

hydrolysis of aspirin to salicylic acid within the corpus tissue. One might also speculate that the submucosa may be the site of the initial injury due to the apparent buildup of aspirin and metabolites at that level.

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Effect of Adsorbed Surfactant on Particle-Particle Interactions in Hydrophobic Suspensions

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Abstract □ The degree of flocculation of sulfamerazine suspensions as represented by relative sedimentation volume was determined as a function of both surfactant and electrolyte concentration. The results emphasize the importance of knowing the location as well as the concentration of the surfactant and are consistent with the Derjaguin, Landau, Verwey, and Overbeek theory.

Keyphrases □ Suspensions, hydrophobic (sulfamerazine)—degree of flocculation, relative sedimentation volume, effects of surfactant (sodium dodecyl polyoxyethylene sulfate) and electrolyte concentration □ Surfactants (sodium dodecyl polyoxyethylene sulfate)—effect on particle-particle interactions in hydrophobic (sulfamerazine) suspensions □ Sodium dodecyl polyoxyethylene sulfate—effect on flocculation of sulfamerazine suspensions □ Sulfamerazine suspensions—effect of adsorbed surfactant on particle-particle interactions □ Flocculation, sulfamerazine suspensions—effects of surfactant and electrolyte concentration

Controlled flocculation has been the subject of many papers over the past 15 years (1-5). Haines and Martin (1, 2) suggested that suspension flocculation can be controlled by modifying the charge surrounding suspended hydrophobic particles by the addition of electrolyte. For example, the addition of aluminum chloride to 2% sulfamerazine suspensions containing dioctyl sodium sulfosuccinate reduced the ζ -potential essentially to zero, producing pharmaceutically stable suspensions characterized by high final sedimentation volumes.

Wilson and Ecanow (3) took issue with the work of Haines and Martin for several reasons: (a) since flocculation was reported to have occurred spontaneously, the true ζ -potential could not have been measured; (b) it was unlikely that van der Waals' forces would be operative with particles greater than 2-5 μm .; and (c) the effect of electrolyte on the surfactant was not taken

into account. During a subsequent investigation, they observed the formation of a precipitate when dioctyl sodium sulfosuccinate at concentrations used by Haines and Martin was mixed with aluminum chloride. Flocculation was interpreted as being due to a chemical reaction between the surfactant and the electrolyte instead of a reduction of the ζ -potential.

Matthews and Rhodes (4-6) studied suspensions of sulfamerazine and griseofulvin prepared with sodium lauryl sulfate, which is precipitated by aluminum chloride, and sodium dodecyl dioxyethylated sulfate, which apparently is not precipitated by aluminum chloride. The addition of aluminum chloride to both suspensions resulted in aggregation. Different sedimentation rates were observed; however, final sediment heights were identical. They interpreted the aggregation mechanism as "flocculation" for the suspension containing sodium lauryl sulfate and as "coagulation" for the suspension containing sodium dodecyl dioxyethylated sulfate. Ecanow *et al.* (7) claimed that both suspensions were "flocculated" on the basis of equal final sediment volumes and sediment compressibility. The difference in sedimentation rate was considered to be a function of aggregate structure, number, and geometry.

Two possible mechanisms have been proposed to explain flocculation (8-10): absorption bridging by the surfactant between suspension particles and cross-linking of suspension particles produced by metal-ion interactions with the adsorbed surfactant. Coagulation is an aggregation process resulting from a reduction in the ζ -potential to a point where attractive forces predominate. The aggregate is dense and nonporous and forms a caked sediment.

Table I—Composition and Sedimentation of Sulfamerazine Suspensions

Concentration of Surfactant ^a in Solution (Equivalent $\times 10^3/l.$), Initial Equilibrium	Surface Coverage	Sodium Chloride Concentration, moles/l.	Relative Sedimentation Volume, H_u/H_0
Series A^b			
3.43	—	1.00	0.91
3.43	---	0.50	0.94
3.43	—	0.24	0.92
3.43	—	0.00	0.91
Series B			
22.6	10.0	1.00	0.60
20.7	10.0	0.50	0.59
18.9	10.0	0.24	0.15
14.2	10.0	0.00	0.59
Series C			
19.6	7.0	1.00	0.56
15.6	3.0	1.00	0.59
11.7	—	1.00	0.60
7.8	—	1.00	0.68
3.9	—	1.00	0.84
1.6	—	1.00	0.97

^a Sodium dodecyl polyoxyethylene sulfate. ^b Initial concentration equal to the CMC in pure water.

Another possible mechanism for flocculation is aggregation at relatively large interparticle distances as predicted by the Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory (6, 11-13). Coagulation is interpreted as aggregation in the primary minimum, resulting in a closely packed, tightly bound aggregate; flocculation is interpreted as aggregation in the secondary minimum, resulting in a loose, weakly bound network. An attractive feature of such an explanation is an allowance for electrolyte effects other than chemical interactions.

This article reports investigations on suspension aggregation and offers the following observations on sulfamerazine suspensions.

EXPERIMENTAL

The surfactant, sodium dodecyl polyoxyethylene sulfate, supplied as a 50% hydroalcoholic solution¹, was purified by diluting with acetone to precipitate the inorganic salts present, filtering, and removing the solvents by vacuum distillation. The purified surfactant as an oil was diluted to a known volume with water and standardized with benzethonium chloride according to the method described by Epton (14) and modified by Weatherburn (15). All concentrations of the surfactant are expressed as equivalents of benzethonium chloride per liter, since the exact molecular weight is not known.

Sulfamerazine² powder was used as received. The mean volume surface diameter and specific surface area were determined³ to be 2.48 μm . and 1.77 m^2/g ., respectively. Adsorption isotherms of the surfactant on sulfamerazine were determined at three concentrations of sodium chloride and in pure water. Thus, it was possible to prepare suspensions in which the relative concentrations of the surfactant adsorbed and free in solution were known.

Suspensions were prepared by adding a known volume of the surfactant solution to a weighed quantity of sulfamerazine powder. The mixture was stirred continuously for 16 hr., at which time it was transferred to a glass sedimentation tube having an inside diameter of 1.9 cm. The suspensions fell into one of three categories: Series

A, prepared at various electrolyte concentrations and an initial concentration of surfactant equal to the critical micelle concentration (CMC) of the surfactant in water; Series B, prepared at various electrolyte concentrations and at surfactant concentrations such that the particle surface was saturated with surfactant; and Series C, prepared at constant electrolyte concentration and various surfactant concentrations.

RESULTS AND DISCUSSION

The Series A suspensions in Table I were prepared with an initial concentration of surfactant equal to the CMC in water. Consequently, the surface of the particles was only partially covered with surfactant. A very high relative sediment volume, H_u/H_0 , was observed, indicating a large degree of aggregation. The sediment was very loosely packed, and the supernate was clear, indicating flocculation.

Cross-linking of surfactant by metal ions, shown to occur with aluminum ion and sodium dodecyl sulfosuccinate and sodium lauryl sulfate (3, 4), seems an improbable explanation for the flocculation of Series A suspensions considering the high degree of flocculation at zero sodium chloride concentration. Such a mechanism would also demand a dependence of H_u/H_0 on electrolyte concentration, which is obviously absent. Adsorption bridging would allow for the lack of dependence on electrolyte concentration but seems an unlikely mechanism for a charged surfactant.

There remains the flocculation mechanism as described by the DLVO theory. The high degree of flocculation at zero electrolyte concentration indicates very little, if any, charge repulsion between particles, *i.e.*, a very small or zero ζ -potential. Such a condition would result only from a very low charge density on the particles which follows from the low initial concentration of surfactant. The DLVO theory predicts that at low ζ -potential and/or relatively large distances, particle particle interactions would be insensitive to electrolyte concentration (16, 17).

The Series B suspensions, by contrast, were prepared at surfactant concentrations such that the particle surface was completely saturated. It follows that the surface charge or ζ -potential at zero electrolyte concentration would be considerably higher than that of the corresponding Series A suspension. This was evidenced by the reduced degree of flocculation, as indicated by the lower relative sedimentation volume.

The addition of 0.24 *M* sodium chloride resulted in a dramatic decrease in the relative sedimentation volume. The sediment was dense (centrifugation reduced H_u/H_0 to 0.14) and the supernate was cloudy, indicative of either a monodispersed or a coagulated system. The sedimentation rate was the slowest of the series, again indicating either a monodispersed (11) or a coagulated suspension, depending on whether flow is laminar or turbulent (9).

Considering that the particles have a negative charge at zero electrolyte concentration:

1. The addition of sodium chloride could increase the adsorption of the surfactant such that at 0.24 *M* electrolyte the ζ -potential is sufficient for a monodispersed state. That adsorption is increased is evident from the data in Table I. Also, the neutralization of charge by counterions would have to be negligible. Electrolyte addition beyond 0.24 *M* would progressively increase adsorption and cause neutralization of the negative charge, with the net effect being a degree of flocculation.

2. The addition of sodium chloride could neutralize the charge on the particles essentially to zero, resulting in a coagulated system. Further addition of electrolyte would charge the particles by adsorption of counterions, reestablishing a degree of flocculation.

It would be impossible to distinguish between these two explanations without further experimental observations. The ζ -potential would go through a maximum in the first and a minimum in the second. The DLVO theory does, however, offer a possible explanation for the behavior of the Series B suspensions, whereas cross-linking does not seem to be applicable.

A similar comparison is found for the Series C suspensions. Cross-linking would predict a direct relationship between the surfactant concentration and H_u/H_0 . The inverse relationship found experimentally is explainable within the framework of the DLVO theory. An increase in surfactant concentrations would increase the surface charge and decrease the degree of flocculation.

It is obvious from these observations that the effect of electrolytes

¹ Richanol S1285, Richardson Co.

² Sulfamerazine USP, American Cyanamid Co.

³ With a Fisher Sub Sieve Sizer.

on flocculation behavior depends not only on the surfactant concentration but also on the location of the surfactant and the degree of surface coverage by the surfactant. Electrolyte effects at one surfactant level can be eliminated or even reversed by changing the surfactant concentration.

It is also suggested that aggregation in a secondary potential energy minimum as described by the DLVO theory is a valid mechanism for interpreting flocculation. Flocculation mechanisms would then be classified as: (a) adsorption bridging, (b) cross-linking or chemical bridging, and (c) DLVO aggregation (secondary minimum). And coagulation would be defined by: (a) film-film bonding, and (b) DLVO aggregation (primary minimum).

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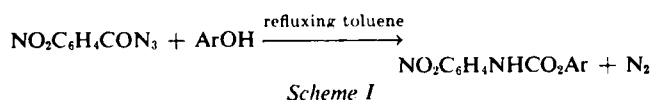
Synthesis and Antifungal Activity of Polyhalophenyl Esters of Nitrocarbanilic Acids VI

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Abstract □ Twenty-two polyhalophenyl esters of *meta*- and *para*-nitrocarbanilic acids were synthesized and tested for antifungal activity against *Candida albicans*, *Penicillium notatum*, and *Aspergillus fumigatus*. The 2,4,6-trichlorophenyl ester of *m*-nitrocarbanilic acid was found to be the most active compound.

Keyphrases □ Nitrocarbanilic acids, polyhalophenyl esters—synthesis, antifungal activity □ Polyhalophenyl esters, nitrocarbanilic acids—synthesis, antifungal activity □ Antifungal agents, potential—synthesis and testing of 22 polyhalophenyl esters of nitrocarbanilic acids

In continuing research with the syntheses of new carbamic acid derivatives (1–5) with antifungal activity, a series of polyhalophenyl esters of *meta*- and *para*-nitrocarbanilic acids was prepared by interaction (Scheme I) of the corresponding nitrobenzoyl azide



with polyhalophenols in refluxing toluene, and physical data were compiled (Table I).

All prepared compounds were tested against *Candida albicans* 28012, *Penicillium notatum* S-13, and *Asper-*

gillus fumigatus CDC 24¹ *in vitro* using BBL Sabouraud dextrose agar medium.

Each compound was tested at 5, 10, and 25 mcg./ml. All compounds were dissolved in acetone at a concentration of 5 mg./ml. These solutions were diluted with hot culture medium to the desired concentrations and autoclaved at 120° for 2 hr. Five replicates of each concentration were prepared.

The antifungal activity of all compounds tested except XIX and XX was insignificant at a concentration of 5 mcg./ml. Compounds XII and XV showed only slight growth inhibition at concentrations of 25 mcg./ml. (Table II).

EXPERIMENTAL²

m-Nitrocarbanilic acid *p*-tolyl ester was prepared as follows. *m*-Nitrobenzoyl azide (1.92 g., 0.01 mole) in 20 ml. of dry toluene was refluxed for 2 hr. To the boiling mixture, *p*-cresol (1.08 g., 0.01

¹ Microorganisms were obtained from the Department of Parasitology, Public Health Institute, Tehran, Iran.

² Melting points were taken on a Kofler hot stage microscope and are uncorrected. The IR spectra were determined with a Leitz spectrograph model III. NMR spectra were obtained on a Varian A 60A instrument. Mass spectra were recorded on a Varian Mat 111 instrument. *m*- and *p*-Nitrobenzoyl azides were prepared according to Curtius *et al.* (6).