minimum. Flocculation in the secondary minimum might be different because of the ease of redispersion.

Detergent Flocculation

Detergent is used here in preference to surfactant to avoid confusion. Surfactant has already been used in a more general connotation than will be implied in this section. Detergents may be of the ionic type or nonionic type.

Ionic Detergents.—The influence of the ionic type on the double layer has been considered already. Neutralization and reversal of charge has been observed on numerous occasions (39, 40, 82). Figure 2 is an example of the control of the sedimentation volume using an ionic detergent. This figure is from a previous publication (86). Tomlinson (87) observed the sedimentation volume of Prussian blue as the adsorbent for cetyltrimethyl-ammonium bromide. The maximum sedimentation volume in water approximately coincided with the minimum sedimentation volume in benzene. The importance of the extent of the lyophilic character of the surface was demonstrated. As an explanation of the inefficiency of the cationic detergents as detergents at concentrations between 1 and 3%, Doscher (88) proposed that these materials are adsorbed as charged aggregates above their critical micelle concentration and that this leads to a more hydrophobic exterior. The hydrophobic surfaces interact to form links between particles.

Nonionic Detergents.—Nonionic detergents have not been studied as extensively as ionics Kuno and Abe (89) observed the adsorption of various polyoxyethylated nonylphenols on calcium carbonate. They detected no adsorption until after the critical micelle concentration was reached. However, on carbon black the adsorption occurred at lower concentrations. Mathai and Ottewill (90) observed the mobility of particles as a function of nonionic surfactant addition. The mobility decreased gradually as the concentration increased. This suggests that the surface charge density remained constant and the increased solvation carried by the nonionic detergent caused the electrokinetic plane of shear to move further into the liquid phase. The nonionic detergent produced some protection against flocculation by electrolytes. Flocculation seemed to result from a compression of the double layer and not by a bridging action. Koelman and Overbeek (91) concluded that some slight stabilization occurs with nonionics as a result of keeping the particles further apart.

Nonionic detergents would be expected to possess lower heats of adsorption than ionics.

Usually the energy involved would not be sufficient to orient the detergent molecule in a manner to produce a much more lyophobic surface. In cases where liquid nonionic detergents produce flocculation, the liquid bridge mechanism may account for their action. In our own laboratory, nonionic detergents have been used to increase the sedimentation volume of flocculated suspensions. Less than a monolayer of surfactant is necesssary; otherwise, the desired mosaic surface character with only a few coagulation centers would not be produced and the effective control of the coordination number would be lost. It is believed that the mosaic surface is effective only during the initial part of the flocculation process. Other controls must exist in the suspension if the slow compaction settling process is to be effectively arrested. Structured or high viscosity vehicles may be sufficient. Additional study is necessary before the above concept can be fully evaluated.

Detergents usually are considered to differ from polymers because often polymers have a very high molecular weight with many active centers spaced along the chain. A detergent usually has a much lower molecular weight and, at most, a few active centers on a single molecule. The importance of this will be emphasized in the section on polymer flocculation.

Liquids as Flocculating Agents

Water has been used for many years to prevent hard settling or clay formation of the pigments in oil base paints. In 1931, Rhodes and Jebens (92) attributed the function of water to the formation of structure within the paint. Fischer (93) describes the mechanism. When a hydrophilic solid is dispersed in oil, a small amount of water is collected by each particle. When two particles touch, the liquid film collects between the particles to form a liquid bridge.

Bloomquist and Shutt (94) observed the sedimentation volume of glass spheres in water and organic liquids. In some organic liquids, only when they are carefully dried, was the sedimentation volume as low as in water. In some cases the sedimentation volume was proportional to the water content; in others the liquid had to be nearly saturated before flocculation was observed. Zettlemoyer (95) reports that less than a monolayer of water may produce flocculation of some systems. It is not clear that such cases are liquid-bridging. Farnand, Smith, and Puddington (96) described the formation of compact aggregates in a liquid medium using liquid-bridge flocculation. The mechanism is essentially the same as that for the granulation of powders. Mild agitation is used to increase the number of collisions and thereby increase the opportunities for the particles to increase their coordination number. When adequate liquid is present to form the links, a compact aggregate results. Obviously, the interfacial tension in the regions of the link provide the forces acting to hold the particles together. Hydrophobic solids in water may be flocculated by adding hydrophobic liquids (97). The mechanism is the same.

In our own laboratories, liquid-bridge flocculation has been found useful. The assumption has been that for it to produce the desired properties, the maximum possible coordination number of the particles must be limited. This is accomplished by a partial coating of the lyophobic surface with a surface-active material. Then the liquid bridging agent is added to produce the flocculation. A product with a large sedimentation volume results. Again, protection against compaction on standing is not inherently present. However, the lower sediment volume suspension that results from compaction is readily redispersed.

Polymers as Flocculating Agents

By far the largest number of pharmaceutical suspensions contain lyophilic polymers as suspending agents. The success of the numerous hydrocolloids to suspend particles in aqueous vehicles is well known. They are used so frequently that it is hard to believe that the details of the mechanism of their action have not been resolved completely. The possible role of bridge flocculation in this suspending action will be explored.

Sensitization and Protection.—Classically, the action of hydrophilic colloids has been studied using particles of colloidal size. Zsigmondy (98) reported that gold sols were protected against coagulation by electrolytes when gelatin was present. Reinders and Bendien (99), using electrophoretic measurements, concluded that the particles were covered completely by the gelatin. Instead of protection, sensitization (less electrolyte required) was observed if the gelatin was present in small amounts. Zsigmondy and Joel (100) concluded that small amounts of gelatin caused the sensitization because the sol tried to envelope the gelatin. This last conclusion is not correct because the aggregates do not form until the shielding of the double layer is reduced by electrolyte addition. In modern terminology, the protection and sensitization are described in terms of the adsorption of the hydrocolloid onto the particles.

Heller and Pugh (101) have discussed the protective action of polymers in terms of steric protection. Only slight interpenetration would be

expected of polymer chains, which extend outward from neighboring particles. These protruding chains keep the particles separated sufficiently to avoid large interactions from dispersion forces. Rebinder (25, 26) describes the protective action as structural protection in the layer around the particle.

Sensitization results because polymer molecules can form bridges between two particles by adsorbing different portions of themselves onto each of two particles. Excess polymer reduces the uncoated area so that the probability of a link forming between two particles is reduced. This simple model has been used by Smellie and LaMer (62) to develop a quantitative theory for the flocculation of phosphate slimes. These investigators were interested in obtaining a high filtration rate. Consequently, the coordination number of the particles in the sediment they find to be optimum for filtration may be higher than desired for maximum sedimentation volume of the suspension. This illustrates the problem previously mentioned; *viz.*, the inability to describe adequately the flocs produced in a given process.

Polymer Adsorption.—It is desirable to consider the adsorption of polymers in more detail before continuing with the discussion of flocculation. Silberberg (102), in presenting a theoretical treatment of polymer adsorption, also reviewed the established facts of polymer adsorption that any theory must include. Some of these facts are of particular interest. The numerous references are not included here; the reader is referred to Silberberg's excellent paper which has an extensive bibliography. The amount of polymer that is adsorbed from solution is an unusually high proportion of the polymer molecules up to some limiting amount; thereafter, increases in polymer concentration in solution have little effect on the adsorption. In the regions of relatively low molecular weight, the amount adsorbed increases with molecular weight of polymer, but at higher molecular weights the amount adsorbed seems to be independent of the polymer molecular weight.

The polymer molecules may be considered as consisting of active centers spaced along the "backbone" of the molecule. The fraction of total segments adsorbed, *i.e.*, actually attached to the particle surface, is less than one-half of the total segments. The adsorption phenomenon is *relatively* insensitive to temperature changes, solvent changes, and even changes in adsorbent surface. (Little wonder that polymers have such universal application.)

The model that is most successful in explaining the observations is based on the adsorption of several adjacent segments of the polymer, and then several other adjacent segments forming a loop out into the vehicle, followed by the adsorption of another group of segments of this same molecule, etc. It had been assumed previously that many loose ends project into the vehicle; but Silberberg's theoretical treatment predicts that at equilibrium the ends are adsorbed and loops stick out into the vehicle. With molecules of this size, the equilibrium arrangement would be approached very slowly. (See the discussion at the end of *Reference* 102.) In a real case, there probably are ends available for adsorption onto bare portions of other particles. The effect of time of agitation was noted by Kraugh and Langston (103) with gelatin adsorbed on quartz. They observed an apparently irreversible effect in the direction of deflocculation. They postulated that when particles are kept apart long enough by agitation one may obtain a gradual rearrangement on the particle to adsorb more free chains onto the particle so that they are no longer available to form bridges.

That polymer bridge flocculation may be important in pharmaceutical suspensions has been suggested previously (86). Because hydrocolloids are macromolecules with numerous hydrophilic regions, it is not surprising that they may be used to flocculate particles. Because they are polyelectrolytes, the influence of pH and of ionic strength may not be negligible. Kraugh and Langston (103) observed an optimum pH for both settling rate and adsorption for gelatin systems.

At least part of the suspending action of hydrocolloids results from their adsorption and the associated flocculation. It is difficult to demonstrate the relative importance of various factors in a given suspension. However, in unpublished studies some insight has been obtained. Using different concentrations of the same suspending agent and the same solid material, a series of suspensions having different sedimentation volumes were prepared. Several techniques (to be described in the next section of this manuscript) were used to evaluate the suspensions. The observations lead us to postulate that the suspending agent is functioning both as a protective colloid and as a flocculating agent, just as in the filtration rate studies of Smellie and LaMer (62). It is performing these functions on different parts of the same particle. When most of the surface is covered, there is little free surface onto which many particles may attach to form polymer bridges. Therefore, the coordination number tends to be low. At lower surface coverage, the
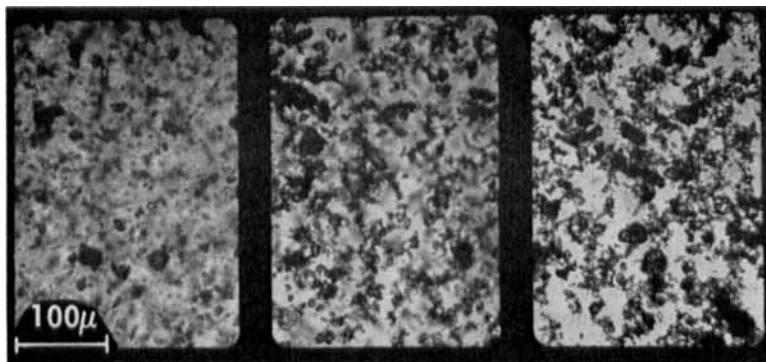
coordination number may be larger and the suspension appears more coarse. Here, the links need not be all polymer bridges.

Methods of Evaluating Suspensions

Techniques for evaluating the character of a suspension have been developed. Many of these have been reviewed by Kinsman and Bowles (81). Dielectric constant methods and electrical conductivity are useful only in nonconducting fluids. Conductivity methods have the further requirement that the particles must be conducting. Nevertheless, these methods have been most revealing of the nature of the flocculation process, see, for example, the work of Voet (57). Other methods, such as light scattering, are useful only in dilute suspensions. Less direct methods are often more easily applied and more suitable for the usual pharmaceutical suspension.

Low Shear Rate.—In our laboratories, it has been demonstrated that suspensions may be elegant products with reasonably long shelf-life stability even when the particles have not attained their maximum possible coordination number. This is demonstrated by agitating the suspension at an extremely low rate. The author uses a round bottle tilted at 45° from the vertical and rotated at 4 revolutions per hour. The bottle is not filled beyond the point where the contents have a triangular cross section if viewed in a plane through the axis of rotation. One pharmaceutically elegant suspension has been found that will "curdle" in less than 1 hour in this apparatus. Other good products withstand this treatment for several hours with no apparent change in their physical characteristics. A suspension that undergoes a significant change in the coordination number of its particles in this device might do so under the mild agitation it would receive in shipment. However, the conditions are not the same and further testing should be conducted.

The acceleration of flocculation at very low levels of agitation has been reported previously (64, 65). Also, some dispersions flocculate under high shear (81, 104). The author has not worked with any pharmaceutical suspensions that behave in this manner.

One experimental lot that contained a suspending agent was observed to "curdle" in less than 45 minutes when subjected to the rotation test. This suspension will be identified as suspension *A*. When it stood on the shelf in a carboy, within 2 months the solids had contracted so that a thin layer of clear liquid existed at the outside edge. Also, large cracks had developed. They extended into, but not through, the total structure of the solids. It is postulated that a slow rearrangement of the particles had occurred on standing; this resulted in a slight increase in the coordination number of the particles (syneresis phenomenon). In small containers the contraction was not obvious except by careful examination.

In discussing the adsorption of polymers, it was stated that the amount of polymer adsorbed is an unusually high fraction up to some limiting amount; thereafter, increases in polymer concentration in solution have little effect on the adsorption. Apparently, the surface becomes almost completely coated with polymer before a high concentration can exist in the equilibrium liquid. However, in the slow rotation experiment with suspension *A*, the suspending agent did not provide complete protection against flocculation; but enough of it must have been in the vehicle to provide sufficient structure to inhibit the flocculation process in the unagitated suspension. Adsorption isotherms can be made to determine the equilibrium concentrations.

Rheology.—Suspension *A* was studied further by using a Couette-type viscometer. The interaction energy was evaluated using the method of Gillespie (105). The Bingham yield values were nearly identical for the suspension and the equilibrium vehicle. Therefore, the presence of significant amounts of suspending agent in the vehicle was demonstrated clearly. Viscoelastic properties of both the suspension and the vehicle were

estimated using a device somewhat like that described by McVean and Mattocks (67). An important difference in technique is that the suspension is not disturbed to introduce a sphere beneath its surface. Instead, a probe is lowered into the aged suspension. The relaxation curve of the suspension demonstrated the existence of a structure that relaxed very slowly. The relaxation plot fit the logarithmic box distribution model. By comparison, the equilibrium vehicle exhibited a very weak structure. The apparatus used was not sensitive enough to permit characterization of the relaxation curve.

Microscopic Observations.—Microscopic observations of suspension *A* were not particularly useful because of the high (13%) solids content. When diluted with equilibrium vehicle to 2.6% solids, no significant flocculation was observed, even after standing for 2 weeks.

Suspension *A* seems to be an example of a suspension containing flocculated particles. However, the flocculation process has been arrested by either the structure and/or the high apparent viscosity of the vehicle. Therefore, the particles have not attained the maximum possible coordination number. Its shelf-life stability in small bottles was satisfactory to qualify as an elegant product.

Similar studies of other suspensions have demonstrated that other conditions also result in an elegant product. For example, a suspension that did not "curdle" in the slow rotation device produced very interesting photomicrographs. To obtain useable photomicrographs, it was necessary to dilute the suspension to one-fifth the original concentration. Both the dilution and the walls of the slide may influence the particle behavior; hence, one cannot be certain that the suspension looks like the photomicrograph. Figure 4 shows the results of this study. The zero time photomicrograph does not show flocculation. After 3.5 hours, noticeable flocculation has occurred. After 45.5 hours, the flocculation has produced the open-scaffold structure. Figure 3 shows the sediment of two suspensions of the same solid content. In one case very little suspending agent was used; both a small sediment volume and a large coordination number resulted. Increased amount of suspending agent resulted in the formation of the scaffold structure and a large sediment volume. The dilution step, necessary to obtain the photomicrographs, reduces the initial flocculation rate to approximately one-twenty-fifth of its rate in the undiluted suspension. Nevertheless, the results demonstrated the need to evaluate a microscope slide

after waiting sufficient time for the flocculation to develop.

To obtain the photomicrographs in Figs. 3 and 4, each slide contained a well about 500 μ deep. This was filled with the freshly stirred suspension. The cover slip was carefully placed over the well and sealed. The slides were stored at 60° from the horizontal so that both sedimentation and flocculation could occur. Without the sedimentation, the high coordination number would not develop.

The observations discussed in the above paragraphs are consistent with the theoretical concepts presented. The basic principles involved in producing colloidally stable dispersions are not sufficient for shelf-life stability. Instead, it is necessary to use a structure produced by the particles themselves.

Phase Volume Ratio

Very little has been said directly about the phase volume ratio. Obviously, the particle population is important since a maximum theoretical limit must exist for the sedimentation volume of a dilute suspension and for the minimum volume of a highly concentrated suspension. The rheological properties will vary with the total solids. Chessick (106) has described methods to increase solid contents of nonaqueous dispersions without other effects. This involves the control of the interactions between particles. Both pediatric drops and parenteral dosages may require very high solids contents. The finished products will involve differences in the desired coordination number, etc., from more dilute suspensions. Particle size control may be of value (107), but the dissolution rate and therein the availability for adsorption may limit the choice of particle size.

It is obvious that there is no single answer to the question, "What conditions produce a stable (shelf-life) suspension?" Nevertheless, some guiding theories and useful techniques are available to the formulator. In an effort to present the above material in a manner as logical as possible, many of the complicating details have been neglected. At present, the body of knowledge available to the formulator provides only the guide lines. Each formulation presents unique problems. These relate to the chemical composition and physical properties of the suspended materials. Even chemically similar materials may exhibit different physical properties. This is especially true of surface properties where trace impurities are often the dominating factor. Consequently, guided empiricism shall continue to be the dominant course toward preparing an

elegant pharmaceutical product. However, as fundamental principles are unveiled, product formulation will shed its empirical character. It behooves the formulator to keep abreast of these developments. It is in this interest that this review has been prepared.

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