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Coagulation and flocculation in suspensions of griseofulvin and polystyrene latex

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Coagulation and flocculation mechanisms have been examined in suspensions of the drug griseofulvin containing anionic surfactants. It has been shown that both mechanisms can give suspensions which are readily redispersible but that flocculation may produce pharmaceutically undesirable effects. The differences between the two phenomena are discussed.

THE need to distinguish between coagulation and flocculation, in colloidal dispersions has been stressed by La Mer (1964). He suggested that the term "coagulation" should be restricted to aggregation involving the reduction of the repulsive potential at the double layer and that "flocculation" should be reserved for aggregation mechanisms where chemical bridging between the particles is involved.

It has been suggested (Ecanow Grundman & Wilson, 1966) that the same distinction must be applied to aggregation phenomena in pharmaceutical suspensions. They studied the physical stability of suspensions of sulphamerazine, wetted with dioctyl sodium sulphosuccinate in the presence of aluminium chloride. This system was previously examined by Haines & Martin (1961), whose conclusions had been criticized by Wilson & Ecanow (1963), because of complications due to electrolyte/surfactant precipitation.

The present paper continues earlier work, Matthews and Rhodes, (1968a, b, c) on flocculation and coagulation in pharmaceutical and model suspensions: the conclusions reached are compared with those of earlier workers.

Experimental

MATERIALS

Griseofulvin fine particle (Glaxo Laboratories, Greenford, Middlesex). m.p. 221°. $\lambda_{max}^{EtOH} = 291$ mμ, E (1%, 1 cm) = 686. Density = 1·440 (determined by sp.gr. bottle). (B.P. 1963 cites m.p. 218–224°; λ_{max} 291 mμ; E (1%, 1 cm) 686.) The particle size distribution of this material has been described by Matthews & Rhodes (1967). It has a modal particle diameter, determined on the Coulter Counter, of 3–4 μ.

Surfactants. The surfactants selected were sodium dodecyl sulphate (SDS, $C_{12}H_{25}SO_4Na$) and sodium dioxyethylated dodecyl sulphate (SDDS, $C_{12}H_{25}\cdot[O\cdot CH_2\cdot CH_2]_2\cdot SO_4Na$), which has only two oxyethylene groups more than SDS. Their chemical similarity therefore allows a direct comparison to be made between their respective properties. Matthews & Rhodes (1968b) have previously shown that SDS is precipitated in the presence of aluminium salts and is analogous to dioctyl sodium sulphosuccinate.

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SDS (Marchon Products Ltd., Whitehaven) had the following manufacturer's analysis: SDS 98·00%, free lauryl alcohol 0·66%, water content 0·72%, sodium sulphate 0·13% and sodium chloride 0·40%. This same batch of material has been shown by Barry & Shotton (1967) to contain 98·6% C_{12}, 1·0% C_{10} and 0·4% C_{14}.

SDDS (pure) was synthesized from dioxyethylated dodecanol which was shown by gas-liquid chromatography to be 98·4% pure. The ether alcohol had a hydroxyl value of 6·08% (theoretical = 6·20%); $n_D^{60} = 1{\cdot}4332$, f.p. 19°. The sodium salt of the sulphate had a sodium content of 5·90% (theoretical 6·12%) and a critical micelle concentration (determined by penacyanole titration), of $2{\cdot}58 \times 10^{-3}$M.

SDDS *commercial* (Empicol ESB3, Marchon Products Ltd). Prepared from a narrow cut lauryl alcohol, was supplied as an aqueous solution which was assayed by titration with M/500 cetrimide using methylene blue as an indicator and the pure SDS as standard. It contained 27·2% w/w calculated as $C_{12}H_{25}\cdot[O\cdot C_2H_4]_2\cdot SO_4Na$ (manufacturers' claim 27·6% w/w).

Proton magnetic resonance spectra of the pure surfactants and of the commercial sample after freeze drying, were consistent with the structures assigned.

Polystyrene Latex. A "Dow" polystyrene latex (Serva Entwicklungslabor, Heidelberg, Germany) was used as a model system. It had a quoted mean diameter of 0·714 μm (electron microscopy gave a mean diameter 0·71 μm).

Water. Distilled water was freshly redistilled from an all-glass still.

Aluminium chloride (British Drug Houses Ltd., Poole): reagent grade, $AlCl_3\cdot 6H_2O$. This was assayed before use by the B.P. 1963 method for alum.

Sodium chloride, barium chloride (British Drug Houses Ltd., Poole): Analar.

METHODS

Flocculation and coagulation in suspensions of griseofulvin and polystyrene latex have been examined by: surfactant/electrolyte compatibility using visual inspection for opalescence and precipitation; and speed of coagulation and flocculation by recording the change of the ratio of settled height to original height with time (Matthews & Rhodes, 1968b); redispersibility and coagulation rates in terms of stability ratios were determined as previously described (Matthews & Rhodes, 1968a,b).

The particle size of the griseofulvin was determined by the method of Matthews & Rhodes (1967), using a two-tube technique with 30 μm and 50 μm apertures.

Results and discussion

SURFACTANT/ELECTROLYTE COMPATABILITY

With 10^{-1}M aluminium chloride, SDS gave a definite immediate opalescence at 10^{-3}M and a flocculant precipitate at 10^{-2} and 10^{-1}M. Both samples of SDDS at the same three concentrations remained clear after one week as did controls containing surfactant and electrolyte alone.

SURFACTANT WETTING PROPERTIES

Suspensions of griseofulvin at a concentration of 2·5% w/v were prepared with the wetting agents alone to determine the optimum concentrations to use. Both samples of SDDS wetted the drug at a concentration of 10^{-3}M but SDS did not. A concentration of 10^{-2}M was effective and was used for both surfactants.

The suspensions were highly deflocculated and the particles sedimented slowly leaving an opalescent supernatant due to very small discrete particles. After storage for 1 week at 25° the sediment volume was 3·5% in both bases. More than 500 revolutions in the redispersing machine (Matthews & Rhodes, 1968b) were necessary to achieve redispersion.

SPEED OF COAGULATION AND FLOCCULATION

It has been claimed (Ecanow & others, 1966) that flocculation involving the precipitation of a surfactant by an electrolyte is a rapid reaction comparable to that of an inorganic reaction in which a precipitate results. These authors observed also that the settling rate of the suspension is *reduced* whereas when coagulation occurs, settling rates are increased and the process leads to caking of the suspension. Since sodium and potassium ions were used to induce coagulation and aluminium ions to induce flocculation, it is difficult to compare the two mechanisms absolutely.

To compare these two mechanisms in essentially similar systems, 2·5% suspensions of griseofulvin were prepared in 10^{-2}M SDS and 10^{-2}M SDDS: (since preliminary coagulation tests had shown identical results with the pure and commercial grades, the latter was used). The suspensions were made up to 90% of the final volume. Volumes of 10 ml of aluminium chloride solution at a tenfold concentration were added at zero time and the suspensions mixed by gentle inversion. Photographs of the suspensions were taken at intervals up to 1 hr and sedimentation volumes were obtained from the photographs, enabling accurate readings to be obtained at short intervals in the initial period. The results are shown in Fig. 1, together with similar readings taken on the suspensions without electrolyte. These were identical for both surfactants.

The results of the test with SDS confirm the statement by Ecanow & others (1966) that flocculation is relatively rapid but contrary to these authors, we found, with griseofulvin, an *increased* rate of settling. The reduced rate noted by Ecanow & others may be due to air entrapment and the presence of glycerol in their suspensions (see later). We found the coagulation of griseofulvin to be slower than the flocculation but only by a factor of approximately two. The aggregates in the coagulated suspension were less granular and the supernatant more opalescent. After 1 hr the sediment volumes were almost identical and only the supernatant served to distinguish them. After storage for 1 week at 25° the suspensions were almost identical apart from the slightly more granular appearance of the flocculated sediment. The sediment volumes were 14% compared with 3·5% in the absence of electrolyte.

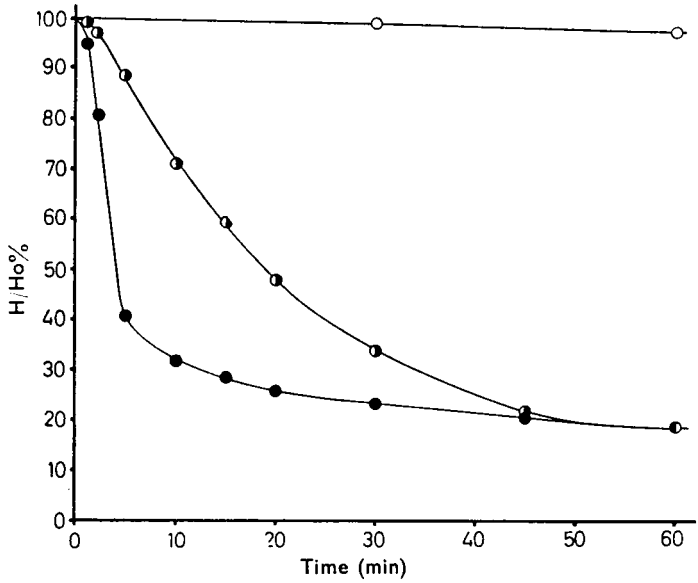

FIG. 1. The ratio of settled height/original height (H/Ho) expressed as a percentage, as a function of time during coagulation and flocculation of 2·5% griseofulvin suspensions. ● 10^{-2}M SDS + 10^{-1}M aluminium chloride. ◑ 10^{-2}M SDDS (commercial) + 10^{-1}M aluminium chloride. ○ 10^{-2}M SDS. ◐ common point.

REDISPERSIBILITY OF COAGULATED AND FLOCCULATED SUSPENSIONS

After storage for 1 week at 25°, the coagulated suspension redispersed completely after 3 revolutions and produced a smooth suspension; the flocculated sample required 14 revolutions and left 2–5 mm aggregates of the drug at the base of the container. Although Ecanow & others (1966) have postulated "the pharmaceutical necessity" of preparing flocculated suspensions, our experiments have suggested that such an approach could lead to pharmaceutically inelegant suspensions containing large aggregates. The inclusion of materials such as methyl cellulose, glycerol or sorbitol may partially obviate this. These aggregates are probably caused by chemical bridging between adjacent particles coated with surfactant, arising as a result of the aluminium ions reacting with the surfactant to give insoluble aluminium lauryl sulphate.

The present experiments suggest that the coagulation mechanism may provide a more suitable basis for producing redispersible pharmaceutical suspensions and it has been previously shown, Matthews & Rhodes (1968b) that this coagulation can be interpreted by zeta potential changes. The statement by Ecanow & others (1966) that coagulation leads to caking has been shown not to apply in this system. However, it has been previously found (Matthews & Rhodes 1968b), that when the modal particle diameter of the drug griseofulvin is increased from 4 to 15 μ, the effect of coagulation on sedimentation volume is less pronounced and may not be possible to apply the coagulation principle to very coarse or dense powders.

LONG-TERM STORAGE OF COAGULATED SUSPENSIONS

The maximum period of storage in the redispersibility experiments was 1 week. Samples of suspensions described previously (Matthews & Rhodes, 1968b) have now been on storage for 9 months at laboratory temperature. These suspensions have experienced a change of sedimentation volume of less than 1% during storage and redispersed to give smooth uniform suspensions after only 5 revolutions in the redispersing machine. This is good evidence that such systems are stable over long periods.

THE COAGULATION MECHANISM

Coagulation in colloidal dispersions is a diffusion phenomenon caused by Brownian motion of the particles, von Smoluchowski (1917). Calculations were made using Stokes law and the equation for the displacement due to Brownian motion, to compare the displacements for different particle sizes and to determine the size ranges in which sedimentation and Brownian motion predominate. These calculations have been made for griseofulvin on the assumption that the particles are spherical although Matthews & Rhodes (1967) have shown that the material is acicular. The results are shown in Fig. 2. The displacements have been calculated

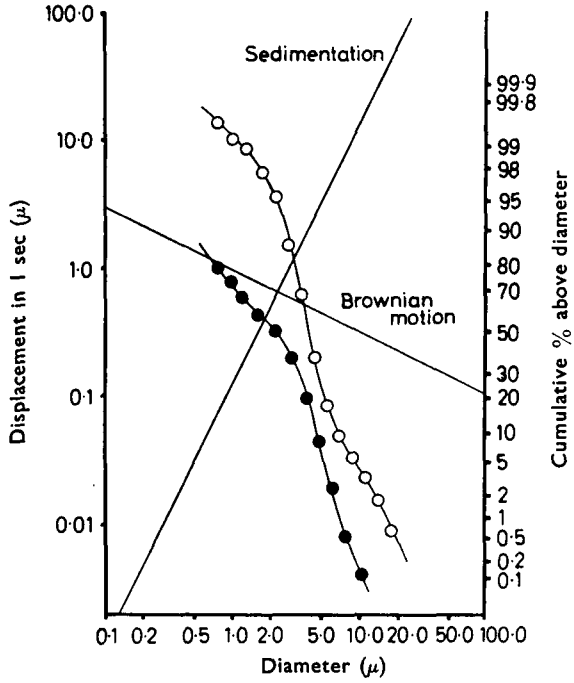

FIG. 2. Theoretical predictions of displacement due to sedimentation and Brownian motion in 1 sec, as a function of diameter for fine particle griseofulvin. Superimposed are cumulative weight % oversize and cumulative number % oversize distributions as a function of diameter. ○ Cumulative weight % oversize. ● Cumulative number % oversize.

for a period of 1 sec which is suggested as a suitable value by Burton (1926). Also shown in Fig. 2 are particle size distributions of fine particle griseofulvin.

The calculations indicate that for a spherical particle of griseofulvin of diameter 2 μ suspended in water, the displacements due to Brownian motion and sedimentation, in 1 sec, are identical. Below this size, Brownian motion predominates, above it, sedimentation. Burton (1926) has suggested that this is the critical diameter for a particle and is the largest diameter which will not settle under sedimentation. Since Brownian motion is random and sedimentation is unidirectional we suggest that at this diameter, sedimentation can still be superimposed on Brownian motion and that the critical diameter for no settling is probably slightly lower than 2 μ. The sample of griseofulvin has 50% by number and 6% by weight of particles with a diameter smaller than 2 μ and so Brownian motion can still be postulated as a major cause of coagulation in this system since it is dependent on the number of particles. Smoluchowski's theory was developed for a monodisperse system and it has been shown by Matthews & Rhodes (1968c) and by Ho & Higuchi (1968) that heterodispersity accelerates coagulation due to Brownian motion. Heterodispersity is also likely to assist coagulation caused by sedimentation since the differential sedimentation velocities will cause particle collisions.

Ecanow & others (1966) do not state the particle size of the sulphamerazine used in their experiments and for reasons which are not stated, they add 50% of glycerol to their suspensions. It has been pointed out by Martin (1960) that glycerol can slow down or halt Brownian motion completely, and we suggest that the inclusion of this material at such a concentration, in an experiment to compare coagulation and flocculation may obscure differences caused by the two phenomena. Ecanow & others point out that in the absence of electrolyte, no sedimentation was observed over a period of seven days.

In a colloidal system, particle collisions result in permanent aggregates because of the van der Waals forces of attraction. Kruyt (1952a) has referred to the theoretical existence of long-range London/van der Waals forces in hydrophobic suspensions in the range 2–5 μ and has stated that coagulation is possible in the secondary minimum that occurs in the energy of interaction curves at about 100–200 mμ distance. We suggest that sedimentation and Brownian motion can cause particles to approach one another to this distance in low electrolyte concentrations and to the primary minimum in high concentrations and thus yield a loosely coagulated structure.

THE EFFECT OF VALENCY ON COAGULATION

Ecanow & others (1966) have observed that Na^+ and K^+ are less effective than Al^{+++} in particle aggregation although the concentrations used are not stated. The Schultze-Hardy rule, Kruyt (1952b), states that the colloidal coagulation values for mono-, di- and tri-valent ions are in the

ratio 100: 1·6: 0·13. If similar principles apply to coagulation of supra-colloidal suspensions, one would expect Na^+ to coagulate a suspension to the same extent as Al^{+++}, only if the Na^+ are present in very high concentration.

In order to test whether the Schultze-Hardy rule applies to supra-colloidal suspensions, the coagulation rate of a 0·7 μ Dow polystyrene latex was determined in the presence of Na^+, Ba^{++} and Al^{+++}. The chlorides of each were chosen to minimize any opposing charge effect. Sedimentation of the 0·7 μ latex did not occur during the experiments.

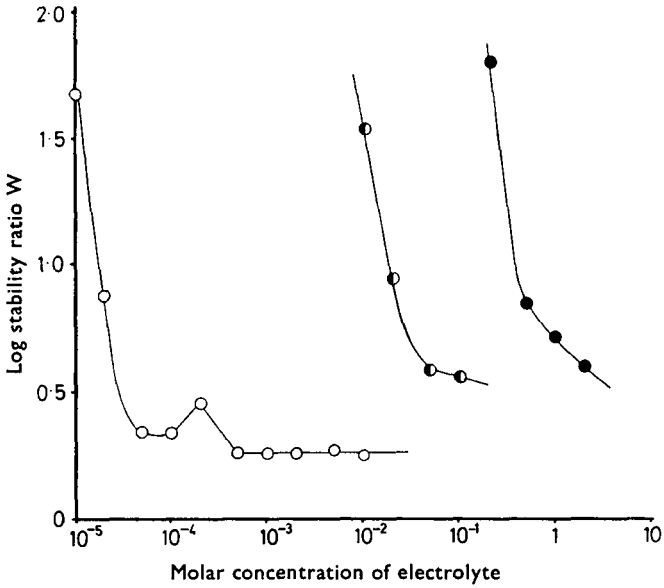

FIG. 3. Log stability ratio W, as a function of electrolyte concentration for a 0·714 μ "Dow" polystyrene latex. ○ Aluminium chloride (from Matthews & Rhodes, 1968a). ◐ Barium chloride. ● Sodium chloride.

The results are shown in Fig. 3. The experimental values of the stability ratios do not reach the theoretical value of unity (log W = O) even in high electrolyte concentrations and the reasons for this kind of situation have been discussed earlier (Matthews & Rhodes 1968a). There is also evidence of curvature in the graphs obtained with the two lower valency electrolytes. This may be a feature of the particle size since the *absence* of curvature was commented on by Ottewill & Shaw (1966) who used polystyrene latices of diameter 0·06–0·42 μ. Despite the curvature we observed, the vertical portions of the graphs were extrapolated to give an estimated coagulation value. These are given in Table 1 together with values for a negatively charged arsenious sulphide sol taken from Kruyt (1952c).

TABLE 1. COAGULATION VALUES OF A 0·714 μ "DOW" POLYSTYRENE LATEX IN DIFFERENT ELECTROLYTES

Electrolyte	Coagulation Value (mmoles/litre)	
	Dow latex	As_2S_3* sol.
NaCl	1000	51
$BaCl_2$	60	0·69
$AlCl_3$	0·05	0·093

* Kruyt (1950c).

These results show that aluminium chloride is a very much more powerful coagulating agent for polystyrene latex suspensions than either barium or sodium chloride even allowing for the Schultze-Hardy rule. The coagulation value for aluminium chloride in this system was even lower than that quoted by Kruyt for the arsenious sulphide sol but within the range of 0·003–0·096 mmole/litre given by this author for various aluminium salts and negatively charged colloids. The results for barium and sodium chloride indicate a considerable variation from those expected and this may be due to the small proportion of sulphonate stabilizer present in these latex polymers, (Higuchi, Okada & others, 1963). This may precipitate in the presence of the trivalent cation but not with the mono-or divalent. In these experiments the coagulation rate in 2M NaCl (11·7% w/v) was not as great as in much lower concentrations of aluminium chloride, and this is further evidence that a direct comparison of aggregation phenomena in electrolytes of different valencies may give different results from those obtained in identical electrolyte systems.

CONCLUSIONS

In devising experiments to distinguish between flocculation and coagulation it is important to limit the number of variables and to exclude secondary phenomena which may obscure important differences. It has been demonstrated that both coagulation and flocculation can produce suspensions of griseofulvin which are readily redispersible after storage and it has been shown that for powders containing particles in the range 0·5–20 μ, coagulation can produce suspensions which are more pharmaceutically elegant than those produced by flocculation. This contrasts with the advice of some other workers.

It has been shown that SDDS is a very suitable wetting agent, despite a foaming tendency: it can be used as a charge conferring agent for subsequent coagulation by aluminium salts. It is suggested that provided it is suitably non-toxic, it would be a useful material for the pharmaceutical formulator.

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