Some Studies of Flocculation Phenomena in Pharmaceutical Suspensions

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The increasing use of suspensions as a form of pharmaceutical preparation has emphasized the need for further evaluation of the factors controlling the physical stability of these systems. A number of attempts have been made recently to prevent impaction of suspensions by controlled flocculation with polyvalent ions. This paper reports the use of a number of experimental techniques, including micro-electrophoresis, the Coulter counter, and standardized stability methods, in studies of the effect of a number of variables upon flocculation and sedimentation, in some systems of pharmaceutical interest.

THE PHYSICAL STABILITY of pharmaceutical suspensions has been the subject of a number of recent research and review articles (1–13). Several workers have found that controlled flocculation is a particularly useful technique for formulating pharmaceutical suspensions, which do not impact on storage (5). In this paper the authors report investigations of flocculation, by polyvalent ions, of an important synthetic drug, griseofulvin, and of a monodisperse model system. Because griseofulvin, like many other modern drugs, is hydrophobic in nature, it was found necessary to include wetting agents. Doscher (14) found that nonionic wetting agents caused changes in flocculation without affecting zeta potential. In this study anionic wetting agents, which have been shown not to precipitate with the flocculating ions, have been selected.

Aluminum chloride was selected as the flocculant since a 3:1 electrolyte was required and aluminum is probably the most suitable trivalent metal with regard to toxicity. Other workers in this field (15) have shown that, above pH 4, hydrolysis products of aluminum ions cause peptization of colloidal systems because of charge reversal. At pH 3 and below, however, the Al^{3+} ion causes flocculation. Experiments were, therefore, restricted to this pH region, although it was realized that a somewhat higher pH value would probably be more suitable for a pharmaceutical formulation.

The effect of a number of variables upon flocculation have been investigated by microelectrophoretic measurement of zeta potential, determination of sedimentation volumes, redispersibility, and stability ratios.

EXPERIMENTAL

Materials—The drug, griseofulvin[1] (16), was chosen for this study because, (a) it is available commercially in two particle sizes (17) of mean particle diameter about 4 and 15 μ, (b) it has a low water solubility, (c) it is stable chemically in aqueous suspension, (d) the molecule has no ionic groupings which could react with polyvalent ions of opposing charge, (e) the powdered drug is difficult to wet and thus is likely to present problems to the formulator, and (f) the drug is often given over long periods of time and a suspension is thus a suitable dosage form, especially for pediatric use.

A total of seven anionic surfactants was screened for possible precipitation with the flocculant by preparing 0.1% solutions of surfactants containing 0.1% aluminum chloride. After storage for 1 week at 25°, solutions of the following surfactants, sodium isopropyl naphthalene sulfonate,[2] sodium dioctyl sulfosuccinate,[3] sodium dodecyl sulfate,[4] and sodium alkyl naphthalene sulfonate[5] showed opalescence. However, solutions of sodium diamyl sulfosuccinate,[6] ammonium lauryl ether sulfate,[7] sodium lauryl ether sulfate,[8] and the sodium salt of sulfated lauryl alcohol ethoxylate[9] remained clear. Further tests for precipitation at high electrolyte concentration and evaluation of wettability with respect to griseofulvin showed that ammonium lauryl ether sulfate was a very suitable surfactant for this study.

The aluminum chloride[10] used in this investigation was reagent grade $AlCl_3 \cdot 6H_2O$. All solutions were prepared with glass-distilled water.

Preparation of Suspensions—The drug was dispersed in solutions of the wetting agent by means of a Silverson[11] mixer/emulsifier. Suspensions were refined for 20 min. and then made up to 90% of the

[1] The authors thank Glaxo Ltd., England, for the gift of generous supplies of griseofulvin.
[2] Aerosol O.S., Cyanamid.
[3] Manoxol O.T., Hardman and Holden.
[4] Sodium lauryl sulfate B.P., Sipons.
[5] Nansa BXS, Marchon.
[6] Aerosol A.Y., Cyanamid.
[7] Empicol EAB, Marchon.
[8] Empicol KSN 27, Marchon.
[9] Empicol ESB3, Marchon.
[10] British Drug Houses, Ltd.
[11] Silverson Ltd., London, England.

final volume. Ninety-milliliter quantities of the suspensions were distributed into 100-ml. graduated cylinders, 10 ml. of the flocculating electrolyte solution at 10 times the required flocculant concentration was added, the cylinders stoppered and shaken. After storage at $25 \pm 0.5°$ for 3 days, the suspensions were examined.

Measurement of Sedimentation Volume—The sedimentation volumes were recorded in terms of the ultimate settled height, H_u, to the original height, H_o, as suggested by Robinson (18) and Ward and Kammermeyer (19).

$$\text{sedimentation volume} = H_u/H_o \quad \text{(Eq. 1)}$$

Measurement of Redispersibility—To standardize evaluation of redispersibility, a machine was constructed which would turn the cylinders through 360° at a constant speed of 20 r.p.m. Experimentation showed that this speed was the optimum for the supernatant liquid to strike the sediment with the maximum force at each revolution. The number of revolutions necessary to restore the suspension to homogeneity was recorded. This design is similar to that described by Lesschafft and De Kay (20), but their apparatus measured redispersibility by shaking the suspensions in a 90° arc not by complete revolution.

Measurement of Electrophoretic Mobility—Electrophoretic mobilities were measured in a flat electrophoresis cell[12] of rectangular cross-section similar to that originally described by Abrahamson (21, 22). The calibration and use of this type of cell has been discussed by Black and Smith (23, 24) and Haines and Martin (6).

The dimensions of the flat portion were 2.11 × 0.51 cm. and the electrodes were zinc/zinc sulfate. A M 2150F2[13] research microscope, fitted with a ×1.5 binocular body and ×17 eyepieces, was used to view the particles. Objectives used were ×10 or ×20 with a long working distance. The uniformity of the fine adjustment of the microscope was checked by recording the thickness of a glass cover slip coated with lycopodium powder over different regions of the fine adjustment. Measurements were made using the most uniform region. Brinton and Lauffer (25) have discussed the need for temperature control and conclude that electrophoretic velocity at constant current is independent of temperature changes within a range of 10°, so that the cell needs to be thermostated only to remove excess heat in order to prevent convection. The flat area of the cell was therefore immersed in a thermostatic bath which was maintained at $25 \pm 0.2°$, by means of circulated water. The power source was a Shandon[14] Vokam power supply unit type 2541, which could be maintained at constant current. The field strength was determined by measuring the current in the cell by means of a multirange milliameter and a Pye[15] conductance bridge and conductivity cell to record the conductivity of the suspension. The field strength was calculated by substitution into Ohm's law. The position of the stationary layers of the cell was calculated by Komagata's equation (26).

$$a = {}^1/_2 \pm \sqrt{{}^1/_{12} + 32/\pi^5 k} \quad \text{(Eq. 2)}$$

where a is the fractional depth from the top of the cell and k is the cell width/depth ratio.

This was checked by recording the mobility of human erythrocytes in 0.067 M standard phosphate buffer at pH 7.4 at the lower stationary level. Abrahamson (21, p. 257) has reported a standard mobility of $-1.31 \mu/\text{sec./v./cm.}$ which is independent of age, race, sex, or blood group. Results obtained on two separate occasions were -1.29 and -1.31 $\mu/\text{sec./v./cm.}$ All measurements were subsequently made at this lower stationary level. For each measurement 20 particles were timed (10 in each direction) over a suitable number of squares in the eyepiece graticule. Times were recorded on a stopwatch, accurate to 0.1 sec.

The cell was cleaned regularly with chromic acid and rinsed with distilled water and acetone between measurements. Great care was taken to avoid air bubbles and the cell was filled and emptied by displacement using vacuum.

Visual Examination of Supernatant—The supernatants of the stored suspensions were examined for evidence of opalescence caused by very small discrete particles, which are slow to settle. This is found in deflocculated suspensions, whereas when flocculation occurs, these very small particles are incorporated in the sedimenting flocs and the supernatant is clear.

RESULTS AND DISCUSSION

Calculation of Zeta Potential—From a consideration of the properties of the electrical double layer at the surface of a particle and the laws of liquid flow, the Helmholtz-Smoluchowski equation can be derived

$$\zeta = \frac{4\pi\eta\mu}{D} \quad \text{(Eq. 3)}$$

where η is the viscosity of the suspending medium, μ is the electrophoretic mobility (velocity per unit field), D is the dielectric constant, and ζ is the zeta potential.

The assumptions made in deriving this equation have been listed by Brinton and Lauffer (25, p. 431). The most important of these are: (a) The product of the Debye-Hückel constant, k, and the radius of curvature of the particle a, is large. (b) The particle surface is nonconducting.

These assumptions are made so that the electric field can be considered parallel to the surface everywhere within the double layer.

Making the assumption that the field is everywhere in the direction of the applied field, Debye and Hückel derived the following equation for spheres which is valid when ka is small:

$$\zeta = \frac{6\pi\eta\mu}{D} \quad \text{(Eq. 4)}$$

Henry (27) has derived an equation valid for any value of ka which can be expressed in the form

$$\zeta = \frac{6\pi\eta\mu}{D} f(ka) \quad \text{(Eq. 5)}$$

When ka is less than 0.1 the 6π factor holds. When ka is greater than 100 the 4π factor holds. When ka is between 0.1 and 100 values of $f(ka)$ can be calculated to correct the general equation.

Matthews and Rhodes (17) have shown that fine-particle griseofulvin has a mean diameter of 3–4 μ measured on the Coulter counter. Using a particle radius of 1.5-μ values of the factor to be used in the Debye-Hückel equation have been calculated for different concentrations of aluminum chloride. These range from 4π at 10^{-2} M and above, to 4.3π at 10^{-5} M and these values have been used in calculating zeta potentials. Similar factors were calculated by Nash and Haeger (13) for a 1:1 electrolyte and alternative correction factors for various electrolytes and for different zeta potentials have been given by Overbeek (28).

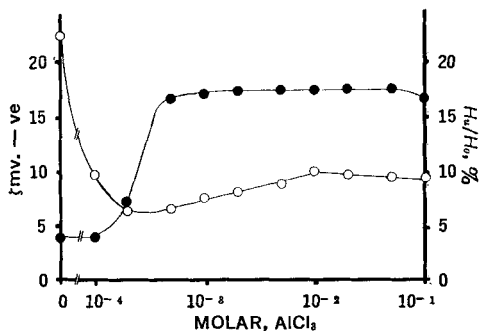**Flocculation at pH 3.0**—The results of flocculation

Fig. 1—Flocculation of fine-particle griseofulvin wetted with ammonium lauryl ether sulfate by aluminum ions at pH 3.0. Key: ●, H_u/H_o; O, zeta potential.

studies at pH 3.0 are shown in Fig. 1 and Table I, the suspension pH had been adjusted to 3.0 by addition of hydrochloric acid.

From Fig. 1 it may be observed that at this pH value, aluminum ions are very effective in causing flocculation of the suspensions. A concentration of 5 × 10^{-4} M aluminum chloride reduced the zeta potential from −22.7 mv. to −6.2 mv., increased the sedimentation volume from 3.5 to 17.0%, and produced suspensions which redispersed after a very few revolutions in the machine (Table I). Higher concentrations of electrolyte produced little further change in the sedimentation volume, but the measured zeta potential rose slightly.

Flocculation at pH 2.0—The above experiment was repeated in 10^{-2} N HCl which gave a constant pH of 2.0 in all systems. The results are given in Table II and Fig. 2.

At this electrolyte concentration, values of ka are always greater than 100 and the 4π factor was therefore used in the zeta potential equation. At this pH value, zeta potentials were greater than at 3.0 and higher concentrations of aluminum chloride (10^{-3} M) were necessary to achieve maximum flocculation. There was no point of inflection in the zeta potential curve and maximum flocculation occurred at about −15 mv. The above experiment was repeated using the coarse-particle griseofulvin (see also Table II and Fig. 2). In this system there is no sudden increase in sedimentation volume but the concentration of $AlCl_3$ at which the rise begins to occur is the same for both materials (approx. 2 × 10^{-4} M). The progressive rise in sedimentation

TABLE I—FLOCCULATION OF FINE PARTICLE GRISEOFULVIN WETTED WITH AMMONIUM LAURYL ETHER SULFATE BY $AlCl_3$ AT pH 3.0

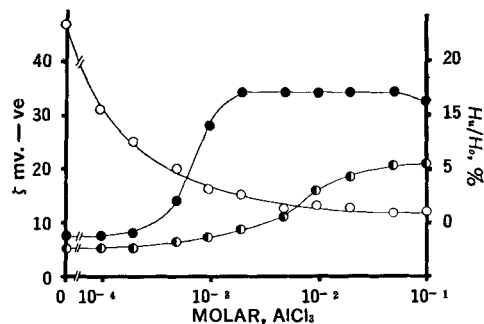| Concn. of $AlCl_3$, M	Sedimentation Volume H_u/H_o, %	Supernatant	No. Revs. to Redisperse
0	3.5	Opalescent	200+
10^{-4}	3.5	Opalescent	200+
2 × 10^{-4}	7.0	Clear	20
5 × 10^{-4}	16.5	Clear	10
10^{-3}	17.0	Clear	5
2 × 10^{-3}	17.5	Clear	5
5 × 10^{-3}	17.5	Clear	5
10^{-2}	17.5	Clear	5
2 × 10^{-2}	17.5	Clear	5
5 × 10^{-2}	17.5	Clear	5
10^{-1}	16.0	Clear	5

Fig. 2—Flocculation of griseofulvin wetted with ammonium lauryl ether sulfate by aluminum ions at pH 2.0. Key: ●, H_u/H_o fine-particle griseofulvin; ◖, H_u/H_o, coarse-particle griseofulvin; O, zeta potential fine-particle griseofulvin.

TABLE II—FLOCCULATION OF GRISEOFULVIN WETTED WITH AMMONIUM LAURYL ETHER SULFATE BY $AlCl_3$ AT pH 2.0

Concn. of $AlCl_3$, M	Fine Particle			Coarse Particle		
	H_u/H_o, %	Supernatant	No. Turns to Redisperse	H_u/H_o, %	Supernatant	No. Turns to Redisperse
0	3.5	Opalescent	200+	2.5	Opalescent	100+
10^{-4}	3.5	Opalescent	200+	2.5	Opalescent	100+
2 × 10^{-4}	4.0	Opalescent	50	2.5	Opalescent	100+
5 × 10^{-4}	7.0	Clear	26	3.0	Opalescent	70
10^{-3}	14.0	Clear	10	3.5	Opalescent	50
2 × 10^{-3}	17.0	Clear	5	4.2	Opalescent	28
5 × 10^{-3}	17.0	Clear	5	5.7	Opalescent	15
10^{-2}	17.0	Clear	5	7.0	Opalescent	12
2 × 10^{-2}	17.0	Clear	5	8.9	Clear	8
5 × 10^{-2}	17.0	Clear	5	10.0	Clear	5
10^{-1}	16.0	Clear	5	10.3	Clear	5

volume was accompanied by an increase in ease of redispersibility, but again no sudden change occurred. This change in behavior, as the particle size increased, indicated the potential utility of a comparison of flocculation of a colloidal system with the same surfactant and electrolyte combination.

Comparison with a Model Colloid—The kinetics of flocculation in colloidal systems was considered by Von Smoluchowski (29, 30) in his theory of rapid coagulation. Smoluchowski showed that when every collision between particles results in aggregation, then the coagulation time, $T_{1/2}$, or time taken for the total number of particles to fall by one-half is given by the equation:

$$T_{1/2} = \frac{1}{4\pi DRN_0} \qquad \text{(Eq. 6)}$$

where D is the diffusion constant of the particles, R is the distance between the center of two particles when flocculation occurs, and N_0 is the original number of particles.

When there is an energy barrier between the particles the rate of flocculation is reduced, since only a fraction, α, of the collisions is effective. Fuchs (31) modified Smoluchowski's theory to enable the energy barrier to be related to a reduced rate of flocculation and introduced the stability ratio, W, which is given by

$$W = 2r \int_{2r}^{\infty} \left[\exp. \left(\frac{V_t}{kT} \right) \right] \frac{dS}{S^2} \qquad \text{(Eq. 7)}$$

where r is the particle radius, S is the distance between the particle centers $= 2r$ at coagulation, V_t is the total energy of interaction between the particles, k is Boltzmann's constant, and T is the absolute temperature.

Matthews and Rhodes (32) have developed a method involving a digital computer and the Coulter counter to estimate W in flocculating monodisperse systems. The method involves comparing the experimental rate of depletion of the singlet species with that which would be expected from theory. The method has been used to investigate the flocculation of a polystyrene latex polymer in the same system of anionic wetting agent and cationic flocculant as was used for the griseofulvin.

The system selected was a 0.714-μ polystyrene latex[16] which can be considered to be on the borders of colloidal dimensions. The particles are of such low density that sedimentation can be ignored and the polymer is devoid of any ionic groupings on the particle surface and thus is a suitable model for the drug. The particles were present at a concentration of 5×10^7 per ml. Wetting agent, $3 \times 10^{-6} M$ ammonium ether lauryl sulfate, was added. The pH was standardized as before by the use of $10^{-2} N$ HCl and the concentration range of aluminum chloride was from 10^{-4} to $10^{-2} M$.

The results of the measurements of stability ratio W and zeta potential against log concentration are given in Fig. 3. The graph of log electrolyte concentration against zeta potential is a straight line, similar to that obtained by Ottewill and Watanabe (33) for a silver iodide colloid coated with an anionic surfactant. The graph of log W against log concentration of electrolyte is also characteristic
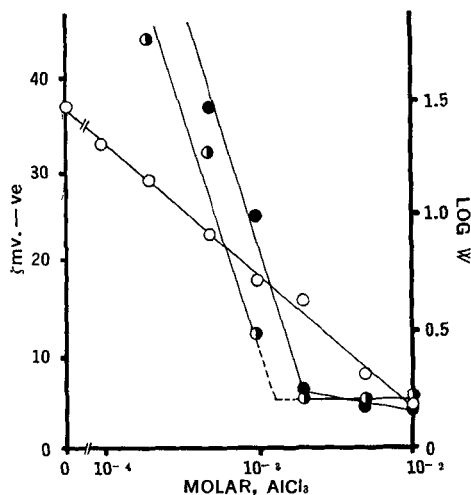

Fig. 3—Flocculation of 0.714-μ latex polystyrene wetted with ammonium lauryl ether sulfate by aluminum ions. Key: ●, log W at pH 2.0; ○, zeta potential at pH 2.0; ◑, log W at pH 3.0.

of a colloid. A rapid decrease in stability occurs at a concentration of about $10^{-3} M$ AlCl$_3$ although the value of log W does not quite reach zero as it should for a true colloid according to the Smoluchowski equation. This may be due to the presence of the surfactant or to the particle size being just above the upper limits of the colloidal range.

A comparison of the flocculation of this model colloid with that of fine-particle griseofulvin (*cf.* Figs. 2 and 3) under identical conditions reveals that the minimum concentration of electrolyte required to produce maximum flocculation is the same in each system ($2 \times 10^{-3} M$). The zeta potential at this point in each system is also identical (-15 mv.).

Measurement of stability ratio as a function of aluminum chloride concentration was also made at pH 3 and the results are also given in Fig. 3. The change from pH 2 to 3 results in a displacement of the vertical portion of the graph toward lower concentrations of electrolyte, in the same way as the vertical portion of the sedimentation height/ aluminum chloride concentration graph was changed for fine particle griseofulvin (*cf.* Figs. 1 and 2).

This is strong evidence that flocculation in systems with a mean particle size of 3 to 4 μ is essentially similar to that in colloidal systems where van der Waals forces are operative. Kruyt (34) has referred to the theoretical existence of long range London/van der Waals forces in hydrophobic suspensions in the 2–5 μ range, and has stated that flocculation is possible in the secondary minimum that occurs in the energy of interaction curve at about 1000–2000 Å. distance. The particles can, therefore, approach one another to this distance and yield a loosely flocculated structure.

It has been noted by earlier workers (8) and by the present authors that flocculation in pharmaceutical suspensions with polyvalent ions is very rapid, and Wilson and Ecanow (8), in their discussion of the earlier work of Haines and Martin (5), stated that flocculation in colloidal systems was, by contrast, a slow process depending on random collisions due to Brownian motion.

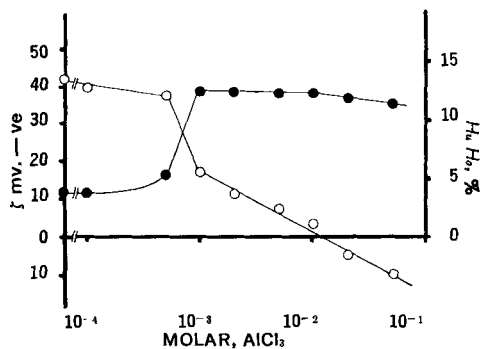The Eq. 6 for the coagulation time shows that it

Fig. 4—Flocculation of fine particle griseofulvin wetted with ammonium lauryl ether sulfate by aluminum ions at natural pH. Key: ●, H_u/H_o; ○, zeta potential in 0.1 M sodium acetate.

is dependent on the total number of particles in the system, and an estimate of the number of particles in the 2.5% w/v fine-particle griseofulvin used above was made, by performing a total count with the Coulter counter using the 30-μ orifice. This gave a value for the suspensions of 1.5×10^8 particles per ml. which would have a coagulation time of 20 min. This is quite in accord with the results obtained in the experiments, since sedimentation and heterodispersity are likely to accelerate the process and the Coulter counter is unable to detect the very fine particles of diameter less than 0.5 μ

Measurement of Zeta Potential by Dilution in Electrolyte—Because of the differences in the shape of the zeta potential/electrolyte concentration graphs between systems with different total electrolyte concentrations (*e.g.*, Figs. 1, 2), it was decided to examine the effect of diluting the suspensions in equal parts of a 1:1 electrolyte solution before measurement.

Suspensions of griseofulvin were prepared as before, using the ammonium lauryl ether sulfate wetting agent and different concentrations of aluminum chloride, but at the natural pH. For measurement of zeta potentials the suspensions were diluted with equal parts of 0.1 M sodium acetate at pH 5.0. The results are shown in Fig. 4. Good correlation between the zeta potential and sedimentation volume was observed with a rapid reduction in zeta potential and increase in sedimentation volume at 10^{-3} M aluminum chloride. Reversal of charge occurred at about 10^{-2} M, as has been noted by other workers (15) using aluminum salts with colloids. Slight reduction in the sedimentation volume occurred in these systems with a low positive zeta potential, which may indicate a small degree of deflocculation.

SUMMARY

It has been demonstrated that in suspensions with a mean particle size in the range 3–4 μ, flocculation is essentially similar in character to that in lyophobic colloids, and that such flocculation is accompanied by changes in the zeta potential of the particles.

Suspensions flocculated in this way may be readily redispersed and although the experiments quoted above only lasted 3 days, other experiments still in progress indicate that controlled flocculation in this way can produce suspensions which remain redispersible over long periods of time. Highly flocculated suspensions are somewhat inelegant due to the coarse appearance of the large flocs.

However, by controlling the amount of electrolyte, it is possible to produce suspensions with just a sufficient degree of flocculation to prevent impaction. However, these results with the different types of griseofulvin, suggest that some consideration of the particle size is necessary to decide the exact amount of electrolyte necessary. Martin (3) has also remarked that the influence of other ingredients such as flavorings, colorings, and preservatives must be considered.

The work reported in this paper strongly supports the utility of the concept of controlled flocculation in the formulation of pharmaceutical suspensions, although it is felt that further research is required into the variables involved before formulation can be placed on a truly rational, rather than an *ad hoc* basis.

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🔑 *Keyphrases*

Flocculation—suspensions
Surfactants—flocculation
pH effect—flocculation
Electrolyte effect—flocculation
Sedimentation redispersibility—suspensions
Stability ratio—suspensions
Zeta potential—suspensions