Use of the Derjaguin, Landau, Verwey, and Overbeek Theory to Interpret Pharmaceutical Suspension Stability

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Abstract □ Earlier work on the coagulation of drug suspensions is extended to other types of drugs and electrolytes. The coagulation mechanism is interpreted using the Derjaguin, Landau, Verwey, and Overbeek theory to predict energy of interaction curves. It is suggested that coagulation occurs at the primary minimum but that the depth of this is restricted due to steric stabilization by the surfactant film. A quantitative estimation of this stabilization is made using a recently published technique. The practical implications of these findings for the pharmaceutical formulator are discussed.

Keyphrases □ Suspensions, pharmaceutical—stability □ Coagulation—suspensions □ Interaction energies—computer prediction □ Stability, suspension—theory, experimental findings

The formulation of a solid-in-liquid drug suspension, which will remain free from impaction on storage, presents a challenging problem to the development pharmacist. One method which has been suggested for approaching this problem has been to use the principle of controlled flocculation (1). Although some workers (2) have questioned whether this procedure can be applied to macroscopic particles, the present authors have shown (3) that both flocculation, probably involving chemical bridging, and coagulation, resulting from zeta potential reduction, can be used to prevent impaction. It has also been shown (4) that comparisons may be made between coagulation in model monodisperse systems and in heterodisperse drug suspensions.

It has been demonstrated previously (3) that Brownian motion and differential sedimentation rates can cause particle collisions and, in the present paper, the coagulation mechanism is investigated further in terms of energy of interaction curves. Earlier work on flocculation and coagulation in suspensions of griseofulvin by aluminum chloride is extended to a sulfonamide (sulfamerazine) and a corticosteroid (hydrocortisone). Coagulation by mono- and divalent electrolytes is also examined to determine the extent of applicability of the Schultze-Hardy rule to supracolloidal suspensions.

THEORY

The theory which describes quantitatively the stability of lyophobic colloids and which enjoys almost universal acceptance is that propounded by Derjaguin and Landau (5) and, independently, by Verwey and Overbeek (6). This theory, known as the D.L.V.O. theory, involves a comparison of the forces of electrostatic repulsion and of van der Waals attraction. The theory ignores the effect on stability of materials such as polymers but, within this restricted framework, it provides an extremely useful basis for understanding stability phenomena.

Potential Energy of Electrostatic Repulsion—The potential energy of repulsion V_R may be expressed in D.L.V.O. theory by the following equation:

$$V_R = \epsilon a \psi_\delta^2 \exp(-Kh)/[(h/a) + 2] \qquad \text{(Eq. 1)}$$

where ψ_δ = the potential at the Stern layer which is usually identified with the experimentally determined zeta potential; a = the particle radius; K = the Debye-Hückel thickness; h = the interparticular distance; and ϵ = dielectric constant. Equation 1 holds for small Ka values and small potentials. For large Ka values and $\psi_\delta < 50$ mv., a condition which may be expected in many pharmaceutical suspensions, Kruyt (7) has given the following approximate expression:

$$V_R = \frac{\epsilon a \psi_\delta^2}{2} \ln[1 + \exp(-Kh)] \qquad \text{(Eq. 2)}$$

van der Waals Attraction—It was suggested by Kallman and Willstatter (8) that the attractive forces between colloidal particles could be quantitized by integrating the van der Waals attraction between their constituent atoms or molecules. Although the attractive potential energy between two atoms is low and decays with the inverse sixth power of the distance, it was shown by de Boer (9) and Hamaker (10) that the total interaction energy between two colloidal particles was sufficient to compete with double-layer repulsion.

The expression derived for the attraction energy, V_A, is

$$V_A = -\frac{Aa}{12h} \qquad \text{(Eq. 3)}$$

where A is the Hamaker constant describing the attraction between two similar particles in a given medium and h is the distance between the particles. This simple equation is not valid when the London forces operate over distances comparable with or larger than 0.1 λ where λ is the wavelength of intrinsic oscillations of the atoms. This is due to the "retardation effect" which is caused by the finite time necessary for electromagnetic waves to travel from one atom to the other atom in which it is inducing a dipole.

Schenkel and Kitchener (11) have analyzed the retardation effect and have derived empirical equations which enable attractive energies to be calculated allowing for this effect. These may be applied to coarse suspensions and aerosols. The equations are:

$$V_A \text{ (fully retarded)} \simeq -(2.45Aa)/(120\pi h^2) \qquad \text{(Eq. 4)}$$

$$V_A \text{ (partially retarded)} = -\frac{Aa}{\pi}\frac{2.45\lambda}{120h^2} - \frac{\lambda^2}{1045h^2} + \frac{\lambda^3}{5.62 \times 10^4 h^4} \qquad \text{(Eq. 5)}$$

Equation 4 may be usefully applied for particle separations greater than 150 Å and Eq. 5 for shorter distances.

Total Energy of Interaction—Since the repulsive and attractive energies are in the same units, they may be summated to produce total energy of interaction curves:

$$V_{\text{total}} = V_A + V_R \qquad \text{(Eq. 6)}$$

These may be of three general types and are illustrated in Fig. 1.

Curve A pertains when $V_R \gg V_A$, *i.e.*, where there is a large repulsive potential at the double layer. In such cases the dispersion will be indefinitely stable provided that the particles are not sufficiently large to sediment under gravity. Curve B shows a high potential barrier which must be surmounted if particles are to approach sufficiently closely to enter the deep primary energy minimum P. If the height of this barrier V_M greatly exceeds the mean thermal energy of the particles, they will not be able to enter P. The value of V_M necessary to prevent this is considered to be approximately 10–20 kT [Napper (12)], corresponding to a zeta potential of approximately 50 mv. The curve reaches a minimum at P, a very small interparticular distance, because of the Born repulsion between adjoining electron clouds.

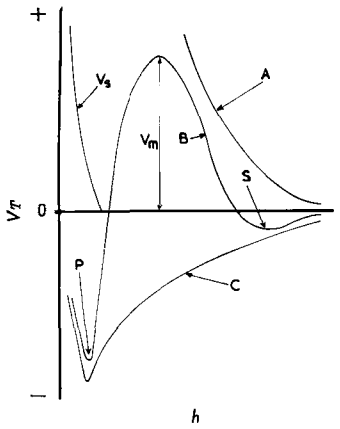

Figure 1—*Total energy of interaction between two particles,* V_T *as a function of interparticulate distance* h.

Curve *B* also has a secondary minimum, *S*, at greater distances; if this is deep enough, approximately 5 kT or greater, loose coagulation is possible. Aggregates formed by particles in the secondary minimum would be readily broken up by dilution or shaking. Schenkel and Kitchener (11) showed that 10-μ polystyrene particles were able to undergo secondary minimum coagulation.

When Curve *C* pertains, the London attraction completely overwhelms electrostatic repulsion and rapid coagulation occurs.

Other Stabilizing Mechanisms—It has been known for many years that substances such as nonionic surfactants may, if adsorbed at the particle surface, stabilize a dispersion in the absence of a significant zeta potential. The structure of various types of adsorbed layers has been considered by Ottewill (13). Early attempts to quantize the steric stabilization due to an adsorbed film have been summarized by Lyklema (14). A more recent approach is that of Ottewill and Walker (15) whose method has been used in the present paper.

The shape of the potential energy of steric stabilization curve V_S is shown also on Fig. 7 (15). It possesses a sharp cutoff at an interparticular distance of $2d$, where d is the thickness of the adsorbed layers and is approximately equal to the fully extended surfactant chain length at nearly monolayer coverage. These authors have studied the effect of a film of the nonionic surfactant $C_{12}H_{25}(OC_2H_4)_6OH$ on the stability of polystyrene latex. It was realized that there are distinct similarities between this surfactant and the anionic alkyl ether sulfates used by the present authors. It is reasonable to suppose that if the repulsion due to the anionic grouping is neutralized by a polyvalent cation, the surfactant will behave similarly to a nonionic. Ottewill (20) has suggested that the same treatment could be applied quantitatively to the system used above with modifications for the shorter chain length of $C_{12}H_{23}(OC_2H_4)_2SO_4$. The repulsive force V_S due to the adsorbed film is expressed in the equation:

$$V_S = \frac{4\pi C^2}{3V_1\rho_2^2}\left(\psi_1 - \chi_1\right)\left(d - \frac{h}{2}\right)^2\left(3a + 2d + \frac{h}{2}\right) \quad \text{(Eq. 7)}$$

where C is the concentration of surface-active agent in the adsorbed layer, V_1 is the molecular volume of the solvent molecules,[1] ρ_2 is the density of the adsorbed film, ψ_1 is an entropy parameter, χ_1 is a dimensionless quantity characterizing the interaction energy of the surface-active agent, d is the length of the surfactant molecule, h is the distance between the particles, and a is the particle radius.

EXPERIMENTAL

Materials—Griseofulvin, fine and coarse particles, ammonium dioxyethylated dodecyl sulfate (ADDS), sodium dioxyethylated dodecyl sulfate (SDDS), and aluminum chloride were those described earlier (3, 4, 16). Sulfamerazine BPC 1954 (Ferryman & Co. Ltd.), m.p. 236° (BPC 1954, 235–239°), specific gravity 1.393, specific surface area 0.60 m.²/g., determined on the Fisher subsieve sizer (16). Hydrocortisone BP (micromilled, Merck Sharp and Dohme Ltd.), m.p. 213.5° (BP 1968, 214°), specific gravity 1.277 ("Merck Index" gives 1.289 for the acetate), specific surface area 5.53 m.²/g. (16). Sodium chloride, calcium chloride (British Drug Houses, Ltd.) Analar. Distilled water was freshly redistilled from an all-glass still immediately prior to use.

Methods—Suspensions were prepared as described previously (4). They were stored in 100-ml. measuring cylinders at laboratory temperatures. Sedimentation volumes were measured as before (4); they are expressed as percentages. Sedimentation volume is defined as the ratio of the ultimate settled height, H_u, to the original height, H_o. Zeta potentials were measured also as before (4).

RESULTS AND DISCUSSION

Effect of Electrolyte Valency on Coagulation—Moderately acidic pH values were necessary (3, 4) for aluminum chloride to induce coagulation because of precipitation of aluminum hydroxide above pH 4.0. This indicated that the coagulation principle might not be applicable to pharmaceutical suspensions, even if problems of taste and toxicity could be overcome. It was decided, therefore, to see whether a divalent or monovalent electrolyte could produce the same effect. Since the earlier experiments had indicated that the mechanism involved was probably similar to that in colloids, it was realized that greater concentration of lower valency electrolytes would be necessary.

To determine whether pH would significantly affect coagulation with these electrolytes, the experiments were performed at pH 3.0 and at natural pH (5–6). Sodium chloride and calcium chloride were chosen as electrolytes and the technique used was as described before (4). The results are shown in Fig. 2, together with the results on aluminum chloride at pH 3.0 for comparison. The results indicate that pH has little effect on the coagulation produced by these salts. The minimum concentration of electrolyte required to produce maximum coagulation was molar for the monovalent salt, 5×10^{-2} *M* for the divalent, and 5×10^{-4} *M* for the trivalent. These are in the ratio of 100:5:0.05 which is in reasonable agreement with the Schultze-Hardy rule values of 100:1.6:0.13. It was noticed that the results obtained with calcium chloride were similar to those obtained with the other electrolytes, *i.e.*, that concentrations of electrolyte greater than the critical value produced little further increase in sedimentation volume. However, with the maximum concentration of calcium chloride employed, 2 *M*, a sudden further increase in sedimentation volume occurred. Since no compatibility tests had been performed with ADDS and mono- and divalent electrolytes, the suspensions experiment was repeated leaving out the griseofulvin.

It was noticed that this large concentration of calcium chloride, 2 *M*, produced a distinct opalescence whereas all of the other solutions remained clear. This precipitation of the surfactant was evidently the cause of the increase in sedimentation height, and this point on the curve can be considered as the point of transition between a coagulation and a flocculation reaction (3).

Reversibility of Coagulation in Suspensions—If coagulation in the system investigated above is dependent primarily on the effect of the cations on the repulsive potential caused by the surfactant, and

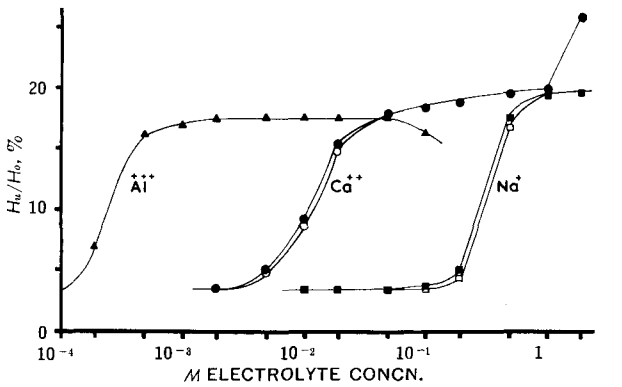

Figure 2—*Coagulation of fine-particle griseofulvin in* 10^{-3} M *ammonium dioxyethylated dodecyl sulfate by aluminum, calcium, and sodium chloride. Key: solid symbols, pH 3.0; open symbols, natural pH.*

[1] This is given as v_1 in the paper which would be the volume fraction of the solvent, but this is a misprint (20).

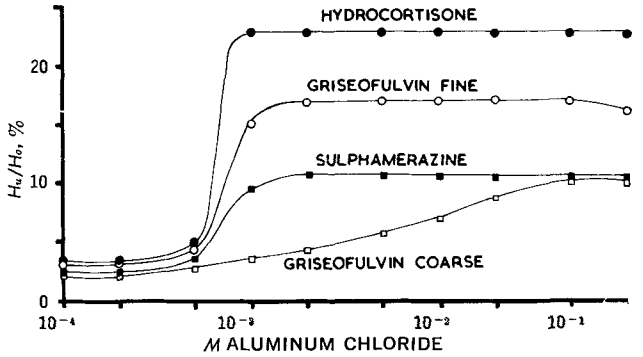

Figure 3—*Coagulation of several drugs in 10^{-3} M ammonium dioxyethylated dodecyl sulfate by aluminum chloride at pH 2.0.*

if no precipitation reaction occurs, the phenomenon should be reversible. This was investigated by preparing a 2.5% suspension of fine-particle griseofulvin in 10^{-3} *M* SDDS and adding 10^{-3} *M* aluminum chloride. The suspension became coagulated and sedimented to leave a clear supernatant. After storage overnight the suspension had a sedimentation volume of 18%. The supernatant (80 ml.) was decanted and replaced by 80 ml. of 10^{-3} *M* SDDS solution at the same pH (4.3). The suspension was redispersed and allowed to sediment again. The suspension was observed to be a typical uncoagulated dispersion and sedimented slowly leaving an opalescent supernatant. After 2 weeks the sedimentation volume was 5.0% and the griseofulvin had impacted on the base of the cylinder. This was considered good evidence that coagulation is reversible and that no irreversible reaction occurs between the surfactant and the electrolyte.

Coagulation in Suspensions of Other Drugs—Since Haines and Martin (1, 17) and Wilson and Ecanow (2) have studied sulfamerazine suspensions, it was decided to extend these investigations to this drug also. Hydrocortisone was also selected as a representative of another important class of drug, which is formulated as suspensions. It was found that ADDS wetted both of these materials at the previously used concentration, 10^{-3} *M*, so suspensions were prepared as before at pH 2.0. The results are shown in Fig. 3, together with results on coarse and fine griseofulvin taken from *Reference 4* for comparison.

The shape of the sedimentation volume–electrolyte concentration graph is identical in each case, the only real difference being the heights of the plateaus. These were, in order of increasing height, griseofulvin coarse particle, sulfamerazine, griseofulvin fine particle, and hydrocortisone. It was considered that this difference between drugs was probably a reflection of their particle sizes and, since the specific surface area was considered to be the most appropriate parameter for comparison, this was determined for each on the Fisher sub-sieve sizer. The results are shown in Table I.

The results confirm that the height of the sedimentation curve plateau is a function of the particle size, although other properties such as the contact angle between the drug and the surfactant may have some influence. This same phenomenon has also been reported in suspensions of inorganic salts by Wolf and Kurtz (18). These results suggest that coagulation can be applied to a wide range of insoluble drugs as a formulation technique.

Interpretation of Coagulation in Pharmaceutical Suspensions by Means of the D.L.V.O. Theory—A number of attempts have been made in the literature to relate the stability of monodisperse latex suspensions to the D.L.V.O. theory, *e.g.*, Schenkel and Kitchener

Table I—Specific Surface Area Results on Drugs Used in Suspension Studies

	Griseofulvin Coarse[a]	Sulfamerazine	Griseofulvin Fine[a]	Hydrocortisone
Specific Surface Area, $m.^2/g.$	0.38	0.60	1.32	5.53

[a] Taken from *Reference 4*.

Table II—Data Used in Determining the Potential Energy of Repulsion

Suspension	Concentration of $AlCl_3$, *M*	Condition	Sedimentation Volumes, %	Debye-Hückel *K*, cm.	Zeta Potential, mv.
1	10^{-5}	Uncoagulated	3.5	1.287×10^6	−46.4
2	10^{-4}	Uncoagulated	4.0	1.835×10^6	−32.7
3	10^{-3}	Coagulated	17.0	3.565×10^6	−17.0
4	10^{-2}	Coagulated	17.5	9.046×10^6	−4.5

(11) and Ho and Higuchi (19). As far as is known, however, no published attempts have been made to compare coagulation in pharmaceutical suspensions with this theory.

Equation 6 can be combined with Eq. 7 to give an expression for the total energy of interaction:

$$V_{total} = V_A + V_R + V_S \qquad \text{(Eq. 8)}$$

A computer program was written to evaluate V_{total} from these equations using the following data.

V_A—The Hamaker constant *A*—Two values of this have been taken, 10^{-13} and 5×10^{-13}, which are stated to be reasonable values for an organic substance in water (11, 19). The Hamaker constant for the surfactant film has been assumed to be the same as for the solvent.

The characteristic wavelength λ of intrinsic oscillations of the atoms was assumed to be 10^{-5} cm. (19).

The particle radius *a*—Three values were studied, 0.5, 1.0, and 2.5 μ. The results are expresssed for particle diameters.

The interparticulate distance *h*—Values from 10 to 800 Å were studied.

V_R—The dielectric constant was taken as 78.54. Since ψ_δ is difficult to determine experimentally, it was approximated to the zeta potential. Watillon and Joseph-Petit (21) have listed papers where this approximation is made.

Four suspensions were prepared containing 2.5% w/v fine particle griseofulvin and 10^{-3} *M* SDDS. The concentrations of aluminum chloride were 10^{-5}, 10^{-4}, 10^{-3}, and 10^{-2} *M*, and suspensions were left at their natural pH values. Zeta potentials and sedimentation volumes were measured as before and the results are shown in Table II.

V_S—The chain length *d* of the surfactant was calculated from molecular models. It was found to be about 25 Å. All other data were taken from Ottewill and Walker (15): $C = 0.26$ g./ml., $\rho_2 = 1.0$ g./ml., $\psi_1 = 0.5$, and $\chi_1 = 0.25$.

The curves obtained for 1-μ particles are shown in Figs. 4 and 5, and the complete results showing the position and depth of the various minima are given in Table III.

The results indicate that, regardless of which value of the Hamaker constant is used, Suspensions 1 and 2 should be highly uncoagulated. This is found in practice. If the higher value of *A* is taken, a secondary minimum should occur between particles in Suspension 2. Verwey and Overbeek (6) give an example of a suspension of 1-μ

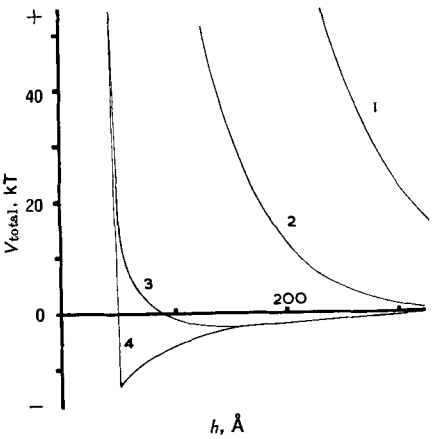

Figure 4—*Total energy of interaction curves for particles of 1-μ diameter in Suspensions 1–4. Hamaker constant:* $A = 10^{-13}$.

Table III—Depth and Position of Primary and Secondary Minima in the Energy of Interaction Curves for Griseofulvin Suspensions

Suspension and Zeta Potential, mv.	Hamaker Constant, $A = 10^{-13}$					
	$d = 1\ \mu$		$d = 2\ \mu$		$d = 5\ \mu$	
	Primary Minimum	Secondary Minimum	Primary Minimum	Secondary Minimum	Primary Minimum	Secondary Minimum
46.4[1]	—	—	—	—	—	—
3.27[2]	—	—	—	—	—	—
17.0[3]	—	−1.82 kT 150 Å	—	−3.61 kT 150 Å	—	−9.0 kT 150 Å
4.5[4]	−12.9 kT 50 Å	—	−25.8 kT 50 Å	—	−64.5 kT 50 Å	
46.4[1]	—	—	—	—	—	−3.1 kT 700 Å
32.7[2]	—	−1.91 kT 360 Å	—	−3.82 kT 360 Å	—	−9.6 kT 360 Å
17.0[3]	−41 kT 50 Å	—	−83 kT 50 Å	—	−206 kT 50 Å	
4.5[4]	−65 kT 50 Å	—	−130 kT 50 Å	—	−325 kT 50 Å	

particles in a solution of 10^{-3} M 1:1 electrolyte where there was a secondary minimum of 6 kT and where loose coagulation could occur. The secondary minimum found above reached a depth of 9 kT for 5-μ radius particles, and this might be an explanation of the slight increase in sedimentation volume that occurred in this suspension (see Table II).

Suspensions 3 and 4 were found in practice to be coagulated to practically the same extent; *i.e.*, they had similar sedimentation volumes and similar redispersibility characteristics. The energy of interaction curves should therefore be very similar in shape. This is only possible if the higher value of the Hamaker constant is taken. If the lower value is taken, Suspension 3 still has a very high maximum and a secondary minimum of similar depth to Suspension 2 described above.

With the value of A of 5×10^{-13}, Suspensions 3 and 4 both show coagulation in the primary minimum but the depth of this is restricted due to the contribution of V_S, which is zero at 50 Å but rises rapidly at lower interparticulate distances. The primary minimum would otherwise plunge to many hundreds of kT at interparticulate distances of about 10 Å. Coagulation in the primary minimum in colloidal suspensions is usually accepted to be irreversible. It was pointed out by Hamaker (22) that the frictional and inertial forces exerted by shaking increase much more rapidly with particle size than forces of adhesion. He gave an example of a suspension of 1-μ particles where the depth of the minimum was about 25 kT or 10^{-12} ergs. Hamaker calculated that a force of 10^{-6} dyne or 10^{-9} g. would be necessary to supply this energy over a distance of 10^{-6} cm. This, he pointed out, was equivalent to 300 times the particle weight. He stated: "Whether it is actually possible to supply forces of this order of magnitude by shaking is, in itself, open to question, though it is not excluded."

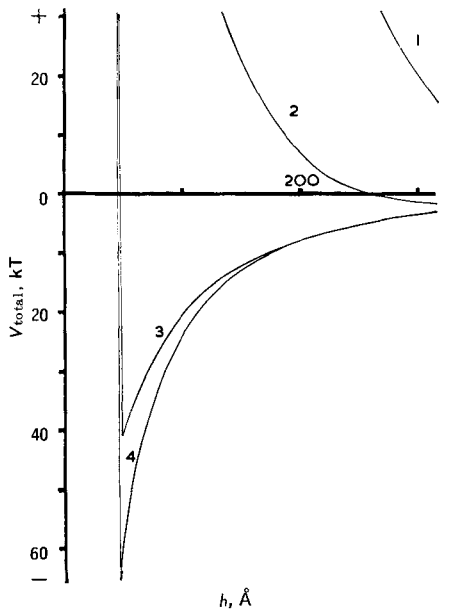

Figure 5—*Total energy of interaction curves for particles of 1-μ diameter in Suspensions 1–4. Hamaker constant:* A = 5×10^{-13}.

The situation would appear to be very similar in the suspensions described above. It should be stressed, however, that because of the irregular shape of the particles and the very open structure of the coagulated cake, the number of points of contact will be very small. In addition to this, surface irregularities, impurities, or sorption of the surfactant in the micellar form may prevent particles from approaching even to a distance of 50 Å and, if this situation pertains, the depth of the minimum will be restricted even further.

These results may also explain why the sedimentation volume–electrolyte concentration graph exhibited a rapid change with fine-particle griseofulvin and a more progressive change with the coarse-particle material. Examination of the two drugs under a microscope showed that the particles in the fine sample were very smooth, whereas in the coarse drug they were much rougher. This might enable the particles in the fine material to approach each other to within the surfactant-restricted primary minimum at a lower concentration of electrolyte than in the case of the coarse particles.

Rheological Examination of the Coagulated Suspensions—It was considered that examination of these suspensions in a viscometer, with a means of applying a variable shear rate, would provide evidence of the interparticular forces occurring in them. Although a Haake Rotovisco apparatus was available, there was no suitable attachment for handling these suspensions.[2] Samples were therefore sent to Baird and Tatlock Ltd. Suspensions 1–4 were prepared as before but the concentration of fine-particle griseofulvin was increased to 25% w/v to give a suitable reading on the instrument. Four readings were taken at different shear rates and commencing with the largest shear rate. The results are shown in Table IV.

Although these results are not conclusive, they do agree with the earlier data. Suspensions 1 and 2 are both basically Newtonian and show the same viscosity at all shear settings. Suspensions 3 and 4 both exhibit pseudoplasticity or plasticity, and there is very little difference between the readings obtained from each. The results on Suspensions 3 and 4 tend to confirm that there are attractive forces holding the particles together but that these forces can be overcome by the application of shear and the suspension can become more fluid. The absence of a complete set of results for increasing and decreasing rates or shear means that it is impossible to tell if the systems are thixotropic. There is clearly scope for further work on the rheology of coagulated suspensions.

[2] The authors thank J. K. Watkins of Baird and Tatlock Ltd., London, for the rheological measurements on the Haake Rotovisco apparatus.

Table IV—Rheological Examination of Griseofulvin Suspensions

Suspension	Shear Rate, sec.$^{-1}$	Viscosity, c.p.s.
1	2620	2.74
	1310	2.74
	873	2.75
	436	2.58
2	2620	2.67
	1310	2.86
	873	2.83
	436	2.83
3	2620	5.08
	1310	5.99
	873	6.94
	436	9.55
4	2620	5.31
	1310	6.20
	873	7.16
	436	9.78

CONCLUSIONS

It is considered that these results provide a good semiquantitative explanation of the coagulation phenomena found, if allowance is made for all the nonideal factors which occur in these suspensions and for the likely errors in ascribing values to some of the parameters.

The following guidelines may be set out for the formulation of a suspension by the coagulation technique.

1. Select a nontoxic anionic surfactant which will wet the drug or drugs and determine the minimum concentration needed. It is desirable to choose a surfactant of an appropriate chain length to ensure that the depth of the energy of interaction curve minimum is of the right order in comparison with the size of the particles. Test the electrolyte for compatibility with the surfactant.
2. Select a suspending agent, if necessary, which will not interact with the surfactant or coagulating electrolyte.
3. Add just sufficient of the electrolyte to produce coagulation in the surfactant-restricted primary minimum.
4. Ensure that the balance between the attractive and repulsive forces is not altered by any additional excipients such as color or preservatives.
5. The state of the coagulated suspension after a comparatively short interval may be considered as a good guide to the long-term storage results of such a suspension. The type of quality control standards applicable to such a suspension are:

(*a*) Control of the particle size of the suspended material by a Coulter counter, Fisher sub-sieve sizer, or other techniques.

(*b*) Measurement of the zeta potential of the final suspension. The standard should probably be a maximum value since the work described above has suggested that further lowering of the parameter has little effect on the nature of the system.

(*c*) Determination of the ratio between the H_u/H_o values of a coagulated and uncoagulated suspension.

(*d*) Evaluation of the rheological properties of the suspension.

(*e*) Measurement of redispersibility after storage.

It is believed that the work in this paper has shown that an adequate comprehension of the interfacial properties of suspensions enables their formulation to be approached from truly rational principles rather than by empirical techniques. As Elworthy (23) has remarked: "The principal point is to understand the interparticulate forces in order to be able to control them." It is the hope of the authors that this paper has contributed, in some measure, to an increase in the understanding of these forces as they affect the interfacial properties of pharmaceutical suspensions.

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