Coacervation of Alkyltrimethylammonium Bromides by Tartrazine, Amaranth, Carmoisine, and Erythrosine

B. W. BARRY[x] and G. M. T. GRAY

Abstract □ The interaction of aqueous solutions of alkyltrimethylammonium bromides (C_{12}-C_{16}) with 0.15 and 15 mmoles/liter aqueous solutions of the anionic dyes tartrazine, amaranth, carmoisine, and erythrosine was studied by phase separation techniques and microscopy between 5 and 95°. Cetrimide–dye systems were also studied in the presence of sodium chloride, sodium sulfate, sodium citrate, and calcium chloride. Between certain surfactant concentrations and temperature limits, a coacervate phase, or an anisotropic phase, formed. Phase separation diagrams, in conjunction with coacervation theory, were used to interpret the effects of surfactant concentration and chain length, of dye concentration and chemical structure, of temperature, and of total ionic strength on the extent of interaction. Differences between the interactions of a hydrophilic dye, tartrazine, and those of amaranth, carmoisine, and erythrosine, which all possess hydrophobic as well as hydrophilic moieties, were shown. Tartrazine functioned as a simple electrolyte and interacted only with the surface charges of surfactant micelles. For the other dyes, interaction was *via* solubilization of a dye–surfactant complex within the micelle, together with ionic surface interactions. Amaranth, carmoisine, and erythrosine induced the formation of surfactant micelles at concentrations far below the CMC's of the surfactants in water. The limits of compatibility of the dyes with the surfactants were also defined.

Keyphrases □ Dyes (tartrazine, amaranth, carmoisine, and erythrosine)—coacervation by alkyltrimethylammonium bromides, phase separation techniques and microscopy, effects of salts on cetrimide–dye systems, effects of surfactant concentration and chain length, dye concentration and structure, temperature, and total ionic strength on interaction, micelle formation □ Alkyltrimethylammonium bromides—interactions with anionic dyes, phase separation techniques and microscopy □ Cetrimide–dye (anionic) systems—interactions studied by phase separation techniques and microscopy, effects of added salts □ Coacervation—tartrazine, amaranth, carmoisine, and erythrosine with alkyltrimethylammonium salts, interactions studied by phase separation techniques and microscopy, phase separation diagrams, possible mechanisms

Coacervation, the term used (1) to describe the separation of a colloidal solution into two liquid layers, one of which is rich in colloidal component and the other poor, is a well-established phenomenon. Dervichian (2) compared the coacervates produced in different systems and showed that many similarities existed between them. Voorn (3) applied a theoretical treatment to complex coacervation of polycations and polyanions to explain many previously reported observations. More recently, attention has been focused on the coacervation of aqueous solutions of cationic and anionic surfactants by inorganic salts (4–10).

In a study of the compatibility of the dye amaranth with long-chain quaternary ammonium bromides, a similar phenomenon was observed (11). In view of the extent of the literature concerning the interactions of dyes with surfactants (*e.g.*, 12–18), it is surprising that no similar findings have been reported.

In a preliminary investigation, under certain conditions other food and drug dyes coacervated aqueous solutions of alkyltrimethylammonium bromides. Furthermore, some aqueous dye–surfactant coacervates showed a different temperature dependence from those formed by interaction of the surfactants with inorganic salts (5, 7). In the latter case, coacervated solutions when warmed became homogeneous at some critical temperature, whereas in the former situation the temperature dependence was reversed.

As food and drug preparations are often subjected to thermal fluctuations, it is important to know and to understand the effects of differing temperatures on the interactions of the constituents of these products. Therefore, the dyes used in the present study were chosen on the basis of two considerations: *(a)* their importance as colorants in the food, drug, and cosmetic industry, which would thus provide further insight into the compatibility of the dyes with the pharmaceutically important long-chain quaternary ammonium bromides; and *(b)* the chemical natures of the dyes, in an attempt to elucidate structure–activity relationships with regard to their effects on coacervation.

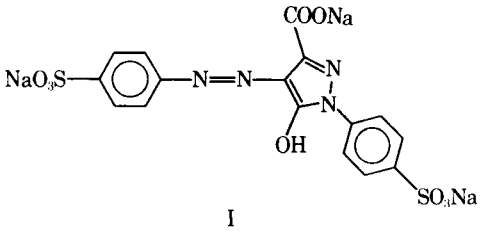
Phase diagrams for the interaction of the dyes with surfactants were constructed. These were used to illustrate the effects of concentration and chain length of the quaternary ammonium bromides, of concentration and chemical structure of the dyes, of temperature, and of added inorganic salts on the extent of coacervation. The morphology of the systems was also examined to determine the nature of the separated phase.

EXPERIMENTAL

Materials—The following dyes were used: tartrazine[1], trisodium salt of 3-carboxy-5-hydroxy-1-*p*-sulfophenyl-4-*p*-sulfophenylazopyrazole (I); amaranth BPC (1954)[1], trisodium salt of 1-(4-sulfo-1-naphthylazo)-2-naphthol-3,6-disulfonic acid (II); carmoisine[2], disodium salt of 2-(4-sulfo-1-naphthylazo)-1-naphthol-4-sulfonic acid (III); and erythrosine[1], disodium salt of 2′,4′,5′,7′-tetraiodofluorescein (IV). All samples were analyzed for their dye content according to a reported method (19). The purity of each dye with respect to its dry weight was: amaranth, 93.3%; carmoisine, 95.5%; tartrazine, 98.4%; and erythrosine, 97.7%. All dyes were used as received. Ancillary dyes used were: Sunset Yellow FCF, disodium salt of 1-(4-sulfophenylazo)-2-naphthol-6-sulfonic acid (V); and Orange II, *p*-(2-hydroxy-1-naphthylazo)-benzenesulfonic acid sodium salt (VI).

The alkyltrimethylammonium bromides used, *i.e.*, hexadecyl-, tetradecyl-, dodecyl-, and trimethylammonium bromides, and cetrimide BP were described elsewhere (11, 20). Since each surfactant was a mixture of homologs, an "average chain length" was calculated by GLC analysis of the surfactants (20). These average values were 15.68, 13.64, 12.40, and 13.56, respectively.

[1] D. F. Anstead Ltd., Billericay, England.
[2] Donated by I.C.I., Ltd., Dyestuffs Division, Manchester, England.



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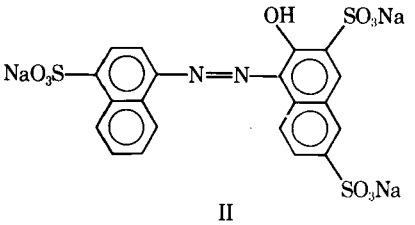

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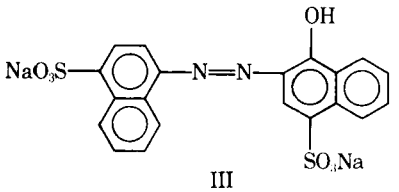

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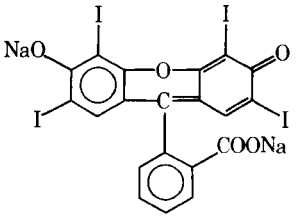

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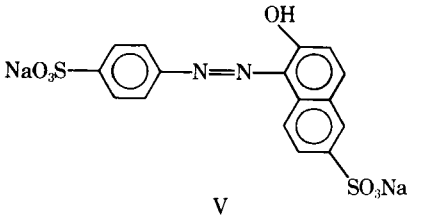

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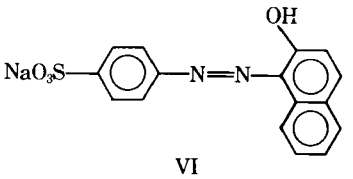

VI

The inorganic salts were analytical grade. Water, double distilled from an all-glass still, had a conductance not greater than 1.2×10^{-6} ohm^{-1} cm^{-1}.

Morphology—With a microsyringe[3], various volumes of 0.15-mmole/liter aqueous dye solutions were mixed on a cavity slide with various volumes of surfactant dissolved in 0.15-mmole/liter aqueous dye solution so that the final volume was 50 μl. A coverslip was sealed in place and the solutions were examined microscopically in normal light and between crossed polars at ×100 and ×400 on a hot-stage[4]. Changes were noted as the temperature was slowly raised. The experiment was repeated using 15-mmoles/liter dye solutions and correspondingly higher concentrations of surfactant.

When the systems were too viscous to be mixed properly on the slide, 10-ml quantities were agitated using a mixer-emulsifier[5] fitted with a microhead; portions were examined as before.

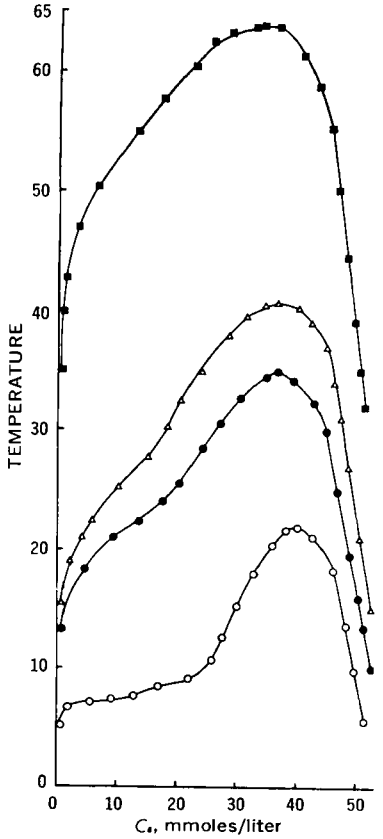

Figure 1—*Diagram showing temperatures and surfactant concentrations at which tartrazine–alkyltrimethylammonium bromide solutions separated into two or more phases. Tartrazine concentration is 15 mmoles/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *tartrazine–hexadecyltrimethylammonium bromide;* △, *tartrazine–tetradecyltrimethylammonium bromide;* ●, *tartrazine–cetrimide; and* ○, *tartrazine–dodecyltrimethylammonium bromide.*

Phase Diagrams—These were constructed as follows. A 10-ml aliquot of an aqueous 0.15-mmole/liter dye solution was pipeted into a covered titration vessel jacketed by a water bath to ensure uniform heating. A clear solution of a suitable concentration of surfactant (2–10 mmoles/liter) in aqueous 0.15-mmole/liter dye solution was added from a semimicroburet.

The mixture was stirred with a magnetic stirrer, and the temperature was measured using a bead thermistor[6] connected to a universal bridge[7] (required because of the small volumes used). The thermistor had previously been calibrated[8] in the range 5–95° so that the temperature could be read correctly to 0.1°.

In the neighborhood of the critical regions, the surfactant–dye solution was added dropwise at constant temperature until coacervation occurred (left-hand boundary of diagrams) or was suppressed (right-hand boundary). Conversely, the surfactant concentration was held constant and the temperature was varied until the solution coacervated. In both cases, the final surfactant concentration and the temperature of the mixture were recorded to provide data at surfactant concentrations below their critical micelle concentrations (CMC's) in water.

To check results, a 0.15-mmole/liter aqueous dye solution was titrated against aliquots of surfactant–dye solution. The relevant final surfactant concentration and the temperature were noted as before.

Phase diagrams of surfactant concentration, in mmoles/liter, *versus* temperature at constant dye concentration were drawn. Since coacervation is a thermodynamically reversible phenome-

[3] Clark Hamilton Manufacturing AG, 7402 Bonaduz GR, Switzerland.
[4] Kofler.
[5] Silverson Machines Ltd., London, England.

[6] Thermistor TH-B12, Radiospares Ltd., London, England.
[7] Wayne-Kerr.
[8] Against National Physical Laboratory thermometers.

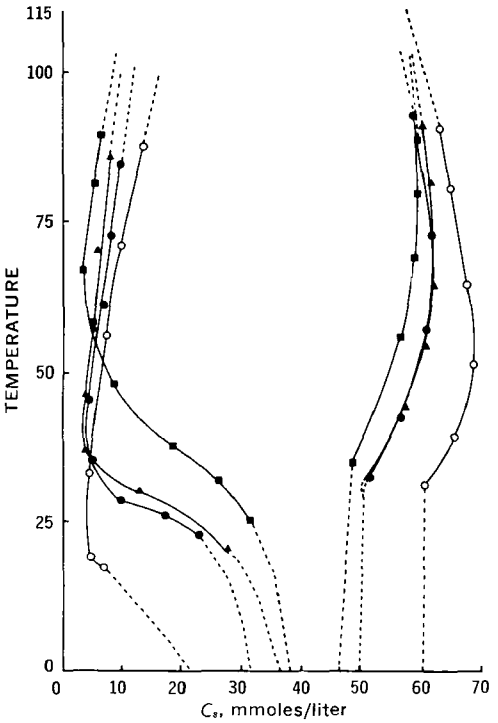

Figure 2—*Diagram showing temperatures and surfactant concentrations at which amaranth–alkyltrimethylammonium bromide solutions separated into two or more phases. Amaranth concentration is 15 mmoles/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *amaranth–hexadecyltrimethylammonium bromide;* ▲, *amaranth–tetradecyltrimethylammonium bromide;* ○, *amaranth–dodecyltrimethylammonium bromide; and* ●, *amaranth–cetrimide.*

non, the phase separation points obtained by these different methods all coincided on the same phase diagram. Thus, the second method was valuable in confirming the location of the phase diagram.

The procedure was repeated using aqueous 15-mmoles/liter dye solutions and clear surfactant-dye solutions containing surfactants at concentrations above their nominal CMC's (usually 200 mmoles/liter). When these mixtures became too viscous for a magnetic stirrer (mainly at ambient temperature), a mixer-emulsifier[5] provided intimate mixing.

Effect of Ionic Strength—The effect of ionic strength on the coacervation of dye–surfactant solutions was investigated. Ten milliliters of aqueous 0.15-mmole/liter dye solutions containing various amounts of sodium citrate was pipeted into the constant-temperature titration vessel. Cetrimide solutions containing 0.15 mmole/liter dye and various concentrations of sodium citrate were added, and the amount added prior to the occurrence of coacervation was noted. The titration was continued until the coacervate dissolved, and the total volume added was noted. The limits of coacervation at constant temperature and at various, constant sodium citrate concentrations were thus found. These were compared with the values found in the absence of sodium citrate; a suitable salt concentration, which had a significant effect on the limits of coacervation, was then chosen. Phase diagrams were constructed as before, using cetrimide and dye solutions containing the chosen concentration of sodium citrate. Phase diagrams were also constructed for sodium chloride, sodium sulfate, and calcium chloride at the same concentration (in milliequivalents per liter) as sodium citrate.

The experiment was repeated using 15-mmoles/liter dye solutions.

Minimum Ratio of Dye to Surfactant Required to Produce Coacervation—The concentration, y, in milliequivalents per liter, of electrolyte (in this case dye) required to produce coacervation in a surfactant system is a linear function of the surfactant concentration. It may be described by the equation:

$$y = Ax + B \qquad \text{(Eq. 1)}$$

where x is the surfactant concentration in milliequivalents per liter, and A and B are constants for any given system. A plot of y against x yields a straight line whose slope, A, provides the value of the minimum ratio of dye–surfactant required to produce coacervation and whose intercept, B, gives the equilibrium concentration of unbound electrolyte.

Bungenberg de Jong and Recourt (5) found that to calculate A for interaction of hexadecyltrimethylammonium bromide with the inorganic salts potassium thiocyanate, potassium iodide, and potassium nitrate, they had to use salt concentrations at "coacervate volumes adapted to the soap concentration," because the values of B varied at different stages of coacervation.

However, in the present work, when coacervation occurred, practically all the dye was bound to the surfactant and B was negligible. Hence, the tedious method of Bungenberg de Jong and Recourt (5) was unnecessary. The minimum ratio of dye–surfactant required for coacervation was thus found by pipeting 1- or 2-ml aliquots of surfactant in aqueous dye of various concentrations into the temperature-controlled glass vessel and agitating with a magnetic stirrer as an aqueous dye solution of the same concentration was added from a 10-ml semimicroburet until an end-point was reached, as shown by persistent turbidity of the mixture. When concordant titers were obtained, graphs of dye concentration, in milliequivalents per liter, *versus* final surfactant concentration, in milliequivalents per liter, were drawn. The experiment was repeated at several temperatures. The gradients and the intercepts of the straight lines were calculated by the method of least squares.

RESULTS

Preliminary Morphological Examinations—Under certain conditions, when aqueous solutions of tartrazine, amaranth, carmoisine, and erythrosine were mixed with the quaternary ammo-

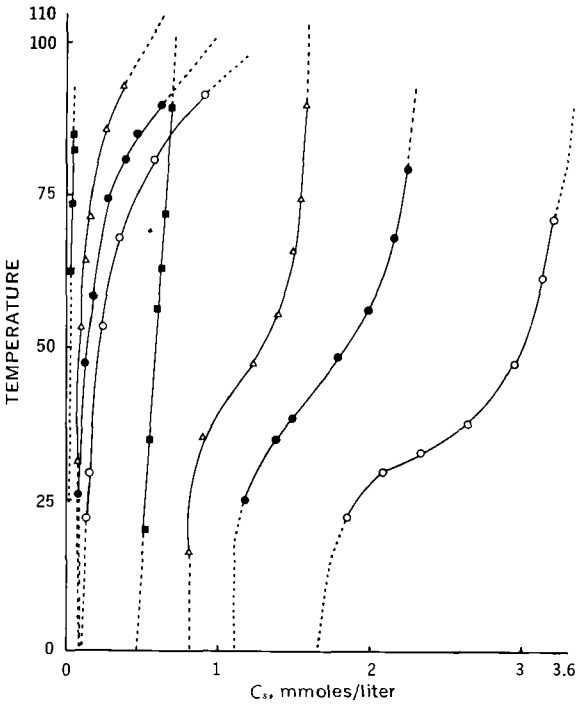

Figure 3—*Diagram showing temperatures and surfactant concentrations at which amaranth–alkyltrimethylammonium bromide solutions separated into two or more phases. Amaranth concentration is 0.15 mmole/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *amaranth–hexadecyltrimethylammonium bromide;* △, *amaranth–tetradecyltrimethylammonium bromide;* ●, *amaranth–cetrimide; and* ○, *amaranth–dodecyltrimethylammonium bromide.*

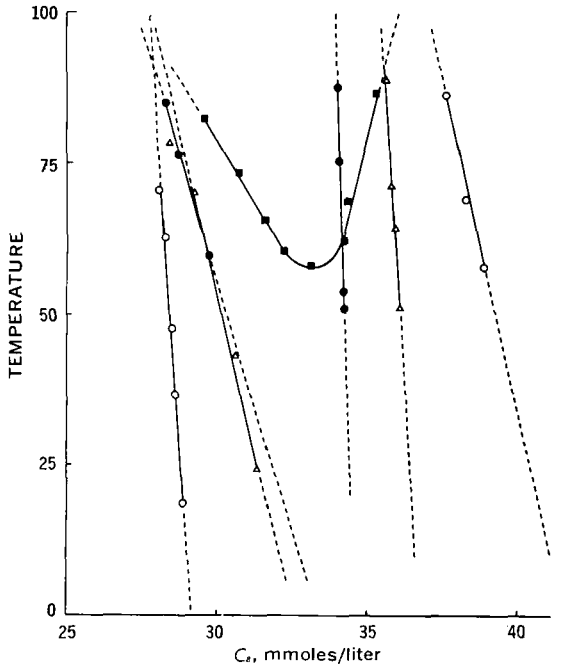

Figure 4—*Diagram showing temperatures and surfactant concentrations at which carmoisine–alkyltrimethylammonium bromide solutions separated into two or more phases. Carmoisine concentration is 15 mmoles/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *carmoisine–hexadecyltrimethylammonium bromide;* △, *carmoisine–tetradecyltrimethylammonium bromide;* ●, *carmoisine–cetrimide; and* ○, *carmoisine–dodecyltrimethylammonium bromide.*

nium compounds, the solutions became turbid. Microscopically, for carmoisine, above 40° the dispersed phase consisted of isotropic, oily droplets and no anisotropic phase was observed, although at temperatures below 40° viscous gels formed. For tartrazine, erythrosine, and amaranth, viscous, mesomorphic phases were often seen, which changed into isotropic, oily droplets as the temperature rose. The temperature at which the dispersed phase became totally isotropic increased with an increase in surfactant chain length. When the turbid dye-surfactant-water systems were equilibrated, two layers formed at temperatures for which the separated phase was isotropic. The bottom layer was a viscous, oily liquid, rich in dye and surfactant. The upper layer was a mobile, clear solution containing little dye or surfactant. This type of phase separation has been termed coacervation (1).

Phase Diagrams—Phase diagrams of the various aqueous dye-surfactant systems are reproduced in Figs. 1–7. (Although a faint turbidity was observed when surfactant was added to an aqueous 0.15-mmole/liter tartrazine solution, microscopic examination yielded no information on the morphology of the species causing the opacity. These dilute systems were not investigated further.) In all dye-surfactant systems studied, phase separation only occurred at certain mixing proportions and temperatures. An excess of dye or of surfactant suppressed coacervation. In some cases there was a maximum temperature for interaction, above which no coacervation occurred. Thus, Figs. 1–7 show that phase separation only took place, at any given temperature, if the system had a composition which fell on, or between, the coacervation limits. Outside the areas defined by these limits, homogeneous solutions formed.

The effect of surfactant chain length on the areas between the coacervation curves differed for each dye. For tartrazine, increasing the chain length increased the area of interaction, whereas for the other dyes the order was usually reversed.

The dye-surfactant-water systems behaved differently with respect to temperature. For the tartrazine systems, warming suppressed coacervation and a maximum temperature for coacervation in each system existed. A plot of this maximum temperature for each surfactant homolog *versus* "average chain length" (see *Materials* section for definition of average chain length) yielded a straight line (Fig. 8), suggesting a simple relationship between the two parameters.

Heating the aqueous 0.15- and 15-mmoles/liter erythrosine-surfactant systems increased the area of coacervation, but the temperature dependence of the amaranth and carmoisine systems was more complex.

The temperatures at which the dispersed amaranth-surfactant and tartrazine-surfactant phases became totally isotropic, as viewed under the polarizing microscope, proved interesting in relation to the phase diagrams. The transition temperatures (anisotropic to fully isotropic) at different mixing ratios for the cetrimide-dye dispersed phases are shown in Fig. 9. At approximately ambient temperature and below, the separated phase showed definite anisotropy and often consisted of irregularly shaped particles. As the temperature rose, these particles rounded off and myelin figures formed. On further heating, the separated phase became isotropic and oily. This anisotropic to isotropic transition occurred over a small temperature range. The starting temperature for the transition was ill defined (approximated by a broken line in Fig. 9). However, the temperature at which the separated phase became totally isotropic was readily measured under polarized light (full line in Fig. 9).

Similar phase transitions were observed when samples of aqueous amaranth or tartrazine containing the other surfactant homologs were heated. The temperature at which the anisotropic to isotropic transition occurred increased as the surfactant chain length increased.

Effect of Ionic Strength—The effects of the relevant inorganic salt concentrations on the dye-cetrimide coacervation curves are shown in Figs. 10–13. With amaranth, carmoisine, and erythrosine, only the effect of salt on the coacervation curves at a dye concentration of 0.15 mmole/liter was studied. The high concentrations of inorganic salt that would have been required to produce a significant effect on the coacervation curves at the higher dye concentration yielded solutions in which the dyes were insolu-

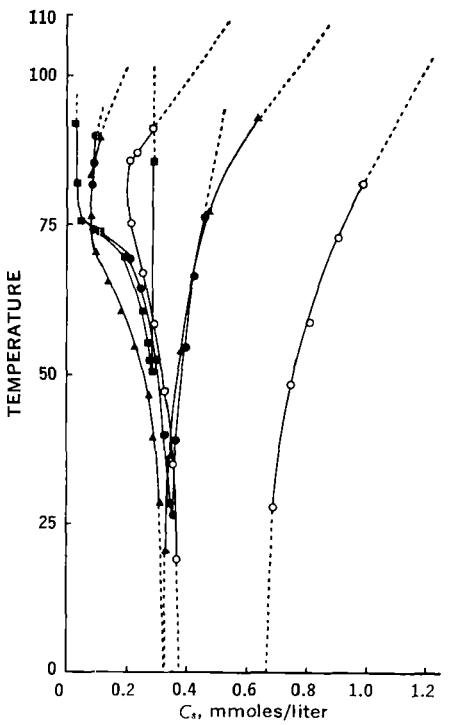

Figure 5—*Diagram showing temperatures and surfactant concentrations at which carmoisine–alkyltrimethylammonium bromide solutions separated into two or more phases. Carmoisine concentration is 0.15 mmole/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *carmoisine–hexadecyltrimethylammonium bromide;* ▲, *carmoisine–tetradecyltrimethylammonium bromide;* ●, *carmoisine–cetrimide; and* ○, *carmoisine–dodecyltrimethylammonium bromide.*

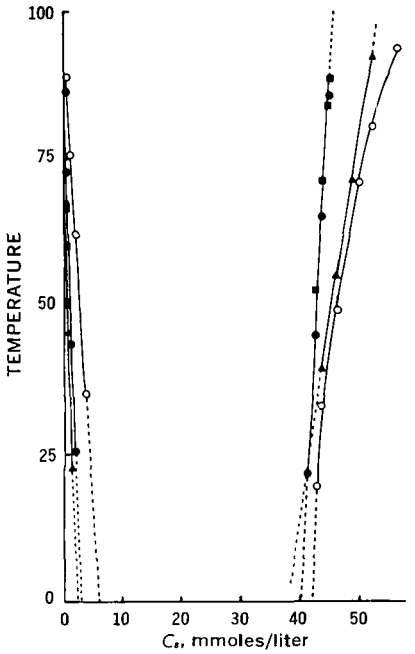

Figure 6—*Diagram showing temperatures and surfactant concentrations at which erythrosine–alkyltrimethylammonium bromide solutions separated into two or more phases. Erythrosine concentration is 15 mmoles/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *erythrosine–hexadecyltrimethylammonium bromide;* ▲, *erythrosine–tetradecyltrimethylammonium bromide;* ●, *erythrosine–cetrimide; and* ○, *erythrosine–dodecyltrimethylammonium bromide.*

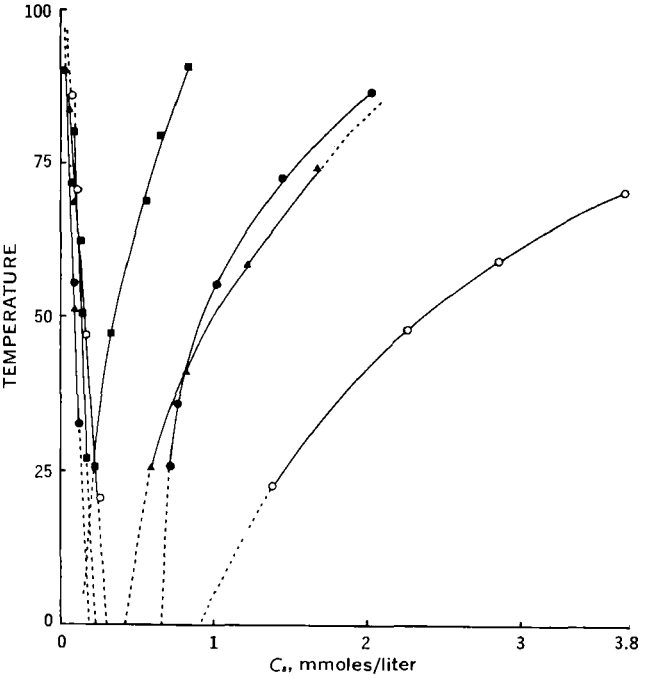

Figure 7—*Diagram showing temperatures and surfactant concentrations at which erythrosine–alkyltrimethylammonium bromide solutions separated into two or more phases. Erythrosine concentration is 0.15 mmole/liter. Surfactant concentration is* C_s, *mmoles/liter. Homogeneous solutions are represented by points outside the phase separation boundaries. Key:* ■, *erythrosine–hexadecyltrimethylammonium bromide;* ▲, *erythrosine–tetradecyltrimethylammonium bromide;* ●, *erythrosine–cetrimide; and* ○, *erythrosine–dodecyltrimethylammonium bromide.*

ble. The effects of the inorganic salts on the other systems may be summarized as follows.

Aqueous 15-mmoles/Liter Tartrazine-Cetrimide System (Fig. 10)—An inorganic salt concentration of 150 milliequivalents/liter reduced the area under the coacervation curve in the order: sodium chloride > sodium sulfate > sodium citrate: sodium chloride > calcium chloride. The position of the maximum in the coacervation curves was also affected.

Aqueous 0.15-mmole/Liter Amaranth-Cetrimide System (Fig. 11)—An inorganic salt concentration of 60 milliequivalents/liter reduced the area under the coacervation curve, and a maximum temperature for coacervation was found. In the absence of salt, no maximum was observed. The effect on the concentration of cetrimide required to induce coacervation was negligible, as shown by the fact that the left-hand limit of the coacervation curve was unaffected by the addition of salt. The order of reduction of coacervation area was: sodium citrate > sodium sulfate > sodium chloride; calcium chloride > sodium chloride.

Aqueous 0.15-mmole/Liter Carmoisine-Cetrimide System (Fig. 12)—An inorganic salt concentration of 30 milliequivalents/liter *increased* the area of coacervation. The right-hand boundary of the coacervation area when sodium citrate was present differed in shape from the corresponding curves obtained when sodium chloride, sodium sulfate, or calcium chloride was the added salt. For the systems containing sodium citrate, the coacervation area was much larger and a peak occurred at an added cetrimide concentration of 1.35 mmoles/liter. For the other systems, there was no peak. The salts had very little effect on the left-hand boundaries of the coacervation areas. The salts *increased* the coacervation area in the order: sodium citrate > sodium sulfate > sodium chloride: sodium chloride = calcium chloride.

Aqueous 0.15-mmole/Liter Erythrosine-Cetrimide System (Fig. 13)—An inorganic salt concentration of 30 milliequivalents/liter decreased the area under the coacervation curve. There was little difference in efficiency between the ions.

Minimum Ratio of Dye to Surfactant for Coacervation—Graphs of the dye concentration required to produce coacervation *versus* surfactant concentration yielded straight lines which

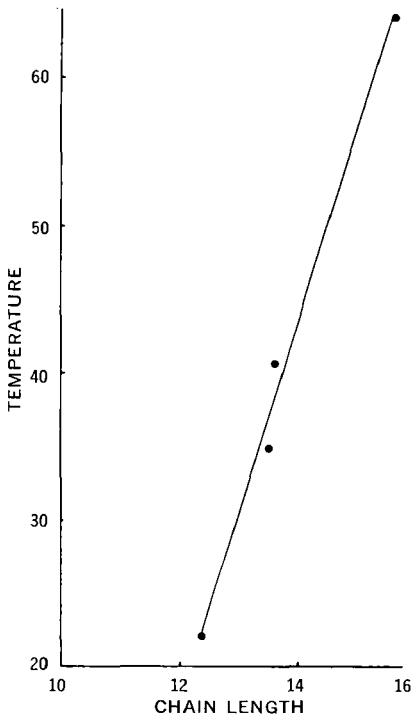

Figure 8—*Plot of maximum temperature for phase separation in tartrazine–alkyltrimethylammonium bromide systems (Fig. 1) versus chain length of alkyltrimethylammonium bromide.*

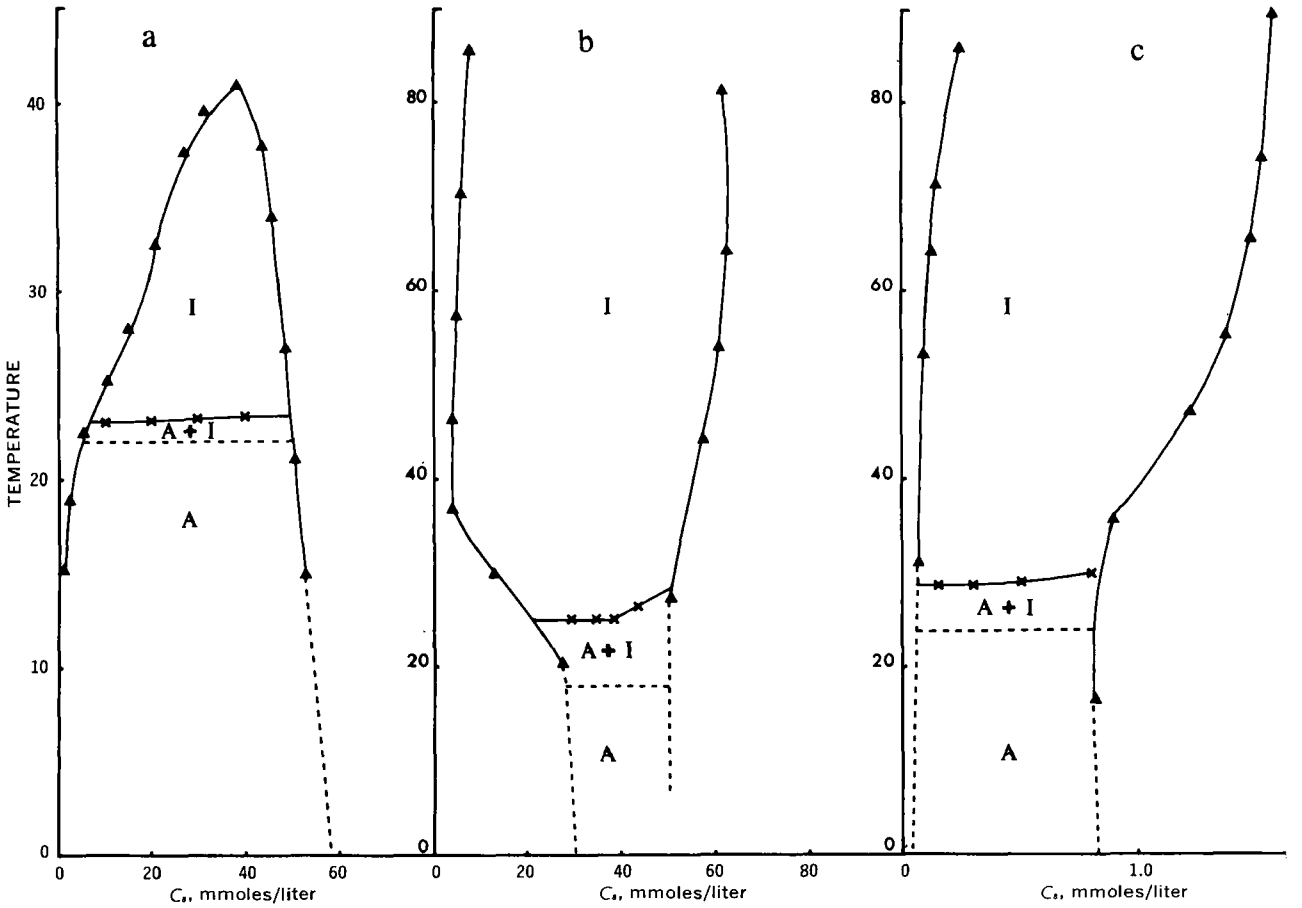

Figure 9—*Diagrams showing temperatures at which dye–tetradecyltrimethylammonium bromide interaction products changed phase, as determined by microscopy:* (a), *15 mmoles/liter tartrazine–tetradecyltrimethylammonium bromide;* (b) *15 mmoles/liter amaranth–tetradecyltrimethylammonium bromide; and* (c) *0.15 mmole/liter amaranth–tetradecyltrimethylammonium bromide. In each case the surfactant concentration is* C_s, *mmoles/liter. Key: I, separated phase is isotropic; A, separated phase is anisotropic; and A + I, separated phase is mixed anisotropic and isotropic.*

passed through, or very close to, the origin. Plots for the tartrazine–tetradecyltrimethylammonium bromide systems at various temperatures are shown in Fig. 14. Similar graphs were obtained when the alkyltrimethylammonium bromides were titrated against the other dyes. The gradients A and the intercepts B (see Eq. 1) were calculated by the method of least squares (Tables I and II). The values of B were, with a few exceptions, within ±1 milliequivalent/liter of the origin. This was within experimental error, so the values of B were assumed to be negligible (*cf.*, Ref. 5).

Two types of behavior were observed:

1. For tartrazine, increasing the chain length of the alkyltrimethylammonium bromide reduced the minimum ratio of dye-surfactant required for coacervation. Furthermore, a plot of the gradient A *versus* temperature at which the experiment was performed, for each of the homologs, yielded a straight line (Fig. 15). At temperatures close to the maxima of the coacervation curves, the minimum volume of dye that coacervated the surfactant-dye solution was not reproducible. Results obtained at these temperatures were not used. Therefore, the data for dodecyltrimethylammonium bromide (which does not coacervate in the presence of tartrazine above a temperature of 22°) cover a restricted temperature range.

2. For amaranth and carmoisine, this ratio was increased with an increase in surfactant chain length. A similar increase with chain length was observed for erythrosine at 60°, but for erythrosine at 35° the ratio increased from the dodecyl to the tetradecyl homolog and then remained constant.

DISCUSSION

When a long-chain quaternary ammonium salt is added to water such that the surfactant is at a concentration above the CMC, an equilibrium develops between surfactant monomers and the micellar species. The withdrawal of the hydrocarbon chains from an aqueous environment into the micelle favors aggregation, whereas the coulombic repulsion of the cationic head-groups at the surface of the micelle opposes aggregation. Therefore, factors that enhance the first phenomenon, or suppress the second, encourage micelle formation and growth. When conditions are favorable, the micelle may become lamellar and grow to such extreme proportions that phase separation, sometimes in the form of a coacervate, occurs. The surfactant micelles in the coacervate are in a more ordered state than in the aqueous solution, but this phase is still optically isotropic and has the appearance of an oil. A con-

Table I—Effect of Temperature on the Minimum Ratio of Tartrazine–Surfactant Required for Coacervation (A) (in Milliequivalents per Liter of Tartrazine: Milliequivalents per Liter of Surfactant) and the Equilibrium Concentration of Unbound Tartrazine (B) (in Milliequivalents per Liter Tartrazine) for Each of the Surfactant Homologs (See Eq. 1)

Temperature	Alkyltrimethylammonium Bromide					
	Dodecyl-		Tetradecyl-		Hexadecyl-	
	A	B	A	B	A	B
10°	0.611	−0.26	—	—	—	—
16°	0.637	0.10	0.578	0.10	—	—
25°	—[a]		0.611	0.14	0.565	0.20
30°	—[a]		0.625	0.42	—	—
35°	—[a]		0.643	0.64	0.594	0.06
50°	—[a]		—[a]		0.641	0.18

[a] No coacervation.

Table II—Values of the Minimum Ratio of Dye–Surfactant Required for Coacervation (*A*) (in Milliequivalents per Liter of Dye:Milliequivalents per Liter of Surfactant) and the Equilibrium Concentration of Unbound Dye (*B*) (in Milliequivalents per Liter) for the Interaction of Amaranth, Carmoisine, and Erythrosine with Each of the Surfactant Homologs at 35 and 60°

Dye	Temperature	Alkyltrimethylammonium Bromide							
		Dodecyl-		Cetrimide		Tetradecyl-		Hexadecyl-	
		A	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Amaranth	35°	0.78	−1.77	0.89	−0.57	0.88	−0.27	0.92	0.03
	60°	0.72	−2.43	0.78	−0.84	0.79	−0.57	0.88	−0.06
Carmoisine	35°	0.77	−0.11	0.95	0.04	0.90	0.12	—[a]	
	60°	0.84	−0.46	0.93	−0.02	0.88	0.12	0.97	0.02
Erythrosine	35°	0.70	−1.04	0.78	−0.26	0.78	−0.20	0.78	0.12
	60°	0.64	−1.62	0.74	−0.54	0.74	−0.52	0.78	−0.02

[a] No coacervation.

sideration of the factors that enhance, or suppress, micellization is a valuable preliminary to the discussion of the coacervates produced by the interaction of tartrazine, amaranth, carmoisine, and erythrosine with the alkyltrimethylammonium bromides. The degree of micellization is affected by the nature and concentration of the surfactant, the addition of other materials, and the temperature of the system. For ionic surfactants: *(a)* The CMC must be reached before micellization occurs. *(b)* With increasing chain length in a homologous series, the CMC decreases and the micellar molecular weight increases. *(c)* Addition of ions of opposite charge quenches the coulombic interactions of the charged headgroups at the surface of the micelle. This promotes micellar growth and, in cases where the quenching is sufficient, coacervation occurs (4–10). *(d)* Compounds with hydrophobic portions such as organic ions of opposite charge (21), alcohols (22), and dyes (11, 13) markedly decrease the CMC. These compounds exert their influence not only on the coulombic forces but also on the hydrophobic interactions of the micelle. Goddard *et al.* (21) found that the effect of short-chain quaternary ammonium ions on the sodium dodecyl sulfate micelle was different from that of inorganic cations. They suggested that this was because the hydrocarbon groups of the organic cations enter the palisade layer of the micelle and affect both the hydrophobic and electrostatic interactions of the surfactants. Shinoda (22) described a relationship between the number of carbon atoms in an alcohol and the CMC-decreasing power of the alcohol. *(e)* Temperature changes may also affect micelle formation. For example, Adderson and Taylor (23) showed that increasing the temperature of long-chain quaternary ammonium bromide solutions increased the CMC. Studies on the thermodynamics of micellization of the surfactants used in the present work (20) showed this to be the situation, although in some cases an initial minimum in the CMC *versus* temperature plots occurred.

A general summary of the effects on micellization of changing the composition and temperature of the alkyltrimethylammonium bromide–dye system is provided in Table III. The variables are listed in the order shown for the sake of clarity of discussion. Since coacervation in aqueous quaternary surfactant solutions is the result of rapid micellar growth, coupled with the reduction of

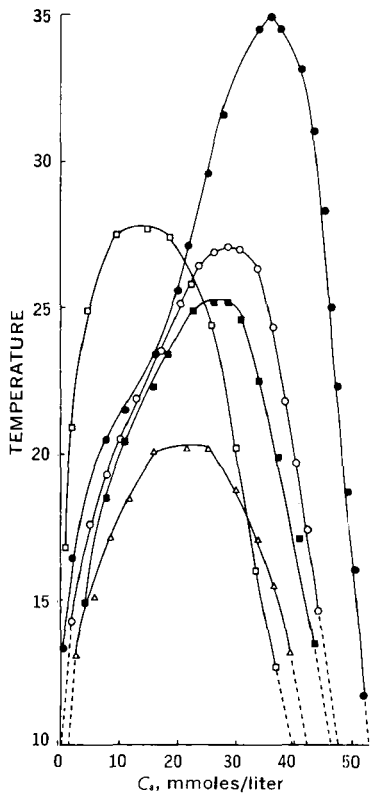

Figure 10—*Effect of inorganic salts on area of coacervation of tartrazine–cetrimide system. Tartrazine concentration is 15 mmoles/liter. Inorganic salt concentration is 120 mEq/liter. Cetrimide concentration is* C_s, *mmoles/liter. Key:* ●, *no salt;* ○, *sodium citrate;* ■, *sodium sulfate;* △, *sodium chloride; and* □, *calcium chloride.*

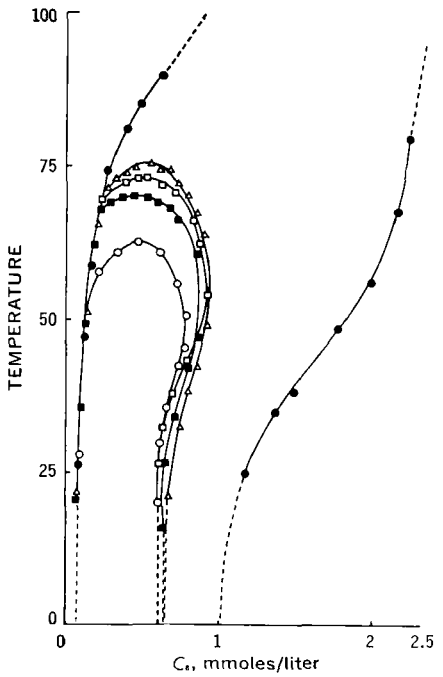

Figure 11—*Effect of inorganic salts on area of coacervation of amaranth–cetrimide system. Amaranth concentration is 0.15 mmole/liter. Inorganic salt concentration is 60 mEq/liter. Cetrimide concentration is* C_s, *mmoles/liter. Key:* ●, *no salt;* ○, *sodium citrate;* ■, *sodium sulfate;* △, *sodium chloride; and* □, *calcium chloride.*

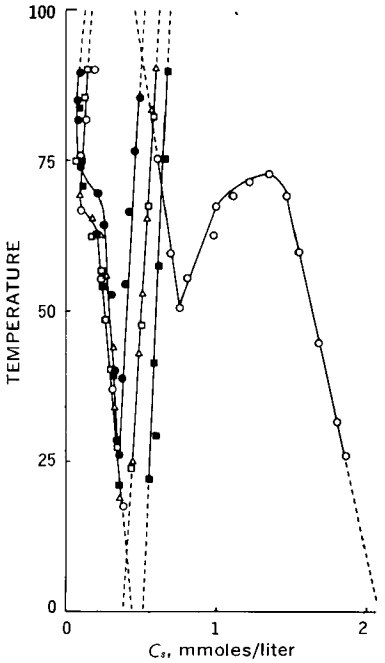

Figure 12—*Effect of inorganic salts on area of coacervation of carmoisine–cetrimide system. Carmoisine concentration is 0.15 mmole/liter. Inorganic salt concentration is 30 mEq/liter. Cetrimide concentration is* C_s, *mmoles/liter. Key;* ●, *no salt;* ○, *sodium citrate;* ■, *sodium sulfate;* △, *sodium chloride; and* □, *calcium chloride.*

the micellar surface charge (7), factors that promote micellization should also encourage coacervation. With these factors in mind, an attempt to explain the complex effects of the dyes on coacervation of alkyltrimethylammonium bromide solutions may be made.

When the composition or temperature of a coacervating system is varied by only a slight amount, the system may be profoundly changed. A sensitive indication of these changes occurs at a critical point where a homogeneous solution separates into two phases. The phase separation is readily observed (the solution becomes turbid) and is thermodynamically reversible. It can thus be used to study the effects of composition and temperature on coacervation. Figures 1–7 show the temperatures at which surfactant solutions of varying compositions become turbid in the presence of dye.

Maximum quenching of the electrostatic repulsion between the micellar cationic head-groups occurs when there is an equivalent amount of negative charges at the surface of the micelle. At this point, the volume of coacervate is at a maximum. An excess of cationic, or anionic, species results in a net positive, or negative, surface charge which tends to suppress coacervation (3). Hence, systems with compositions that fell on, or inside, the coacervation boundaries were turbid, whereas those which fell outside the boundaries were clear. Therefore, the right-hand boundaries of the coacervation areas denote the minimum ratio of surfactant–dye required to suppress coacervation or, conversely, the minimum ratio of dye–surfactant required to induce coacervation (Tables I and II). The left-hand boundaries denote the minimum ratio of dye–surfactant required to suppress coacervation.

Since more is known about the factors inducing coacervation in aqueous solutions of the alkyltrimethylammonium salts, the discussion of the different coacervation curves begins by considering the right-hand boundaries of the coacervation areas.

Tartrazine–Alkyltrimethylammonium Bromide Systems—Tartrazine (I) is a very polar molecule with no strictly hydrophobic portions. Only criteria *(a)*, *(b)*, *(c)*, and *(e)* (Table III) need be considered in the tartrazine–alkyltrimethylammonium systems. *(a)* In distilled water, tartrazine is a doubly charged anionic molecule, in which both sulfonate groups are fully dissociated. (Potentiometric titration showed that the COONa group started to dissociate at about pH 8.5.) It is very effective in quenching the coulombic interactions of the quaternary ammonium groups at

Table III—Effects on Micellization of Changing the Composition and Temperature of Alkyltrimethylammonium Bromide Systems

Change in the System	Effect on Micellization
(*a*) Increase in number of dye anions (up to stoichiometric amount) at surface of micelle	Increases
(*b*) Increase in surfactant concentration	Increases
(*c*) Increase in surfactant chain length	Increases
(*d*) Addition of dye with hydrophobic portion	Increases
(*e*) Increase in temperature	Decreases

the surface of the micelle, so that large anisotropic micelles with low surface charge may be built up. This, of course, favors coacervation. *(b)* For coacervation to occur, an adequate amount of surfactant must be present. Below the CMC, the surfactant does not aggregate into micelles and one would not expect to find coacervation of the surfactant solution. When the tartrazine concentration was 0.15 mmole/liter, turbidity was produced at surfactant concentrations that were below the CMC's of the surfactants in water. However, the turbidity was very faint and microscopic examination yielded no information on the morphology of the separated phase. When the tartrazine concentration was 15 mmoles/liter, the surfactant concentrations at the right-hand boundaries of the coacervation areas were well above the CMC. In these systems, the turbidity was easily observed and a coacervate layer was readily produced. *(c)* Table I shows that as the surfactant chain length increases, the minimum amount of tartrazine required to produce coacervation decreases. This is expected on the basis that the longer the chain length the bigger is the micelle and, therefore, less electrolyte is required to promote micellar growth to limiting proportions. *(e)* Adderson and Taylor (23) showed that the CMC of aqueous alkyltrimethylammonium bromide solutions increases as the temperature increases, due to increased thermal agitation. Therefore, to maintain coacervation, more electrolyte must be added. Table I and Fig. 15 show that the minimum ratio of dye–surfactant required for coacervation

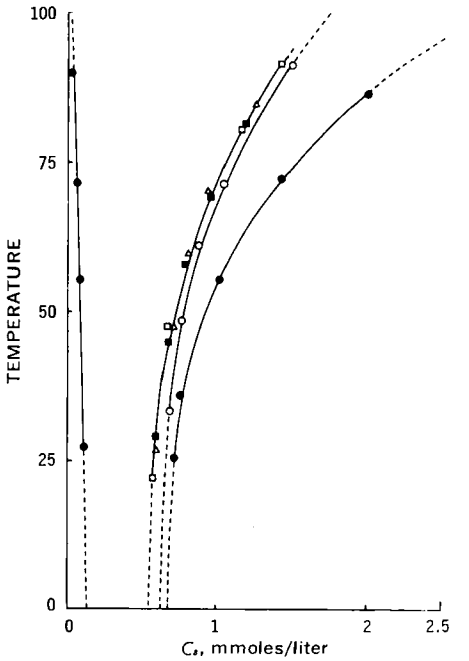

Figure 13—*Effect of inorganic salts on area of coacervation of erythrosine–cetrimide system. Erythrosine concentration is 0.15 mmole/liter. Inorganic salt concentration is 30 mEq/liter. Cetrimide concentration is* C_s, *mmoles/liter. Key:* ●, *no salt;* ○, *sodium citrate;* ■, *sodium sulfate;* △, *sodium chloride; and* □, *calcium chloride.*

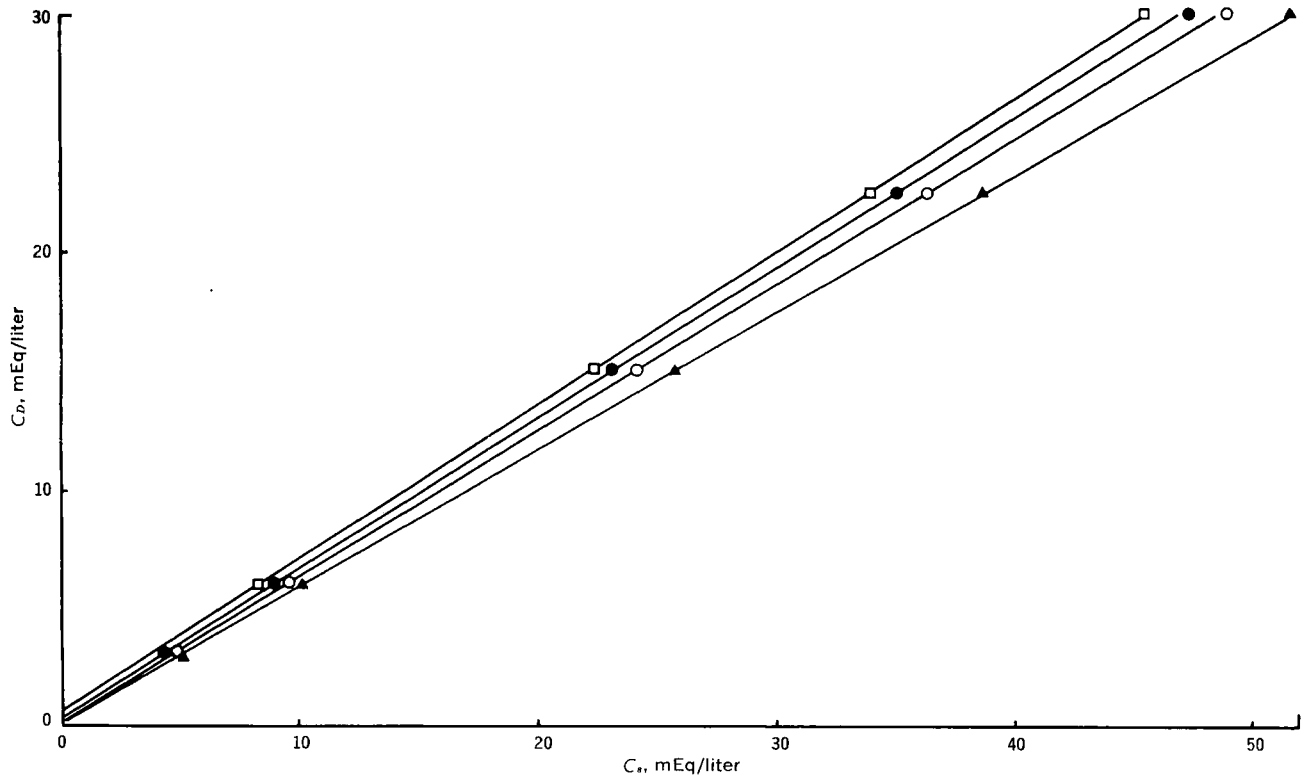

Figure 14—*Plots of tartrazine concentration* (C_D, *milliequivalents/liter*) *required to produce coacervation of tetradecyltrimethylammonium bromide solution at different temperatures* versus *tetradecyltrimethylammonium bromide concentration* (C_s, *milliequivalents/liter*). *Key:* ▲, *16°;* ○, *25°;* ●, *30°; and* □, *35°*.

increases linearly with temperature. Furthermore, Fig. 1 shows that, for each surfactant homolog, a maximum temperature for coacervation is reached. This maximum temperature decreases as the surfactant chain length decreases, as expected on the basis of *(c)*. At temperatures about 15–20° below the maximum temperature, the separated phase has such a high degree of order that it is optically anisotropic (*cf.*, Fig. 9*a*).

In summary, the factors that promote coacervation of aqueous alkyltrimethylammonium bromide systems by tartrazine are: surfactant and tartrazine concentrations above a limiting concentration, large chain length, and low temperature. These criteria are identical to those found in coacervating systems of alkyltrimethylammonium salts with inorganic electrolytes (5, 7).

Amaranth–Alkyltrimethylammonium Bromide Systems—Amaranth (II) carries three sulfonate groups that are totally dissociated in distilled water and also possesses two hydrophobic naphthalene nuclei. Therefore, it interacts with the micelle not only through the ionic groups but also through London–van der Waal's association forces. All five criteria listed in Table III are involved in the amaranth–surfactant interactions. Several authors reported the formation of mixed micelles in aqueous surfactant–dye solutions (13, 14, 24). However, for amaranth, an arrangement that permits maximum association between the naphthalene nuclei of the dye and the hydrocarbon chains of the quaternary surfactant micelle does not allow maximum interaction of the dye's sulfonate groups with the quaternary ammonium groups at the surface of the micelle. The converse is also true. Therefore, there are two possible positions for the amaranth molecule in contact with the surfactant micelle. (The values of B in Table II show that only a negligible amount of amaranth is *not* bound to the micelle.)

Position (i)—The amaranth molecule lies flat on the surface of the surfactant micelle. In this position, all three sulfonate groups are involved in the quenching of the interactions of the quaternary ammonium groups. However, this does not allow any interaction between the hydrophobic portions of the amaranth and the micelle.

Position (ii)—The amaranth molecule is partially inserted into the micelle, such that two sulfonate groups are level with the quaternary ammonium ions at the surface of the micelle and the azo-linked naphthalene rings penetrate the hydrocarbon interior of the micelle. In this position, the naphthalene nuclei and the hydrocarbon chains associate by nonpolar forces. However, one sulfonate group must penetrate the interior of the micelle. This sulfonate group is probably solubilized in the interior of the micelle as part of an ion-pair formed with a molecule of surfactant. Lindman and Ekwall (25) previously reported the formation of strongly bound ion-pairs in sodium caprylate–caprylic acid systems. Furthermore, three-dimensional atomic models[9], built to scale, show that the amaranth molecule may fit into a lamellar surfactant micelle as described, to yield a fairly ordered arrangement. Such a lattice arrangement must exist to allow liquid crystal formation at lower temperatures (Figs. 9*b* and 9*c*).

How this postulate fits the experimental observations and the criteria listed in Table III may now be examined. *(a)* The contribution of an amaranth molecule to the quenching of the electrostatic repulsions of the quaternary ions at the surface of the micelle depends upon how it associates with the micelle. In Position (i), all three sulfonate ions may interact with the surface of the micelle to provide maximum electrostatic quenching. In Position (ii), only two sulfonate groups are involved in surface interactions. Therefore, in this position an amaranth molecule is less effective in producing coacervation than it is in Position (i). *(b)* Systems containing 15 or 0.15 mmole/liter amaranth (and, therefore, surfactant at concentrations that were well above and well below their CMC's in distilled water) produced coacervates that could be readily studied (Figs. 2 and 3). This is in contrast to tartrazine where only the systems at the higher concentration could be examined; this underlines the influence of the hydrophobic portion of amaranth on the reduction of the CMC. *(c)* In the quaternary surfactant systems containing tartrazine, increasing the chain length of the surfactant decreases the amount of electrolyte required for coacervation. However, in the amaranth systems, increasing the surfactant chain length has the additional effect of increasing the solubilization of the dye–surfactant ion-pair in the interior of the micelle.

Hence, hexadecyltrimethylammonium bromide micelles bind more amaranth in Position (ii) than tetradecyl micelles which,

[9] Orbit Molecular Building Set, R.J.M. Exports Ltd., Oxford, England.

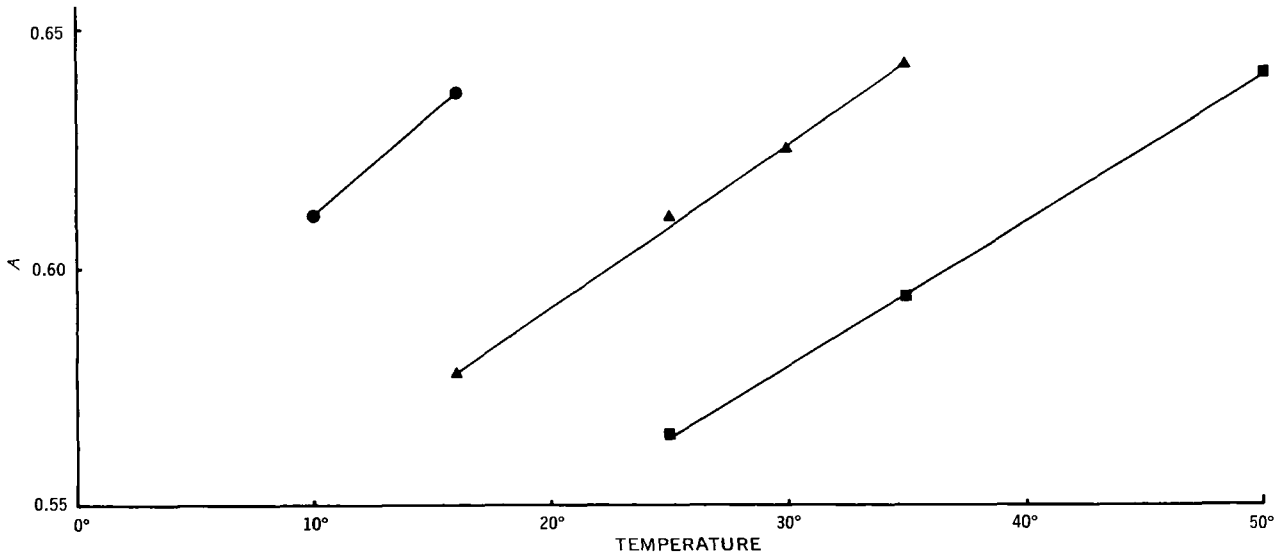

Figure 15—*Plots of gradient* A *(obtained from Table I) for the tartrazine–alkyltrimethylammonium bromide systems* versus *temperature. Key:* ■, *tartrazine–hexadecyltrimethylammonium bromide;* ▲, *tartrazine–tetradecyltrimethylammonium bromide; and* ●, *tartrazine–dodecyltrimethylammonium bromide.*

in turn, solubilize more dye than the dodecyl homolog. But dye bound in this position is less effective in producing coacervation than dye bound in Position (i). Therefore, increasing the surfactant chain length has two opposing effects. The one that predominates decides the amount of dye required to produce coacervation. *(d)* Figures 2 and 3 show how the hydrophobic portion of amaranth markedly alters the phase diagrams as compared to dyes where there is no hydrophobic group (Fig. 1). The discussion of the effects of the hydrophobic group is included in the discussion of the other criteria. *(e)* In alkyltrimethylammonium systems containing tartrazine or inorganic salts, warming tended to suppress coacervation. However, when amaranth is present, raising the temperature has a greater disruptive effect on weak van der Waal's interactions than on strong electrostatic associations. This favors the binding of amaranth to the micelle at Position (i), where it is more effective in quenching the coulombic interactions. Therefore, increasing the temperature also has two opposing effects on coacervation.

It is evident that the main differences of the amaranth systems compared to those of tartrazine arise because of the extra mode of interaction of amaranth with the micelle. An increase in the amount of amaranth solubilized in the interior of the micelle increases the ratio of dye–surfactant required for coacervation and displaces the right-hand boundaries of the coacervation areas to the left. As shown in Table II and by the right-hand boundaries of Figs. 2 and 3, the effect of increasing chain length is predominantly to increase solubilization; *i.e.*, the ratio of amaranth–surfactant required to produce coacervation increases in the order hexadecyl homolog > tetradecyl homolog; cetrimide > dodecyl homolog. Furthermore, an initial temperature increase displaces the right-hand boundaries to the right, because the decreased solubilization of amaranth overshadows the effect of the increased energy of activation for micellization. However, at higher temperatures, the latter effect becomes more important and the right-hand boundaries tend to level off with increased temperature (Figs. 2 and 3) and even to curve to the left (Fig. 2).

Carmoisine–Alkyltrimethylammonium Bromide Systems—The molecular structure of carmoisine (III) is similar to that of amaranth, except for the number of sulfonate groups, the position of the substituents, and the position of the azo-linkage. However, the carmoisine phase diagrams (Figs. 4 and 5) differ markedly from those of amaranth. In an auxiliary investigation, Sunset Yellow FCF (V), which is related to amaranth but contains a slightly different hydrophobic nucleus and has only two sulfonate groups, did not induce coacervation in solutions of tetradecyltrimethylammonium bromide. However, Orange II (VI), which has the same structure as sunset yellow but contains one less sulfonate group, brought about phase separation of solutions of this surfactant. The separated phase was optically anisotropic at room temperature but isotropic, oily globules formed at about 100°. These observations indicate that the extent of hydrophobic interaction, as well as the quenching of the electrostatic interactions, is important in determining whether phase separation takes place and the nature of the separated phase.

Carmoisine is more hydrophobic than amaranth and may be solubilized in the form of a surfactant–dye complex to a greater extent than amaranth. As a result, the right-hand boundaries of the phase diagrams are displaced to the left. The ratio of dye–surfactant required for coacervation (Table II) increases in the order hexadecyl homolog > tetradecyl homolog; cetrimide > dodecyl homolog. Furthermore, at temperatures below about 50°, so much of the complex is solubilized in the hexadecyltrimethylammonium bromide systems that the electrostatic quenching at the surface of the micelle is not sufficient to bring about coacervation.

The data for the more concentrated systems are restricted to temperatures above 50°, because at lower values the systems gelled, inhibiting complete mixing.

Erythrosine–Alkyltrimethylammonium Bromide Systems—The structure of erythrosine differs greatly from those of amaranth and carmoisine and is similar only in that it, too, has polar and nonpolar regions. A planar arrangement of the molecule is impossible because of steric hindrance between the xanthene and benzene rings, but it appears that the molecule is still partially inserted into the micelles, as shown by the fact that the right-hand boundaries of the coacervation areas (Figs. 6 and 7) are similar to those obtained with carmoisine. This suggests that a similar mechanism for interaction operates.

So far, only the right-hand boundaries of the coacervation areas have been considered. The shape and position of the left-hand boundaries provide a measure of the solubility of the dye–surfactant product in excess dye. The solubility varies with the nature and concentration of the dye, surfactant chain length, temperature, and ionic strength.

Striking differences occur between the left-hand boundaries of the coacervation areas for the three azo dyes: tartrazine, amaranth, and carmoisine (Figs. 1–5). For tartrazine, an initial large increase in solubility with increase in temperature occurs after the paracrystalline phases have melted to form a coacervate, as exemplified by the tartrazine–tetradecyltrimethylammonium bromide system (Fig. 9*a*). The solubility then continues to increase with temperature until a coacervate is no longer produced.

For the other azo dyes, amaranth and carmoisine, a different phenomenon must be present. Frank (26) found that, although micelles were not present to any appreciable extent in solutions of sulfonated azo-dyes in water, rod-like micelles formed when inorganic salts were added. These micelles were readily destroyed by warming the solutions. It is possible that the quaternary ammonium bromides also promote the formation of dye micelles, which could then solubilize the dye–surfactant complex, thus preventing the formation of a coacervate. Evidence for the existence of such

a mechanism is provided by the following: *(a)* the areas of solubility at the left-hand side of the coacervation diagrams decrease with an increase in temperature (the dye micelles are heat labile); *(b)* the areas of solubility are greater with 15-mmoles/liter dye solutions than with 0.15-mmole/liter dye solutions (presence of a CMC for formation of dye micelles); and *(c)* the areas of solubility are greater in the carmoisine systems than in the amaranth systems (carmoisine is more hydrophobic than amaranth, so it is more likely to form micelles). However, apart from what may be inferred from the phase diagrams (Figs. 2–5), there is no experimental evidence for the presence of such a phenomenon. A detailed discussion of the left-hand boundaries is, therefore, not possible.

The complex formed between erythrosine and the alkyltrimethylammonium bromides is so insoluble that solutions become turbid when only small amounts of surfactant are added to a dye solution (Figs. 6 and 7). Increasing the temperature slightly decreases the solubility of the complex.

Effect of Ionic Strength on Phase Diagrams—In general, inorganic salts suppress complex coacervation of polycations and polyanions (3, 27). This effect increases with an increase in the valency of the inorganic ions. However, exceptions to this rule are known (27). Furthermore, some inorganic ions coacervate ionic surfactant solutions (4–10). It is desirable to know the effects of ionic strength on the coacervation produced by interaction between the dyes and alkyltrimethylammonium bromides. The effects of constant concentrations of sodium chloride, sodium sulfate, sodium citrate, and calcium chloride are shown in Figs. 10–13. For tartrazine, amaranth, and erythrosine, the areas under the coacervation curves are decreased by the addition of salts at the concentrations studied, but the order differs in all three cases. For carmoisine, the area under the coacervation curve is *increased* on addition of inorganic salts and a secondary coacervation area is observed in solutions containing sodium citrate (Fig. 12).

In summary, it is evident that these dye–surfactant interactions are very complex, as emphasized by the many works published that attempt to elucidate the mechanisms involved. For example, Colichman (24) claimed that his results, obtained from surface and interfacial tension titrations of long-chain quaternary salts in bromphenol blue and bromthymol blue solutions, showed: "the micellar nature of the quaternary-dye ion-pair compound as formed in aqueous solutions." Kondo *et al.* (17) used the terms "zones of flocculation" and "deflocculation number" to define the extent of interaction of a number of acid dyes with dodecylpyridinium bromide. Zografi *et al.* (14) studied the interactions between Orange II and several long-chain quaternary ammonium salts from the point of view of the electronic and steric configuration of the surfactant. However, in all of these and in many other studies, no mechanism was proposed that could fully explain all of the observed phenomena of the dye–long-chain quaternary ammonium salt interactions.

In addition to these studies, reports (12, 13) were made concerning the interactions of anionic surfactants with cationic dyes. Again, differing theories for the mechanism of interaction were advanced.

The present work was initiated to solve some of the unanswered questions. In some aspects, this goal has been achieved, but in others the authors have succeeded only in raising further questions. The "reversibility" of the interactions in the dye–alkyltrimethylammonium bromide systems studied has been explained by showing the presence of a coacervate phase and applying the coacervation theory of Voorn (3) which Cohen and Vassiliades (7) showed was applicable to coacervation of long-chain quaternary ammonium salts by oppositely charged ions. The difference between coacervates obtained from solutions of the quaternary salts on addition of an essentially hydrophilic anion on one hand and anions containing hydrophilic *and* hydrophobic moieties on the other has also been shown. An attempt has been made to interpret the differences observed between the members of the latter category. However, the conclusions drawn are essentially inductive, and additional work must be performed before their validity can be confirmed. It has also been shown that dye induces formation of surfactant micelles at concentrations that are well below the CMC's of the surfactants in water. For example, Fig. 9*c* illustrates that at 40°, a coacervate is present at concentrations of tetradecyltrimethylammonium bromide of less than 0.1 mmole/liter. The CMC of this homolog was 3.6 mmoles/liter at 40° (28). Since coacervation in surfactant solutions is dependent on the formation of anisotropic micelles (7), this implies that the CMC has been reduced about 40-fold. However, the exact nature of the micelles formed in this region is less certain. Here, too, additional work is required.

From the practical point of view, it is obvious that when the surfactants and dyes are present in the same preparation, they must be mixed in proportions that are not close to stoichiometric amounts. It is preferable that there be an excess of surfactant over the stoichiometric amount of dye. Furthermore, the effect of the total ionic strength on the stability of the solution must be examined in detail.

SUMMARY

The interactions of the dyes tartrazine, amaranth, carmoisine, and erythrosine with alkyltrimethylammonium bromides of chain length C_{12}–C_{16} were investigated by phase separation techniques. Between certain surfactant concentrations and temperature limits, phase separation occurred. Microscopy showed that the separated phase was either a coacervate or an anisotropic phase or both. The effect of sodium chloride, sodium sulfate, sodium citrate, and calcium chloride on the extent of coacervation of cetrimide–dye systems was investigated. Phase separation diagrams for all dye–surfactant systems showed marked differences between the systems. The minimum ratio of dye to surfactant required for coacervation varied markedly with different dye–surfactant systems with respect to the effect of surfactant chain length and to temperature. Inorganic salts also produced different effects on the extent of phase separation in each system investigated.

The differences were attributed to the presence, or absence, of a hydrophobic nucleus in the dye molecule. It is suggested that when the dyes and surfactants are present in the same preparation, they be mixed in proportions that are not close to stoichiometric amounts. The effect of total ionic strength of the preparation must also be carefully investigated.

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Effect of Selected Surfactants, above and below the CMC, on Aspirin Solubility

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Abstract □ Representative classes of surfactants in aqueous solutions, above and below the CMC, were studied for their solubilizing effects on suspensions of aspirin USP crystals. The solubilization study was performed for up to 5 hr in a Clark-Lubs buffer, pH 2.4, and at 37 ± 0.4° to simulate closely the gastric environment. Both free and total salicylic acid were determined spectrophotometrically at 296.5 nm in pH 7.4 buffer maintained at 5°. Ranked in order of decreasing solubilizing effectiveness were the following: cetylpyridinium chloride (above CMC) > polysorbate 20 > benzalkonium chloride (above CMC) > polysorbate 80 > dioctyl sodium sulfosuccinate. The apparent solubility of aspirin was increased approximately 17% by cetylpyridinium chloride in solution above (approximately 0.2%) its CMC; in contrast, cetylpyridinium chloride and benzalkonium chloride, in solution below the CMC, decreased the apparent solubility of aspirin. At the levels of surfactant concentrations and pH studied, the concurrent increase in aspirin hydrolysis was not seen to be significant.

Keyphrases □ Aspirin in aqueous suspension—solubilizing effect by cetylpyridinium chloride, benzalkonium chloride, polysorbates 20 and 80, and dioctyl sodium sulfosuccinate above and below their CMC's □ Solubilizing effect of surfactants above and below CMC—aspirin in aqueous suspension □ Surfactant effect—solubilization of aspirin in aqueous suspension

During the past few years, numerous high molecular weight compounds functioning as surfactants have been successfully formulated in pharmaceutical and cosmetic preparations because of micellar solubilization. These included nonionic surfactants such as polysorbates for solubilizing drugs such as aspirin, hydroxybenzoic acid, and phenobarbital (1).

In this study an attempt was made to investigate representative classes of surfactants for their influence on aspirin solubility under conditions closely simulating the human gastric environment. The objective was to search for relatively nontoxic compounds that could enhance the solubility of aspirin in the acid pH of the gastric fluids without resulting in a concomitant increase in aspirin hydrolysis. Such surfactants might potentially be formulated in soft gelatin capsule or compressed tablet dosage forms of aspirin for improved bioavailability of the drug. The poor solubility of aspirin in water is a contributing factor to its irritant effect on the gastric mucosa. Aspirin crystals could be lodged physically in the rugae of the gastric mucosa to cause serous erosion and hemorrhages in the presence of even moderate amounts of acid (2). Its rapid dissolution and consequent absorption in the body seemed desirable because of these reasons.

EXPERIMENTAL

Materials—The six surface-active compounds originally chosen for this study, representing the nonionic, cationic, and anionic classes, were: polysorbate 20[1], polysorbate 80[1], benzalkonium chloride[2], cetylpyridinium chloride[3], dioctyl sodium sulfosuccinate[4], and sodium lauryl sulfate[4], all USP, NF, or analytical reagent grade. Sodium lauryl sulfate produced a precipitate in the pH 2.4 buffer solution during preliminary tests and was therefore abandoned for further study.

CMC Determinations—The critical micelle concentration (CMC) data for the various surfactants were obtained by the surface tension method (3) employing a surface tensiometer[5]. It was preferred over other literature methods for determining the CMC because of its simplicity and reproducibility. The inflection point in the slope when the logarithm of concentration of a surfactant was plotted against the surface tension of its solution represents the CMC. The solvent was a Clark-Lubs buffer with potassium chloride and hydrochloric acid adjusted to pH 2.4.

Solubility Determinations—The solubility data for aspirin were obtained by placing 350 mg of aspirin USP crystals[4], which would be in excess of its solubility, in 25 ml of the "solvent" contained in erlenmeyer flasks. These surfactant solutions were fresh dilutions of the more concentrated stock solutions that had previously been equilibrated by stirring using a magnetic stirrer for 24 hr at room temperature. Just prior to commencing the solubility study, the diluted surfactant solutions were equilibrated at 37 ± 0.4° in a water bath for at least 1 hr. These aspirin suspensions, prepared in triplicate for each strength of aspirin, were agi-

[1] Atlas Chemical Industries.
[2] Ruger Chemical Co.
[3] K & K Labs.
[4] Fisher Scientific Co.
[5] Roller-Smith Rosano surface tensiometer.