

Flocculation of Sulfamerazine Suspensions by a Cationic Polymer

JOEL L. ZATZ*, LARRY SCHNITZER, and PRAMOD SARPOTDAR

Received April 9, 1979, from the College of Pharmacy, Rutgers—the State University of New Jersey, Piscataway, NJ 08854. Accepted for publication June 11, 1979.

Abstract □ Flocculation by a cationic polymer of sulfamerazine suspensions containing a wetting agent was evaluated. Suspensions with sufficient surfactant concentrations to ensure complete wetting were deflocculated. When the anionic surfactant, dioctyl sodium sulfosuccinate, was used as a wetting agent, the suspensions were flocculated over a limited polymer concentration range. Flocculation was attributed to simultaneous interaction of a polymer molecule with more than one particle. At higher polymer concentrations, the particles were covered completely with polymer, leading to repulsion between the particles and deflocculation of the suspensions. The polymer concentration required for flocculation provided evidence for interaction between the anionic surfactant and the cationic polymer. Suspensions containing a nonionic surfactant also were flocculated using various polymer concentrations. When a surfactant mixture was employed in the suspensions, the peak sedimentation volume of flocculated systems and the concentration of polymer at the peak depended on the surfactant mixture composition.

Keyphrases □ Sulfamerazine—suspensions, flocculation, cationic polymer, anionic and nonionic surfactants □ Flocculation—sulfamerazine suspensions, cationic polymer, anionic and nonionic surfactants □ Cationic polymer—sulfamerazine suspensions, flocculation, anionic and nonionic surfactants

Resistance to caking is a principal objective in pharmaceutical suspension formulation (1). Suspensions that form a voluminous, porous sediment upon standing may be shaken by hand to reconstitute a uniform product and to allow correct dose transfer. Suspensions that sediment in this manner are referred to as flocculated systems.

Deflocculated suspensions, in which the internal phase has been dispersed into individual particles, usually appear more elegant when first prepared. They sediment more slowly than flocculated suspensions but produce a dense, compact layer of solid material at the container bottom. Such suspensions are difficult to redisperse and, consequently, are not suitable as pharmaceutical dosage forms.

BACKGROUND

Two possible formulation avenues were suggested (2). One uses a structured vehicle to avoid settling altogether. The other (the more usual approach) involves a flocculation process, resulting in a system that sediments and is then readily redispersed prior to use.

Salts may function as flocculating agents. Previous work on flocculation mainly concerned the valence and concentration effects of simple salts. Little study has been made of the flocculation of pharmaceutical suspensions by polymers. Although polymers commonly are included in suspensions as thickening or structuring agents, they also may function by adsorbing onto suspended particles and altering the attraction or repulsion between particles.

Smellie and LaMer (3) used polymers to clarify turbid water containing low dispersed phosphate concentrations. The polymer actions were ascribed to a bridging mechanism in which the long polymer molecules joined two or more particles together. Polymer adsorption is a key requirement for bridging. However, since complete coverage of the dispersed particles by polymer molecules makes it unlikely that the same polymer molecule will attach to more than one particle, too high a polymer concentration may reduce the flocculation efficiency or inhibit it altogether. These mechanisms are similar to the "sensitization" and "protection" of hydrophobic sols by polymers (4).

Subsequent investigations confirmed the validity of a bridging mechanism in polymer flocculation (5–8). Charge neutralization may be involved in the attachment of the polymer to the particle surface (5), although a nonionic mechanism also may be operative (6). The first study of polymer flocculation in pharmaceutical systems (7) concerned the effect of xanthan gum in several suspensions. Flocculation of some anions by xanthan gum also was investigated (8).

Surfactants often are employed as wetting and dispersing agents in suspensions. However, surfactants were not included in any of the polymeric flocculation studies reported. Since flocculation is basically an interfacial phenomenon and surfactants accumulate at interfaces, they may influence the action of polymers. The present investigation concerned the effect of a cationic polymer on the flocculation state of sulfamerazine suspensions containing surfactants.

EXPERIMENTAL

Sulfamerazine was USP grade. Dioctyl sodium sulfosuccinate¹ and polysorbate 40² were employed as wetting agents. The polymer preparation (I) was a commercial cationic flocculant³, supplied as an aqueous solution containing 30% active material (9). All other chemicals were reagent grade and were used as supplied.

To prepare 100 ml of sulfamerazine suspension, 10 g of the drug was placed in a glass mortar. Twenty milliliters of an aqueous solution containing the wetting agent was added to the powder, and the concentrated suspension was mixed thoroughly. The polymer preparation (when present) then was added as a concentrated aqueous solution by pipet, and the suspension was mixed for <1 min and transferred into a 100-ml graduated mixing cylinder. The mortar was rinsed several times with distilled water. The rinsings were added to the graduated cylinder, and sufficient distilled water was used to make up to volume. The suspension was shaken thoroughly and then permitted to settle.

The suspensions were allowed to stand until no further changes were observed in the sediment height. The sediment volume then was recorded.

Surface tension was measured by the Wilhelmy plate method.

RESULTS AND DISCUSSION

Sedimentation volume, F , was used as an indication of flocculation in the suspensions. The value of F is determined by:

$$F = \frac{V_u}{V_0} \quad (\text{Eq. 1})$$

where V_u is the ultimate sediment volume and V_0 is the total suspension volume.

The deflocculated suspension sedimentation volume is relatively small. Flocculated systems exhibit higher F values. In the suspensions studied, no changes in the sediment volume were observed after about 5 days.

Figure 1 shows the effect of the I concentration on the sedimentation volume of sulfamerazine suspensions in the absence of any surfactant. The F value decreased when the I concentration in the suspension reached 0.1%. However, even at 1%, a small amount of sulfamerazine powder floated at the top of the suspension. The F decrease corresponded to lowering of the surface tension, γ , of the medium by the polymer (Fig. 2). The critical sulfamerazine surface tension is 32 dynes/cm (10). Apparently, γ is not lowered sufficiently by the polymer to allow complete wetting.

The relationship between surfactant concentration in the absence of I and sedimentation volume is shown in Fig. 3. There were slight differ-

¹ Aerosol OT, American Cyanamid.

² Tween 40, ICI America.

³ Primafloc C-3, Rohm & Haas.

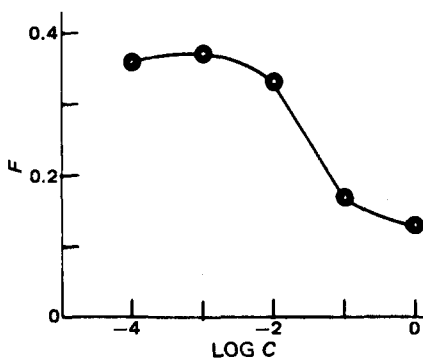


Figure 1—Sedimentation volume of sulfamerazine suspensions in the presence of various I concentrations.

ences in F values between the surfactants at low concentrations, but the experimental points were close enough for a single curve to describe all of the data. At low surfactant concentrations, F was comparatively high but powder wetting was incomplete. Wetting improved with an increase in surfactant concentration, becoming essentially complete at about 0.1%. At this concentration, F reached its minimum value. The sedimentation volume at higher surfactant concentrations was the same. The same F also was observed in suspensions containing 1% of the polymer and no surfactant (Fig. 1). The members of this group of suspensions behaved similarly and exhibited the characteristics of the deflocculated state, evident from the turbidity observed during sedimentation and the slow settling rate. After standing for about 1 week, a cake formed in the bottom of the cylinders.

In systems containing a surfactant, the polymer effect on flocculation depended on the surfactant. Figure 4 contains plots of sedimentation volume as a function of I concentration in suspensions wetted with dioctyl sodium sulfosuccinate. At low I concentrations, there was no effect on the flocculation state of the suspensions. A sedimentation volume increase occurred in suspensions containing 0.2% of the anionic surfactant (curve 1, Fig. 4) when the I concentration approached 0.1%. This sedimentation volume change indicates that the suspensions became flocculated, as confirmed by their appearance. Large particles were visible, and they settled quickly, leaving behind a clear supernate. The flocculated suspensions could be resuspended with little effort, even after standing for about 6 weeks, in contrast to the deflocculated systems. A higher I concentration (1%) caused a reduction in sediment volume to 0.15, indicating that the suspensions were deflocculated.

The experiments were repeated using a higher dioctyl sodium sulfosuccinate concentration (1.0%) in the suspensions. The same pattern was

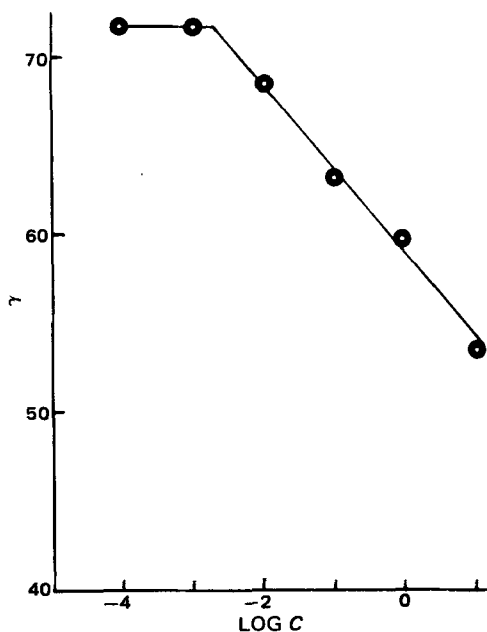


Figure 2—Surface tension of aqueous I solutions as a function of concentration.

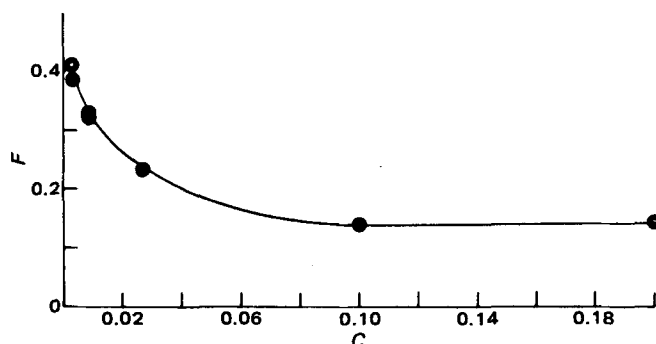


Figure 3—Sedimentation volume of sulfamerazine suspensions in the presence of various concentrations of surfactants in the absence of I. Key: O, polysorbate 40; and ●, dioctyl sodium sulfosuccinate.

found as with the lower surfactant concentration (curve 2, Fig. 4), but the amount of I required to induce flocculation was higher. This result does not rule out an adsorption-dependent flocculation mechanism, but it does implicate a polymer-surfactant interaction as one important factor controlling the suspension properties.

The polymer action does not apparently involve disruption of the adsorbed dioctyl sodium sulfosuccinate film on the particle surface, although the evidence for this conclusion is indirect. It may be assumed that the air-water and particle-water interfaces are similar in that the kinds of forces responsible for adsorption are similar and surfactant orientation is the same (*i.e.*, the charged end of the surfactant molecules faces the bulk water phase). Removal of surfactant from the air-water surface by the polymer should be accompanied by a surface tension increase since the surface tension of the polymer solutions (Fig. 2) is higher than that of dioctyl sodium sulfosuccinate at the concentrations used. Instead, the changes in surface tension were quite small. The surface tension of 0.2% aqueous dioctyl sodium sulfosuccinate was 26.9 dynes/cm.

In surfactant solutions containing 0.1 and 1.0% of I, the surface tension was 26.0 dynes/cm, implying that the surfactant remains adsorbed at the air-water surface and, by inference, at the particle-water interface in the presence of added polymer.

A suggested explanation for the flocculating effect of the polymer is outlined in Fig. 5. Adsorbed surfactant carries a negative charge to the surface of the sulfamerazine particles. The particles repel each other (Fig. 5a) and, in the absence of I, the suspensions are deflocculated. Added polymer interacts with the excess surfactant in solution and also with the adsorbed molecules. At relatively low polymer concentrations, a limited number of polymer segments are available and the free surfactant molecules and micelles in solution compete effectively with the negatively charged particles for polymer. Increasing the polymer concentration makes more segments available, so a polymer molecule can interact simultaneously with two particles (Fig. 5b). The joining of adjacent particles probably is due to bridging resulting from simultaneous adsorption to more than one particle, although it is difficult to exclude an electro-

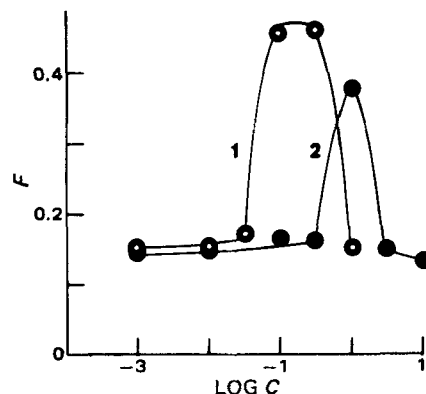


Figure 4—Sedimentation volume of sulfamerazine suspensions containing dioctyl sodium sulfosuccinate in the presence of various I concentrations. Key: curve 1, 0.2% dioctyl sodium sulfosuccinate; and curve 2, 1.0% dioctyl sodium sulfosuccinate.

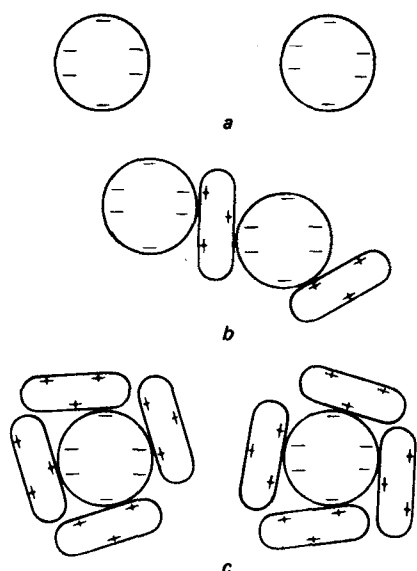


Figure 5—Suggested mechanism for the behavior of I in suspensions. Key: a, low polymer concentration, deflocculated suspension; b, flocculation by bridging; and c, deflocculation at high polymer concentrations.

static component (11). At much higher polymer concentrations, polymer molecules can still attach to particle surfaces but the chance of joining two particles together is greatly reduced because many other polymer molecules are readily available for adsorption. As a result, the particles become surrounded with a polymer sheath (Fig. 5c) whose charge again causes particle separation and suspension deflocculation.

The effect of raising the surfactant concentration according to this model would be to reduce the number of free polymer segments available for adsorption. Particle-polymer interaction cannot occur until higher polymer concentrations are reached. This pattern was actually observed (Fig. 4).

The influence of the polymer on suspensions containing the nonionic surfactant, polysorbate 40, is shown in Fig. 6. Deflocculated suspensions were obtained at very low and very high I concentrations. An increase in sedimentation volume was observed when the I concentration was between 0.001 and 0.01%. These suspensions were judged to be partly flocculated. The supernatant suspension medium was considerably clearer, and the sedimentation rate was more rapid than with the deflocculated systems. These suspensions did not cake. In comparison to flocculated suspensions containing the anionic surfactant, dioctyl sodium sulfosuccinate, the suspensions with the nonionic agent appeared less coarse.

As shown by a comparison of Figs. 4 and 6, the suspensions containing the nonionic surfactant had significantly smaller sedimentation volumes. The amount of polymer required to induce flocculation in these systems was about 1% of that needed in suspensions containing the anionic surfactant. The flocculation pattern as a function of the I concentration is consistent with a bridging mechanism. As with the suspensions in which dioctyl sodium sulfosuccinate was used, an excess of polymer molecules reduced the probability of polymer adsorption on more than a single particle, resulting in deflocculation.

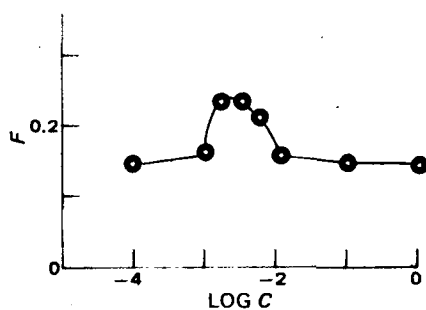


Figure 6—Sedimentation volume of sulfamerazine suspensions containing polysorbate 40 in the presence of various I concentrations.

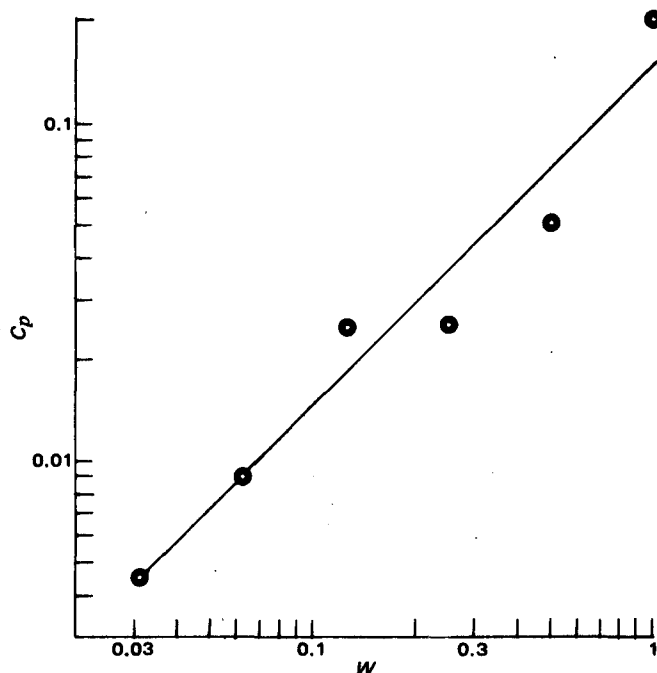


Figure 7—Relationship between the I concentration at peak flocculation as a function of the weight fraction of dioctyl sodium sulfosuccinate in the surfactant mixture.

Because the choice of wetting agent influenced the sedimentation volume of flocculated suspensions and the polymer concentration needed for flocculation, additional experiments were performed to determine whether these characteristics could be manipulated by using a surfactant mixture in the suspensions. The total surfactant concentration was maintained at 0.2%, but the relative concentrations of dioctyl sodium sulfosuccinate and polysorbate 40 were varied. For each surfactant combination, a series of sulfamerazine suspensions containing a range of I concentrations was prepared.

Plots of sedimentation volume as a function of the concentration of I had the same shape as the curves in Figs. 4 and 6. From these plots, the peak sedimentation volume and C_p , the concentration of I at the peak, were determined. The relationship between the I concentration required for maximum flocculation and the weight fraction of dioctyl sodium sulfosuccinate in the surfactant mixture is shown in Fig. 7. A log-log plot was used because of the large concentration range. The slope is unity, indicating a linear dependence of C_p on the content of dioctyl sodium sulfosuccinate. This relationship was anticipated because of the interaction between the polymer and dioctyl sodium sulfosuccinate discussed earlier.

The suspensions in which the weight fraction of dioctyl sodium sulfosuccinate in the surfactant mixture was less than 0.25 had peak sedimentation volumes of 0.23–0.26, which were quite close to those for suspensions containing only the nonionic surfactant. When the weight fraction of dioctyl sodium sulfosuccinate was 0.25 or greater, the sedimentation volume increased as the proportion of the anionic surfactant was increased, reaching its highest value in suspensions containing only dioctyl sodium sulfosuccinate.

These experiments demonstrated the feasibility of adjusting the surfactant combination to manipulate suspension properties. Thus, it was possible to produce adequately flocculated suspensions using a smaller amount of I than was necessary with dioctyl sodium sulfosuccinate alone as a wetting agent.

REFERENCES

- (1) B. A. Haines and A. N. Martin, *J. Pharm. Sci.*, **50**, 228 (1961).
- (2) E. N. Hiestand, *ibid.*, **53**, 1 (1964).
- (3) R. H. Smellie, Jr., and V. K. LaMer, *J. Colloid Sci.*, **13**, 589 (1958).
- (4) J. T. G. Overbeek, in "Colloid Science," vol. 1, 1st ed., Elsevier, New York, N.Y., 1952, pp. 317, 318.
- (5) H. E. Ries and B. L. Meyers, *Science*, **160**, 1449 (1968).

