

Easton's

Pharmaceutical

Sciences

1985

MACK PUBLISHING COMPANY

Easton, Pennsylvania 18042

ensive 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 $\nu/4$ or $5kT$ energy. Many anchor groups may be attached to the loop section of the molecule and cannot adsorb at the 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. 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 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 affected to essentially the same forces as those described for denders 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 an important role than in powders under certain conditions.

Effect of Charges—A solid particle or a droplet of an electrically 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 surface ions preferentially adsorbed at the interface.

The particle charge gives rise to a surface potential, ψ_0 , at the interface (see Fig 21-13). The potential will fall to zero at some distance away from the surface depending on the concentration of the counter-ions in the external-phase region. 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 layers. The specific adsorption of counter-ions in the Stern

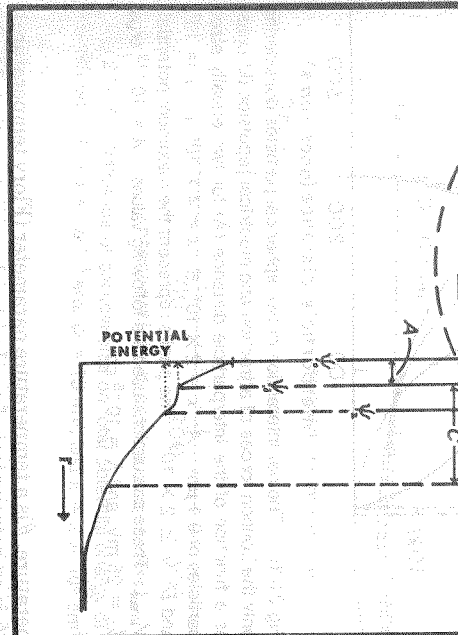


Fig 21-13. The electrical double layer and the symbols used to describe the potential at various points. A: The Stern layer, B: the plane of shear, and C: the sphere of influence of the diffuse double layer.

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

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

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_i , 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

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

Zeta Potential—When a charged particle surface is placed in an electrical field, it will migrate toward the electrode with the opposite charge. The force exerted on the particle and the bound solvent molecules are also very close to the Stern Layer but slightly farther from the particle surface. While the exact relation between the zeta potential, ψ_z , and ψ_a is not clear, it is proposed that ψ_a and ψ_z are of the same order of magnitude but ψ_z is slightly smaller. If, in addition, ψ_0 is small and there is little special counterion binding at the interface, the zeta potential will also reflect the changes in it. The surface potential, ψ_0 , and the surface charge density, the number of charges per unit area, by the Gouy-Chapman diffuse electrical theory.

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

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

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

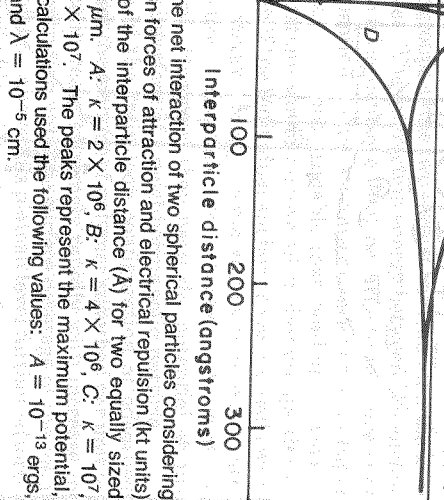


Fig 21-15. Influence of particle size on total potential energy of interaction. $A = 5 \times 10^{-13}$ erg, $\psi = 25$ mV, and $\kappa = 2 \times 10^6 \text{ cm}^{-1}$.

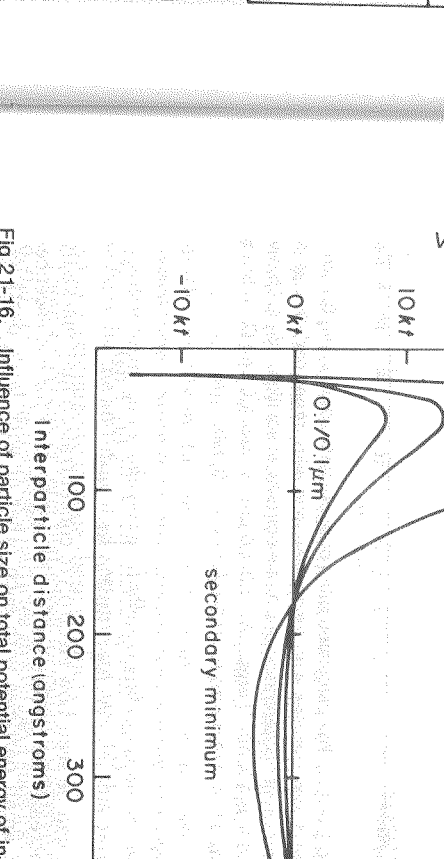


Fig 21-16. Influence of particle size on total potential energy of interaction. $A = 5 \times 10^{-13}$ erg, $\psi = 25$ mV, and $\kappa = 2 \times 10^6 \text{ cm}^{-1}$.

the net interaction of two spherical particles considering forces of attraction and electrical repulsion (kT units) of the interparticle distance (\AA) for two equally sized μm . $A = 2 \times 10^6$, $B = 4 \times 10^6$, $C = 10^7$, $\times 10^7$. The peaks represent the maximum potential. Calculations used the following values: $A = 10^{-13}$ ergs, and $\lambda = 10^{-5}$ cm.

temperature parameter (Flory temperature), θ is the adsorbed polymer layer, r is the radius of the V_s is the volume fraction of adsorbed polymer region, and V_1 is the molecular volume of the particles. When the interparticle distance, H , is less greater than 0; for $H \geq 2\delta$, $V_s = 0$. For additional information see references 5 to 14, at the after.

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

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

tical calculations of the potential energy of repulsion, energy of attraction, and of adsorbed polymer repulsion index B of a communication by Schneider, Stavchansky, *J Pharm Ed 42: 280, 1978*.

trolytes, the double-layer thickness may be so small that it will have no significant effect on the stability of a sterically stabilized system, 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."⁷ 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.

particles (or cholesterol gallstones) in the presence of neutralizing amines and quaternary ammonium compounds. The dissolution rates are manyfold in the presence of high electrolyte concentration. Hence, the dissolution of cholesterol gallstones by pe of the gallbladder with sodium cholate micellar solution interfacial barrier-controlled in the absence of salt aqueous diffusion layer-controlled in sodium chloride solutions.

Flocculation Kinetics

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

$$\frac{dN}{dt} = -4\pi DRN^2$$

where dN/dt is the disappearance rate of particles/cc, distance between the centers of the two particles in cm, N is the number of particles per ml, and D is the diffusion coefficient. Eq 24 shows that the flocculation reaction molecular, the rate being proportional to the square particle concentration. If D is replaced by the Einstein relation, $D = kT/6\pi\eta a$, and $R = 2a$, the Smoluchowski constant for rapid flocculation is predicted by

$$K = 4\pi DR = \frac{4kT}{3\eta}$$

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

$$t_{1/2} = \frac{3\eta}{4kTN}$$

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

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

$$J/I = \frac{\eta a^2 g}{2kT}$$

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

calculated rates of aggregation of 0.1 μm , 0.5 μm , and 1.0 μm with themselves and with larger particles as a function of a 1-1 electrolyte in solution. ψ_0 is 25 mV. A: 1.0/1.0 μm ; B: 0.5/1.0 μm ; C: 0.5/0.5 μm ; E: 0.1/0.5 μm ; F: 0.1/0.1 μm .

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

Now electrolyte concentration may markedly influence the aggregation (or coalescence) with each other or with large particles. ≈ 2 to 4×10^6 for $\psi_0 \approx 25$ mV, it can be seen that the rate of aggregation (or coalescence) of particles with themselves or larger particles may be of magnitude greater than that for two 0.5- μm particles.

Suspensions may undergo dissolution and reprecipitation because of the recognized variation of particle size, expressed mathematically as

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

Solubility of a spherical crystal of radius r . S_∞ is the solubility of an infinitely large crystal ($r = \infty$), M is the molar weight, ρ is the density, γ is the crystal/solvent interfacial energy, R is the gas constant, and T is the absolute temperature. Different approximations can be obtained with these different particle sizes are not spheres, and γ values are different for different crystal faces. Table IX shows the effect of particle size on the solubility for various particles. It is evident that with particles of small size, S values become appreciably greater than those for large particles, hence the tendency for very fine particles to grow at the expense of larger particles. This difference in solubility explains why very fine particles of certain substances.

IX—Solubility of Small Particles

r (m)	S/S_∞
1	7.12 S_∞
0.1	1.01 S_∞
0.01	1.001 S_∞

$\gamma = 100 \text{ ergs/cm}^2$, $\rho = 1$

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 flocculated, and settle relatively slowly, they can form cake at the bottom of the container when they eventually settle. Such a sediment can be extremely difficult to dispense.

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

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

Flocculation and Deflocculation—Zeta potential is a measurable indication of the potential existing at the surface of a particle. When ψ_z is relatively high (25 mV or more) repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be *deflocculated*. Even when brought 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 lowering of ψ_z . At some concentration of the added electrolyte the forces of repulsion are lowered sufficiently to allow forces of attraction to predominate. Under these conditions particles may approach each other more closely and form aggregates, termed flocs. Such a system is said to be *flocculated*.

Some workers restrict the term *flocculation* to the agglomeration 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 potential energy curve of two interacting particles and coagulation as aggregation in the primary minimum. In this chapter the term *flocculation* is used for all aggregations, irrespective of mechanism.

The continued addition of the flocculating agent can lead to the above process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anionic particles can lead to deflocculation. The addition of more anions can lead to flocculation. The addition of more cations can lead to deflocculation. This has been achieved with the required magnitude, deflocculation can occur again. The only difference from the starting suspension 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.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.