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Short Communication

Effect of formulation additives on flocculation of dispersions stabilized by a non-ionic surfactant

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Non-ionic surfactants are employed in pharmaceutical and cosmetic disperse systems as wetting agents, emulsifiers and stabilizers. Interfacial properties of these surfactants are significantly influenced by their state of dissolution (Shinoda, 1967). Various additives, such as salts, may influence the hydration of the polar portion of non-ionic surfactants and consequently alter the phase inversion temperature of emulsions (Shinoda and Takeda, 1970). Certain alcohols caused an increase in hydration of polyoxyethylene nonylphenol ethers, while others had the opposite effect (Marszall, 1977).

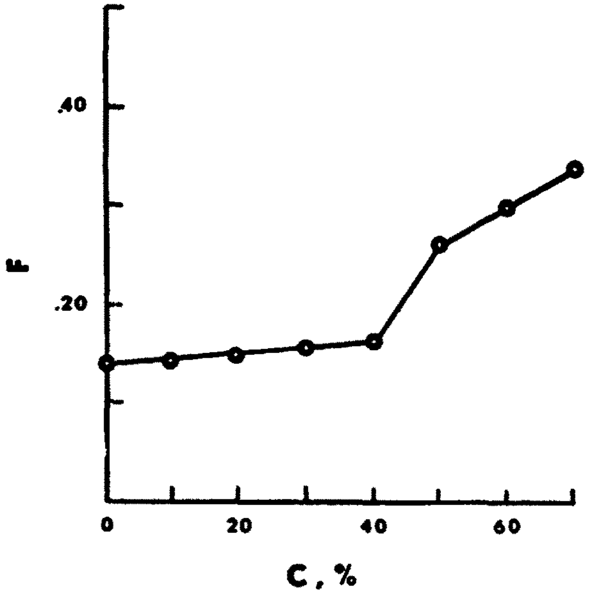
An important factor in the shelf life stability of pharmaceutical suspensions is the state of flocculation of the particles. Deflocculated suspensions tend to cake. Flocculated systems, on the other hand, are generally much easier to redisperse and are preferred for this reason (Haines and Martin, 1961). In suspensions that contain non-ionic surfactants such as wetting agents, dispersing agents or stabilizers, it is likely that additives that affect the hydration state of the surfactants may also alter the degree of flocculation of the suspensions. By judicious selection of additives, the formulator would have additional control in manipulating the characteristics of pharmaceutical suspensions.

The additives chosen for study were sodium sulfate and propylene glycol. Sulfamerazine suspensions and mineral oil emulsions were used as model dispersions to assess the effect of the additives.

Polysorbate 40 (Tween 40, ICI America) and Sulfamerazine U.S.P. (American Cyanamid) were used as received. All other materials were reagent or U.S.P. grade.

Suspensions. Twenty ml of a 2% aqueous polysorbate 40 solution was added to 10 g of sulfamerazine in a mortar. After dispersion, an additive, if present, was added as an aqueous solution. After thorough agitation, the suspension was transferred to a mixing cylinder. The mortar was rinsed with water and the cylinder was made up to 100 ml with water. The suspension was agitated in the cylinder for about 0.5 min and then permitted to sediment.

Emulsions. A large quantity of a primary emulsion, sufficient to make all the emulsions in an experimental series, was first produced. The finished emulsions were made by dilution of the primary emulsion with aqueous solutions containing an additive, if present. This technique was adopted to obviate differences in emulsion stability that might be caused by slight variations in manufacturing technique if the emulsions were



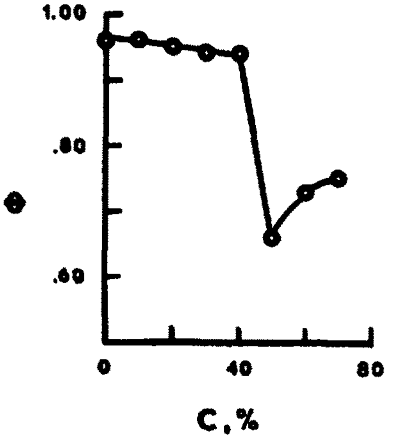


Fig. 1. Effect of propylene glycol concentration (%v/v) on sedimentation volume of sulfamerazine suspensions containing polysorbate 40.

Fig. 2. Effect of propylene glycol concentration in the aqueous phase (%v/v) on relative cream volume of mineral oil emulsions.

prepared individually. Each emulsion contained 60 ml of primary emulsion, which consisted of 40 ml of mineral oil, 3 ml of polysorbate 40 and 17 ml of water. The primary emulsion was prepared by incorporating the surfactant and mineral oil, heating to 60°C, and adding the mixture to water at 60°C with agitation in a high shear mixer (Homomixer). The primary emulsion was then cooled, with agitation.

To determine cloud point, a 0.2% surfactant solution containing sodium sulfate or propylene glycol, where appropriate, was heated on a hot plate until turbidity was observed. Repeated measurements on the same solution were within 1°C. With different batches of solution, cloud point values were within 1°C of the mean.

The sulfamerazine suspensions were permitted to stand until the volume of sediment did not change for at least two weeks. The flocculation state of the suspensions was assessed using the sedimentation volume, F, defined as the ratio of the ultimate volume of sediment to that of the total suspension. Fig. 1 shows the effect of propylene glycol on F. At 40% propylene glycol or less, F ranged from 0.14 to 0.16. These suspensions were deflocculated and, in fact, became impossible to redisperse after standing for about two weeks. With propylene glycol concentrations of 50% or higher, the sedimentation volume increased showing that the suspensions were now flocculated. The flocculated suspensions were capable of redispersion by inversion and shaking of the mixing cylinders.

None of the emulsions inverted or cracked. The emulsions were permitted to stand for 21 days and the relative cream volume, ϕ, was measured. ϕ is defined as the volume of cream divided by that of the total emulsion. According to this stability criterion, a value of 1 for the relative cream volume represents an emulsion of high stability. Less stable emulsions have smaller values of ϕ. Unlike F, ϕ is a time dependent quantity that may be influenced by various kinetic factors such as density and viscosity.

Fig. 2 is a plot of the relative cream volume of mineral oil emulsions as a function of propylene glycol concentration in the aqueous phase. The increase in density in water solution due to propylene glycol is quite small but viscosity does increase significantly (Jones and Tamplin, 1952) and is expected to affect creaming rate, especially at high concentrations. The increase in viscosity probably accounts for the rise in ϕ with increasing propylene glycol concentration in emulsions containing 50–70% propylene glycol. The precipitous drop in ϕ that occurs when the propylene glycol content goes from 40 to 50% is all the more remarkable because the viscosity is being increased. The sharp change in emulsion properties (Fig. 2) and in suspension flocculation (Fig. 1) occur over the same propylene glycol concentration range.

Sulfamerazine suspensions containing 5% sodium sulfate of less were deflocculated while those with higher concentrations were flocculated. All of the emulsions containing sodium sulfate had about the same value of ϕ (0.6). But the medium, which was cloudy at low sodium sulfate concentrations, became clear when the sodium sulfate concentration was higher than 5%. This may be due to flocculation of emulsion globules dispersed in the medium. As with propylene glycol, changes in both suspension and emulsion properties took place at the same sodium sulfate concentration.

At low propylene glycol concentrations, the cloud point of surfactant solutions was

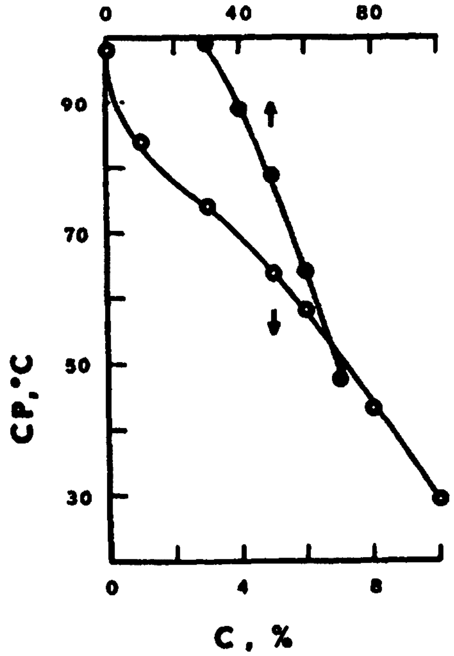


Fig. 3. Cloud point of polysorbate 40 solutions, 0.2% w/v, as a function of additive concentration. ○, sodium sulfate; ●, propylene glycol.

elevated to over 100°C, beyond our measuring capability (Fig. 3). This increase agrees withe the findings of Marszall (1977), who worked with propylene glycol concentrations up to 1 M. At a propylene glycol concentration of 30%, the cloud point dropped to just below 100°C, and then decreased with further rise in propylene glycol concentration. Sodium sulfate caused a monotonic reduction in cloud point (Fig. 3), in agreement with previous observations (Shinoda and Takeda, 1970).

The cloud point data indicate that propylene glycol (at concentrations of 30% and above) and sodium sulfate cause dehydration of polyoxyethylene groups on the surfactant molecule. It seems likely that dehydration is involved in the effect of these additives on the properties of suspensions and emulsions described above.

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