# Physical Stability of Sulfaguanidine Suspensions

R. D. C. JONES*, B. A. MATTHEWS†, and C. T. RHODES‡

**Abstract** □ The effects of several variables—electrolyte, type, and concentration of surfactant and nature of vehicle—upon the physical properties of sulfaguanidine suspensions have been investigated. It is shown that the concept of controlled flocculation may usefully be applied to the formulation of pharmaceutically acceptable suspensions of this drug.

**Keyphrases** □ Sulfaguanidine suspension—physical stability □ Stability, sulfaguanidine suspension—electrolyte, surfactant, vehicle effects □ Sedimentation volume—sulfaguanidine suspension □ Redispersibility—sulfaguanidine suspension

Sulfaguanidine is an extremely useful antibacterial drug which is virtually nonabsorbed from the gastrointestinal tract. It is therefore particularly effective in the treatment of localized gastrointestinal infections. Because the drug does not enter the blood stream, it may be given in quite large doses, even to very young children. In the treatment of dysentery, doses of 3 g. three times daily are common and doses of 5 g. are sometimes used for severe cases.

The choice of a suspension rather than a tablet or capsule is often controlled by patient acceptability. While solid dosage forms are often supplied to adults, the treatment of children, particularly the very young, is easier with a suitably flavored suspension. There are a number of proprietary suspensions containing sulfaguanidine available for both pediatric and adult use.

In order to ensure uniformity of dosage, it is the aim of the pharmaceutical formulator to produce a preparation for which the minimum of shaking will cause homogeneous distribution of drug. It has been shown that the concept of controlled flocculation may be usefully applied to pharmaceutical suspensions (1–4). In the present paper the authors report studies which show how controlled flocculation may be applied to the formulation of sulfaguanidine suspensions.

## EXPERIMENTAL

**Materials**—Sulfaguanidine BPC,[1] cetyltrimethylammonium bromide,[2] polysorbate 80,[2] aluminum chloride reagent grade, glycerol BP, glass-distilled water.

**Particle Size**—The particle size of the sulfaguanidine used in this investigation was determined using a model B Coulter counter in the manner previously described by Matthews and Rhodes (5) and Short *et al.* (6). Raw Coulter data were converted to percentage weight and percentage number oversize by a computer program. The results shown in Fig. 1 represent the mean of three determinations.

**Sedimentation Volume**—The sedimentation volumes of test suspensions were determined at intervals during storage by the method previously described (3).

Sedimentation volume is defined as the ratio of the ultimate settled height, $H_u$, to the original height, $H_o$.

[1] Supplied by British Drug Houses, Poole, England.
[2] Tween 80, supplied by Honeywell Atlas Ltd., London, England.

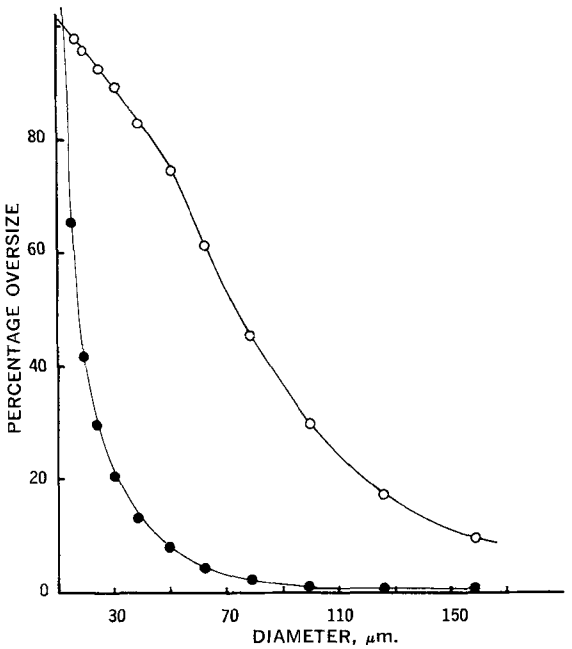


**Figure 1**—*Particle size spectrum of sulfaguanidine BPC. Key:* ●, *number; and* ○, *weight.*

**Redispersibility**—To standardize evaluation of redispersibility, the machine described by Matthews and Rhodes (3) was used. This rotates the measuring cylinders in which the suspensions were stored through 360° at a constant speed of 20 r.p.m.

**Preparation of Suspensions**—Preliminary tests were performed to determine the type and concentration of surfactant to wet the drug. Of the surfactants screened, cetyltrimethylammonium bromide (CETAB) and polysorbate 80 were shown to have satisfactory wetting properties at $1 \times 10^{-2}$ *M* and were compatible with the aluminum chloride used as the flocculating agent.

Suspensions were prepared by dispersing 5 g. of drug in 50 ml. of double strength surfactant solution ($2 \times 10^{-2}$ *M*) by means of a Silverson mixer (Silverson Ltd., London, England); 40 ml. of water and 10 ml. of electrolyte solution (10 times the required concentration) were then added. The measuring cylinders containing the suspensions were then stoppered and shaken well before storage at laboratory temperature (about 18°). Suspensions containing glycerol were prepared as before, being made to volume with a suitable glycerol–water mixture.

## RESULTS AND DISCUSSION

The particle size spectrum of the sulfaguanidine BPC used in this project is shown in Fig. 1. Although official, this material is of a comparatively large particle size, larger than many formulators would choose to use in suspensions. This further demonstrates the need for more official standards on particle size (5–7). However, the studies of controlled flocculation reported in this paper are substantially independent of particle size. Of course, with a different concentration of drug or with a drug of different particle size, minor modification in electrolyte or surfactant concentration might be required.

Results of the study of suspensions of sulfaguanidine wetted by $10^{-2}$ *M* polysorbate 80 in the presence of different concentrations of aluminum chloride as flocculating agent are shown in Fig. 2.

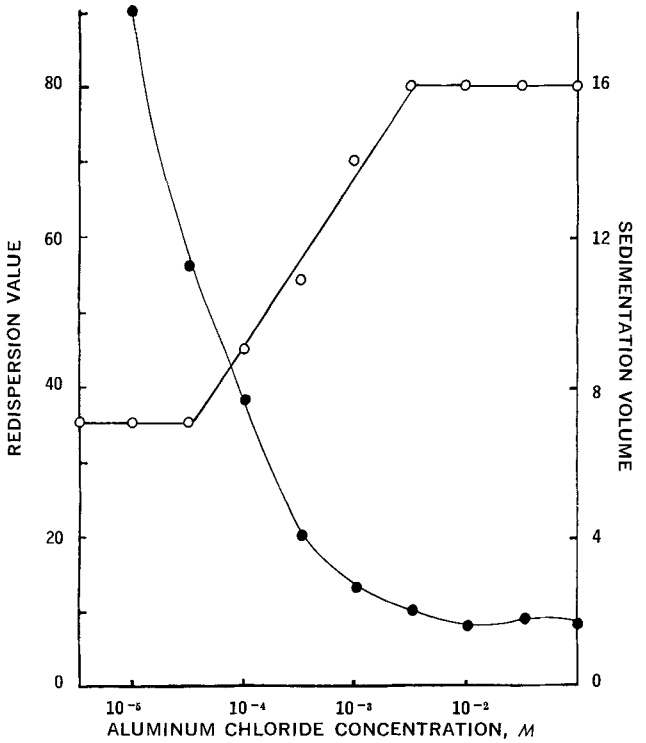


**Figure 2**—*Flocculation of sulfaguanidine, wetted by polysorbate 80, by aluminum chloride. Key: ○, sedimentation volume; and ●, redispersion value.*

It can be seen that there was a steady increase in sedimentation volume from about $5 \times 10^{-5}$ *M* aluminum chloride until a maximum value of about 16% at $5 \times 10^{-3}$ *M*. Increase in concentration of aluminum chloride above this concentration produced no corresponding increase in sedimentation volume. The progressive rise in sedimentation volume was accompanied by an increase in the ease of redispersibility, as is evidenced by the number of revolutions of the redispersing apparatus required to return the system to a homogeneous state. These results may readily be interpreted in terms of

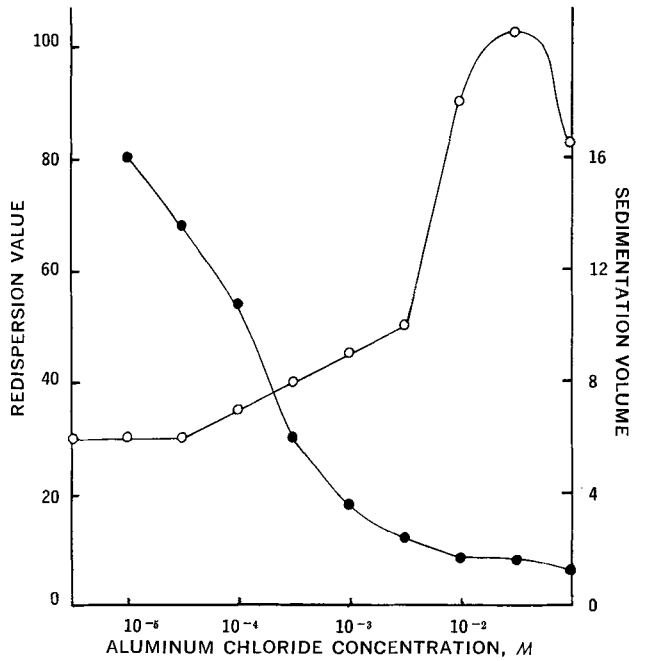


**Figure 3**—*Flocculation of sulfaguanidine, wetted by CETAB, by aluminum chloride. Key: ○, sedimentation volume; and ●, redispersion value.*

**Table I**—Effect of Glycerol upon Suspensions of Sulfaguanidine Wetted by CETAB and Partially Flocculated by Aluminum Chloride, $10^{-2}$ *M*

| Glycerol Concentration, % w/v | Sedimentation Volume | Redispersion Value 1 week | Redispersion Value 6 weeks |
|---|---|---|---|
| 0 | 18.0 | 8 | 8 |
| 10 | 17.6 | 8 | 8 |
| 15 | 17.6 | 8 | 9 |
| 20 | 17.8 | 8 | 9 |
| 25 | 18.4 | 10 | 11 |
| 30 | 18.6 | 12 | 13 |
| 35 | 19.0 | 14 | 14 |
| 40 | 19.3 | 16 | 16 |
| 45 | 19.5 | 16 | 16 |
| 50 | Diffuse, inelegant suspension | — | — |

the changes in energies of interaction between the suspended particles caused by adsorption of ions from solution. It has recently been shown that calculated energies of interaction for griseofulvin are in qualitative agreement with experimental stability results (8, 9). The general theory relating such values as zeta potential sedimentation volume and redispersibility has been previously discussed in some detail (1, 3). The sedimentation volumes of the flocculated systems are high because the floccules form rapidly and insufficient time is available for the formation of a tight, impacted cake. Thus, the ease of redispersibility increases with electrolyte concentration since relatively small forces can accomplish destruction of the nonimpacted floc, whereas the reverse situation obtains in the deflocculated system. The results shown in Fig. 3 for suspensions wetted by CETAB are similar. However, it is noteworthy that with this surfactant an increase in the concentration of flocculating agent above $5 \times 10^{-2}$ *M* produced a reduction in sedimentation volume.

Having determined the optimum aluminum chloride concentration for the two surfactants, some studies were made of the effect of glycerol upon the sulfaguanidine suspensions. Four series of suspensions were prepared for this study, two sets for both surfactants, with and without aluminum chloride. The results are shown in Tables I–IV.

In the series of suspensions wetted by CETAB, in the presence of aluminum chloride, there was a small but significant increase of sedimentation volume as the glycerol concentration is increased until at 50% glycerol the products are quite inelegant. There was, however, a substantial increase in the redispersion value. A possible factor to be taken into account in considering this finding is that with the increase in viscosity of the medium the speed at which the redispersing machine operated was not great enough to redisperse the floccules. It is suggested that when redispersibility tests are used on suspensions in which the vehicle is other than aqueous, considerable care should be taken in the theoretical interpretation of such data since the effective shear at the particle–particle junctions in the floccules will vary with the viscosity and density of the continuous phase. In detailed studies of such systems, it might be useful to vary the redispersing force by modifications in apparatus design or speed of operation.

**Table II**—Effect of Glycerol upon Suspensions of Sulfaguanidine Wetted by CETAB, with No Added Electrolyte

| Glycerol Concentration, % w/v | Sedimentation Volume | Redispersion Value 1 week | Redispersion Value 6 weeks |
|---|---|---|---|
| 0 | 6.0 | 100+ | 100+ |
| 10 | 7.4 | 83 | 100+ |
| 15 | 9.7 | 76 | 100+ |
| 20 | 10.3 | 64 | 100+ |
| 25 | 11.1 | 58 | 100+ |
| 30 | 11.6 | 41 | 100+ |
| 35 | 12.0 | 36 | 100+ |
| 40 | 13.0 | 24 | 100 |
| 45 | 13.0 | 18 | 94 |
| 50 | Diffuse, inelegant suspension | — | 86 |

Table III—Effect of Glycerol upon Suspensions of Sulfaguanidine Wetted by Polysorbate 80 and Partially Flocculated by Aluminum Chloride, $5 \times 10^{-3}$ *M*

| Glycerol Concentration, % w/v | Sedimentation Volume | Redispersion Value 1 week | Redispersion Value 6 weeks |
|---|---|---|---|
| 0 | 16.1 | 9 | 9 |
| 10 | 16.1 | 9 | 9 |
| 15 | 16.2 | 9 | 10 |
| 20 | 16.5 | 11 | 11 |
| 25 | 16.8 | 13 | 12 |
| 30 | 17.0 | 14 | 14 |
| 35 | 17.2 | 15 | 16 |
| 40 | 17.2 | 16 | 17 |

Table IV—Effect of Glycerol upon Suspensions of Sulfaguanidine Wetted by Polysorbate 80, with No Added Electrolyte

| Glycerol Concentration, % w/v | Sedimentation Volume | Redispersion Value 1 week | Redispersion Value 6 weeks |
|---|---|---|---|
| 0 | 6.0 | 100+ | 100+ |
| 10 | 7.1 | 100+ | 100+ |
| 15 | 7.7 | 89 | 100+ |
| 20 | 8.6 | 74 | 100+ |
| 25 | 10.1 | 58 | 100+ |
| 30 | 10.6 | 42 | 100+ |
| 35 | 11.2 | 34 | 100+ |
| 40 | 11.6 | 26 | 98 |

The change in sedimentation volume recorded in Table I is considerably less than had been expected. It is possible that this finding could be due to interaction between the aluminum ion and glycerol which would affect the availability of flocculant electrolyte, reducing the degree of flocculation of these systems. However, the authors have not been able to find literature substantiation of this hypothesis. This possible explanation is supported by the difference in effect which the glycerol had upon the redispersion values of the flocculated and unflocculated systems. Values increased for the systems with electrolyte but decreased for the deflocculated systems.

From the results shown in Table II, it can be seen that in the absence of flocculating agent, there was a marked increase in the sedimentation volume with increase in glycerol concentration. There was also a substantial increase in the ease of redispersibility as the glycerol concentration was increased. In the absence of electrolyte the sedimentation volume is controlled by such factors as viscosity and density of vehicle and the degree of heterogeneity of the dispersed phase. For any given system there is a critical particle size at which sedimentation will occur. Comparison of the redispersion values shown in Tables I and II shows that while the electrolyte-flocculated systems show no change in redispersion value over a 5-week period, the other systems show a marked decrease in the ease of redispersibility. This finding further points up the advantage of controlled flocculation.

Tables III and IV show the results obtained when polysorbate 80 was used as the wetting agent. The results are broadly similar to those obtained with the CETAB systems. Again, the change in sedimentation value with increasing glycerol concentration is very much greater in the absence of electrolyte, indicating the possibility of interaction between the flocculant and glycerol. Also, the effect of glycerol upon the redispersion value differs for the two systems in the same way as in the CETAB study.

The results reported in this paper further demonstrate the utility of the controlled flocculation technique in suspension formulation. Sulfaguanidine, wetted by a suitable surfactant, may be flocculated by aluminum chloride to give a pharmaceutically elegant preparation. Such suspensions may be readily redispersed, and tests have shown that even after prolonged storage such products retain satisfactory physical properties; whereas in the absence of electrolyte, impaction becomes increasingly evident. The addition of glycerol to the flocculated systems did not produce the added effect which was expected. Reasons for this behavior are the subject of further investigation.

## REFERENCES


(1) B. A. Haines, Jr., and A. N. Martin, *J. Pharm. Sci.*, **50,** 228 (1961).

(2) B. A. Matthews and C. T. Rhodes, *ibid.*, **57,** 557(1968).

(3) *Ibid.*, **57,** 569(1968).

(4) B. A. Matthews and C. T. Rhodes, *J. Pharm. Pharmacol.*, **20,** 2045(1968).

(5) B. A. Matthews and C. T. Rhodes, *J. Pharm. Sci.*, **56,** 838 (1967).

(6) P. M. Short, S. V. Lincoln, and C. T. Rhodes, *Die Pharm.*, **6,** 319(1969).

(7) P. M. Short, E. T. Abbs, and C. T. Rhodes, *Can. J. Pharm. Sci.*, **4,** 8(1969).

(8) B. A. Matthews and C. T. Rhodes, *Pharm. Acta Helv.*, **45,** 52 (1969).

(9) B. A. Matthews and C. T. Rhodes, paper presented to the International Pharmaceutical Conference, London, England, 1969.


## ACKNOWLEDGMENTS AND ADDRESSES


Received August 8, 1969, from the *School of Pharmacy, Portsmouth College of Technology, Portsmouth, Hampshire, England.*

Accepted for publication October 31, 1969.

The authors thank P. M. Short for assistance in particle size analysis.



* Present address: Hafod, Heol Isaf, Penparcau, Aberystwyth, Wales.

† Present address: J. R. Geigy A. G., CH-4000 Basel 21, Switzerland.

‡ Present address: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver 8, BC, Canada.