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Report

Stabilization of Sulfamerazine Suspensions by Xanthan Gum

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Suspensions of sulfamerazine (10%) containing 0.2% docusate sodium were deflocculated because of repulsion between the negatively charged particles. Flocculation was induced by salts or by xanthan gum, which is anionic, in the presence of salts at concentrations below those at which salt flocculation resulted. The amount of gum necessary to produce a flocculated system was lower the higher the concentration of salt present. Calcium chloride and magnesium chloride were considerably more effective in this regard than sodium chloride. Gum flocculation produced aggregates with fewer particles and weaker bonding forces than did salt flocculation. The sedimentation rate of the suspensions decreased 5 to 10 times for each 0.1% increase in the gum concentration.

KEY WORDS: suspensions-flocculation by xanthan gum; xanthan gum-effect on suspension flocculation and sedimentation; suspensions-effect of xanthan gum on sedimentation; sulfamerazine suspensions.

INTRODUCTION

Xanthan gum is an anionic polysaccharide of microbial origin that is used to retard sedimentation in suspensions and other disperse systems. Dilute aqueous solutions of xanthan gum are pseudoplastic. At concentrations of 0.3% and above, a gel-like state was observed at low shear (1).

The flocculation state in pharmaceutical suspensions is of interest chiefly because deflocculated systems tend to form a compact sediment that is extremely difficult to redisperse. Flocculated systems settle to yield a bulky sediment that can usually be resuspended by hand shaking.

Several aqueous hydroxide and carbonate suspensions became more highly flocculated in the presence of xanthan gum (2). Flocculation resulted from simultaneous adsorption to more than one particle, leading to bridging of particles by polymer molecules (3). The adsorption mechanism involved charge attraction between the positively charged particles and the negatively charged gum molecules. Flocculation of magnesium carbonate by xanthan gum was diminished in the presence of docusate sodium, an anionic surfactant, due to competition for adsorption sites on particle surfaces (4).

Silica suspensions, which are negatively charged, were not flocculated by xanthan gum (2). This was presumably due to the fact that both the gum molecules and the suspended particles had the same charge, preventing adsorption.

Sulfamerazine suspensions that utilized docusate sodium as a wetting agent remained deflocculated in the presence of low concentrations of xanthan gum (5). This was attributed to the negative charge on the particle surface (6), which prevented gum adsorption. This research was extended to sulfamerazine suspensions containing added salts (sodium chloride, magnesium chloride, calcium chloride) to determine whether reduction of polymer–particle repulsion would alter the degree of flocculation.

MATERIALS AND METHODS

Materials

Sulfamerazine USP powder (American Cyanamid) had a median particle size of 4.5 μm (5). Xanthan gum (Keltrol, Kelco Division, Merck and Co.) and docusate sodium (Aerosol OT, American Cyanamid) were used as received. All salts were reagent grade.

Preparation of Suspensions

Surfactants, salts, and xanthan gum were incorporated as aqueous stock solutions. All solutions as well as the water used in suspension preparation contained 0.1% methylparaben and 0.02% propylparaben as preservatives. Each suspension was prepared individually with a counterrotating mixer (Brookfield Engineering). The general procedure was to disperse 20 g of sulfamerazine in 80 ml of a 0.5% stock solution of docusate sodium for 10 min. The salt solution was added next, followed by the xanthan gum stock solution. After adding water to bring the total volume to 200 ml, the suspension was mixed thoroughly for 5 min. Each formulation was prepared in duplicate. The pH of the sulfamerazine suspension containing 0.2% docusate sodium was 5.95.

Sedimentation

The sedimentation volume was monitored in 100-ml cylinders. After a period of time, which varied with the gum concentration, the volume of sediment no longer changed with time and the sedimentation volume (*F*), defined as the ratio of the ultimate volume of the sediment to that of the suspension, was recorded.

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Resuspendibility

After standing for 6 months, the resuspendibility of sedimented suspensions was evaluated by inverting and shaking the suspensions by hand. Some suspensions, classified as "caked," could not be redispersed regardless of the amount of shaking.

Microscopy

Suspension samples were observed under bright-field illumination at 100× and 250× magnification. Deflocculated suspensions consisted of individual particles and the field appeared uniform. With flocculated systems, aggregates were observed, while other sections of the field contained relatively few particles.

RESULTS AND DISCUSSION

Flocculation

Values of the sedimentation volume for suspensions containing 0.033 *M* sodium chloride are plotted as a function of the xanthan gum concentration in Fig. 1. The values for 0.3 and 0.4% gum, although shown in the figure, are uncertain because, despite the long time for standing, sedimentation was so slow that it may not have been complete in these suspensions. At this salt concentration, the addition of xanthan gum to the suspension resulted in an increase in the sedimentation volume.

The combined effect of several concentrations of sodium chloride and xanthan gum on sedimentation volume is shown in Fig. 2. Suspensions that did not contain gum were deflocculated at all sodium chloride concentrations studied except for 0.33 *M*. At every sodium chloride concentration, the addition of xanthan gum resulted in a rise in the sedimentation volume whose magnitude depended on the gum concentration.

Figure 3 contains sedimentation volume data for suspensions containing magnesium chloride. Although the curves for 0.133 and 0.2% xanthan gum intersect, it was generally found that the sedimentation volume was increased by the addition of xanthan gum to the suspensions.

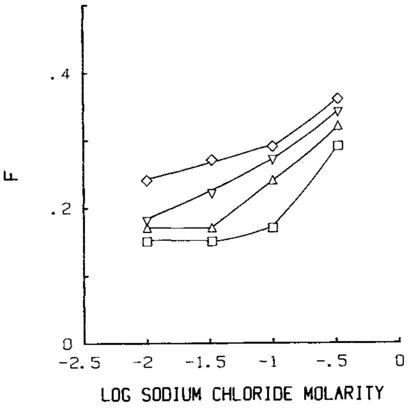

Fig. 2. Sedimentation volume of sulfamerazine suspensions containing sodium chloride and xanthan gum. (□) No xanthan gum; (△) 0.067% xanthan gum; (▽) 0.133% xanthan gum; (◇) 0.2% xanthan gum.

Assuming that the value of the sedimentation volume is directly related to the degree of flocculation (7), the data in Figs. 2 and 3 indicate that the suspensions became more flocculated as the xanthan gum concentration was raised. This was confirmed by microscopy (Table I). As an example, suspensions containing 0.033 *M* sodium chloride and either 0 or 0.067% xanthan gum were deflocculated. Suspensions containing higher xanthan gum concentrations (0.133% and above) were flocculated. The same pattern of behavior was observed with suspensions, containing other sodium chloride concentrations or other salts, that were deflocculated in the absence of gum. In no case did the addition of xanthan gum result in deflocculation.

It is apparent that, for each salt, the higher the salt concentration, the lower is the concentration of xanthan gum needed to produce a flocculated suspension, indicating a synergistic effect of salt and polymer. In general, those suspensions that were flocculated were easy to resuspend, while the deflocculated suspensions caked.

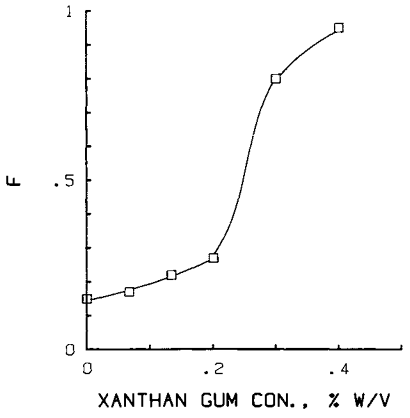

Fig. 1. Sedimentation volume of sulfamerazine suspensions containing 0.033 *M* NaCl.

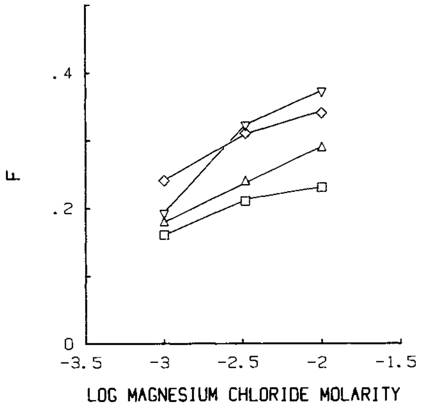

Fig. 3. Sedimentation volume of sulfamerazine suspensions containing magnesium chloride and xanthan gum. (□) No xanthan gum; (△) 0.067% xanthan gum; (▽) 0.133% xanthan gum; (◇) 0.2% xanthan gum.

Table I. Minimum Xanthan Gum Concentration Required for Flocculation of Sulfamerazine Suspensions

Salt	Molarity	Lowest xanthan gum concentration at which suspensions were flocculated (%, w/v)
None	—	0.2
NaCl	0.01	0.2
	0.033	0.133
	0.1	0.133
	0.33	0
$CaCl_2$	0.001	0.133
	0.0033	0
	0.01	0
$MgCl_2$	0.001	0.133
	0.0033	0.067
	0.01	0

The major difference between the effect of sodium chloride and that of salts of divalent cations was that the concentration of divalent salt required to cause suspension flocculation was much lower than that of monovalent salt (Figs. 2 and 3, Table I). Considering that the drug particles were negatively charged, these results are in agreement with the Schultze–Hardy rule.

The deflocculated nature of sulfamerazine suspensions containing no xanthan gum or added salt can be understood in terms of repulsion between the negatively charged particles (6). Electrolytes reduce this repulsion, shifting the balance in favor of attractive (van der Waals') forces, which results in flocculation. It has previously been shown that the effectiveness of salts in flocculating coarse pharmaceutical suspensions by reduction of double-layer repulsion is related to the charge of the counterion, in agreement with DLVO theory (8).

The action of xanthan gum as a flocculant differs from that of salt. Under the microscope, suspension particles flocculated by the gum were smaller and much less dense than the aggregates that resulted from salt flocculation.

There was also a difference in behavior when suspensions were diluted with distilled water to 10 times their original volume. Suspensions that had been flocculated by salt remained flocculated and were easily resuspended after settling. Suspensions that had been flocculated by polymer at low salt concentrations generally became deflocculated and settled into a compact cake. These results suggest a lower net energy of particle attraction due to the gum, although it is possible that desorption of polymer is responsible for the change in flocculation state upon dilution.

The reduction by salts in the concentration of gum needed for flocculation may be rationalized in terms of the bridging model (9–11). Because both gum molecules and sulfamerazine particles have a negative surface charge (3,6), repulsion would prevent adsorption, which is a prerequisite for bridging. The addition of salt reduces electrostatic repulsion, permitting adsorption to take place. The concentration of salt required is lower than that needed for flocculation by the salt alone.

Although the consistency of the suspensions increases substantially as the gum concentration is raised, we do not believe that viscosity per se played a major role in determining the sedimentation volumes that were measured. The values reported in Figs. 2 and 3 were stable for some time. Furthermore, the effect of salts on aqueous solutions containing 0.2% or less gum is to lower the viscosity (1), while the sedimentation volume increased as the salt concentration was raised.

Sedimentation Rate

Most of the sedimentation curves were linear for a period of time before beginning to level off. Rates obtained from these initial values were calculated and mean values are listed in Table II. Group I contains suspensions whose salt concentrations were insufficient in themselves to induce flocculation. They were flocculated by the gum. Group II suspensions were flocculated at the salt level used. In the absence of xanthan gum, sedimentation was essentially complete within a few days. The initial sedimentation rate for these suspensions was estimated to be greater than 7 cm/day.

From the data in Table II, it is evident that sedimentation rate was inversely related to the concentration of gum present. This is shown graphically in Fig. 4, in which the logarithm of the average initial sedimentation rate for each group in Table II is plotted against the xanthan gum concentration. An increase in the xanthan gum concentration of 0.1% resulted in a decrease in the rate of sedimentation of about 5 to 10 times among the sulfamerazine suspensions investigated. Suspensions containing 0.4% xanthan gum exhibited minimal sedimentation during a 5-month period. Nevertheless, pourability was not adversely affected.

A second trend apparent from examination of Table II and Fig. 4 is that the sedimentation rate tended to be higher in those suspensions containing sufficient salt to cause flocculation in the absence of xanthan gum. This is related to the higher particle density and aggregation tendency found with salt flocculation than with polymer flocculation. Depending on the arrangement of primary particles within the floc, a certain amount of the medium will be trapped. The density of the floc is therefore lower than that of a single particle by itself. Other factors being equal, loosely structured flocs would settle more slowly because they have a density closer to that of the medium than tightly knit flocs.

Table II. Mean Sedimentation Rates in Sulfamerazine Suspensions

			Sedimentation rate (cm/day) at a xanthan gum concentration (%, w/v) of			
Group[a]	Salt	Molarity	0.133	0.2	0.3	0.4
—	None	—	0.45	0.12	0.009	0.001
I	NaCl	0.033	0.50	0.20	0.012	0.001
II		0.33	0.93	0.25	0.051	0.008
I	$MgCl_2$	0.001	1.2	0.16	0.018	0.001
II		0.01	1.1	0.30	0.022	0.006
I	$CaCl_2$	0.001	1.0	0.16	0.030	0.001
II		0.01	2.3	0.75	0.17	0.009

[a] Group I contains polymer-flocculated suspensions. Group II contains salt-flocculated suspensions.

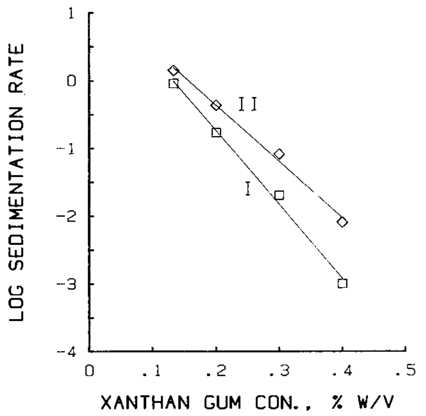

Fig. 4. Mean sedimentation rate as a function of xanthan gum concentration. (I) Gum-flocculated systems; (II) salt-flocculated systems.

CONCLUSIONS

Xanthan gum, although anionic, can act as a flocculant for sulfamerazine particles, which are negatively charged, in the presence of salts. The gum concentration needed to cause flocculation was inversely related to the concentration of salt. Salt effects were in accord with the Schultze–Hardy rule and the DLVO theory, confirming that salts act by reducing repulsion between charged particles and between particles and gum molecules. Suspension characteristics depended on the flocculation mechanism, which was different for xanthan gum and the electrolytes.

Sedimentation kinetics were strongly influenced by the xanthan gum concentration. Floc size and density, which depend on the flocculation mechanism, are secondary factors in sedimentation.

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