(21) E. D. Goddard, O. Harva, and T. G. Jones, *Trans. Faraday Soc.*, **49**, 980(1953).
(22) K. Shinoda, *Bull. Chem. Soc. Jap.*, **26**, 101(1953).
(23) J. E. Adderson and H. Taylor, *Proc. Int. Congr. Surface Active Substances*, 4th, Brussels, Belgium, 1964, 613.
(24) E. L. Colichman, *J. Amer. Chem. Soc.*, **73**, 1795(1951).
(25) B. Lindman and P. Ekwall, *Kolloid Z.*, **234**, 1115(1969).
(26) H. P. Frank, *J. Colloid Sci.*, **12**, 480(1957).
(27) H. G. Bungenberg de Jong, in "Colloid Science," vol. 2, H. R. Kruyt, Ed., Elsevier, New York, N.Y., 1949.
(28) B. W. Barry and G. F. J. Russell, *J. Colloid Interface Sci.*, **40**, 174(1972).

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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.

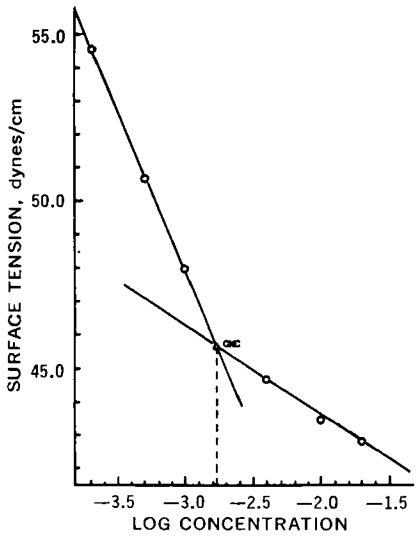

Figure 1—*Surface tension (dynes per centimeter) as a function of the logarithm of concentration (w/v %) of polysorbate 80 when determined at 25° in pH 2.4 Clark-Lubs buffer solution. Point of inflection represents the CMC.*

tated on a mechanical shaker immersed in a constant-temperature bath at the rate of 120 vibrations/min. At suitable intervals, flasks were removed and the contents were quickly filtered, with the aid of a filter[6] and syringe holder, through No. 2 Whatman filter paper. Suitable aliquots of the clear filtrate were pipeted and diluted in ice-cold pH 7.4 buffer.

The free salicylic acid referred to in this work was that produced by the hydrolysis of aspirin during the agitation period in the buffered surfactant solutions at 37 ± 0.4°. The absorbance of the sample, maintained at 5° to avoid further hydrolysis, was determined at a wavelength of 296.5 nm on a double-beam spectrophotometer[7] equipped with a constant-temperature water circulator[8]. The total salicylic acid content of each sample was determined by first hydrolyzing it with 1 *N* sodium hydroxide solution for 10 min before neutralization with 1 *N* hydrochloric acid solution and final dilution to volume in volumetric flasks with pH 7.4 buffer. The Beer's law plot was obeyed in the concentration range of 0–30 μg/ml of salicylic acid under this condition. A factor of 1.3 was applied to the total salicylic acid value obtained to compute for the total amount of aspirin dissolved.

RESULTS AND DISCUSSION

Figure 1 shows clearly the CMC inflection point of the curve obtained with polysorbate 80. This was typical of all other surfac-

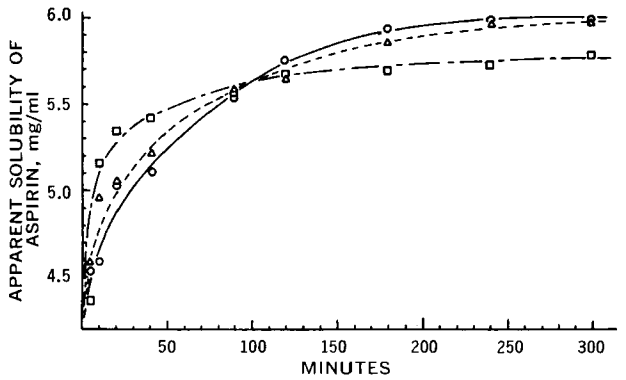

Figure 2—*Effect of polysorbate 20 on the apparent solubility of aspirin as a function of time at 37° in pH 2.4 buffer. Key: △, above CMC; ○, below CMC; and □, buffer control.*

[6] Millipore.
[7] Perkin-Elmer.
[8] Lauda-Brinkmann circulator, model K-2/R.

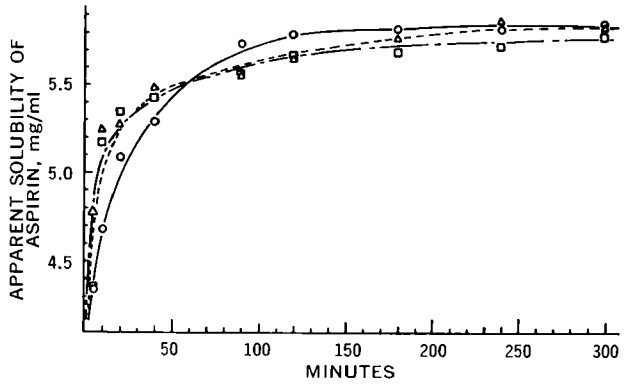

Figure 3—*Effect of polysorbate 80 on the apparent solubility of aspirin as a function of time at 37° in pH 2.4 buffer. Key: △, above CMC; ○, below CMC; and □, buffer control.*

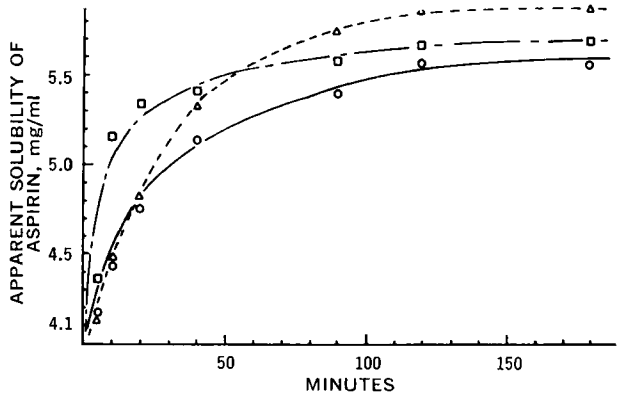

Figure 4—*Effect of benzalkonium chloride on the apparent solubility of aspirin as a function of time at 37° in pH 2.4 buffer. Key: △, above CMC; ○, below CMC; and □, buffer control.*

tants studied. These CMC values, however, differed somewhat from those reported in the literature because of differences in solvent composition (4), pH (5), and temperature. Results of the apparent solubilities of aspirin exposed to the different surfactants, based on calculations of the free and total salicylic acid determinations, are listed in Table I. Figures 2-6 show graphically these apparent solubilities of aspirin exposed to the various surfactants, above and below the CMC, and in relation to the control containing no surfactant. Since the solubility of a compound is generally dependent on the concentration of the solubilizing agent, effects by two levels of surfactant strength (arbitrarily one above the CMC and the other below the CMC) would be of interest. Studies on submicellar concentrations of the surfactant were included because of the inevitable and considerable lowering of the surfac-

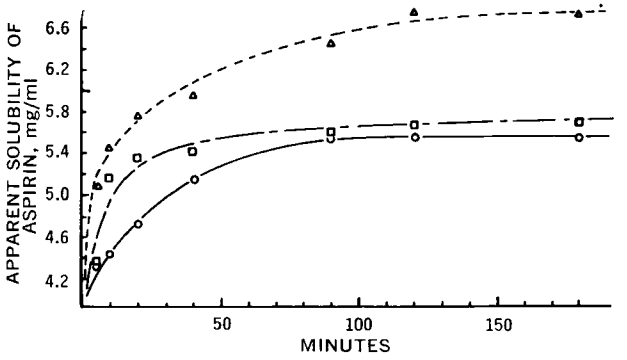

Figure 5—*Effect of cetylpyridinium chloride on the apparent solubility of aspirin as a function of time at 37° in pH 2.4 buffer. Key: △, above CMC; ○, below CMC; and □, buffer control.*

Table I—Apparent Solubilities (Milligrams per Milliliter) of Aspirin in pH 2.4 Buffer Containing Different Surfactants at 37°

Surfactant	Concentration of Surfactant	Minutes								
		5	10	20	40	90	120	180	240	300
Polysorbate 80	Above CMC	4.78 ±0.03[a]	5.24 ±0.03	5.27 ±0.05	5.48 ±0.04	5.57 ±0.02	5.64 ±0.02	5.76 ±0.07	5.86 ±0.04	5.83 ±0.04
	Below CMC	4.33 ±0.05	4.68 ±0.12	5.09 ±0.11	5.30 ±0.08	5.74 ±0.05	5.79 ±0.01	5.81 ±0.03	5.81 ±0.02	5.85 ±0.05
Polysorbate 20	Above CMC	4.59 ±0.06	4.96 ±0.03	5.05 ±0.07	5.21 ±0.03	5.59 ±0.03	5.64 ±0.04	5.85 ±0.01	5.97 ±0.02	5.98 ±0.00
	Below CMC	4.54 ±0.03	4.58 ±0.02	5.06 ±0.04	5.10 ±0.07	5.50 ±0.08	5.75 ±0.03	5.94 ±0.02	5.97 ±0.02	5.97 ±0.02
Dioctyl sodium sulfosuccinate	Above CMC	4.03 ±0.06	4.25 ±0.09	4.27 ±0.05	4.61 ±0.14	5.24 ±0.02	5.52 ±0.08	5.76 ±0.02	5.79 ±0.00	5.81 ±0.04
	Below CMC	3.98 ±0.03	4.39 ±0.04	4.74 ±0.05	5.05 ±0.03	5.48 ±0.03	5.68 ±0.03	5.79 ±0.00	5.78 ±0.06	5.79 ±0.00
Cetylpyridinium chloride	Above CMC	5.09 ±0.04	5.47 ±0.21	5.76 ±0.21	5.97 ±0.15	6.44 ±0.11	6.72 ±0.02	6.73 ±0.05		
	Below CMC	4.32 ±0.13	4.44 ±0.10	4.72 ±0.02	5.14 ±0.04	5.55 ±0.03	5.55 ±0.03	5.55 ±0.03		
Benzalkonium chloride	Above CMC	4.14 ±0.18	4.49 ±0.09	4.82 ±0.08	5.33 ±0.10	5.76 ±0.09	5.87 ±0.03	5.87 ±0.03		
	Below CMC	4.17 ±0.06	4.44 ±0.06	4.77 ±0.21	5.15 ±0.06	5.41 ±0.06	5.57 ±0.04	5.57 ±0.06		

[a] ± Standard deviation.

tant concentration after the oral administration of a drug dosage form by dilution with the gastric fluids. The attainment of isotonicity was deemed not to be an important consideration in this situation.

The graph drawn for cetylpyridinium chloride (Fig. 7) presents a typical example of the percentage hydrolysis of the aspirin suspensions due to the effects of the surfactant as averaged from three determinations. It may also be seen from Fig. 7 that the percentage hydrolysis of aspirin assumed a near linear relationship with respect to time after an initial lag period of approximately 20–25 min. This is roughly analogous to the report by James (6) for the rate of hydrolysis of an aspirin suspension at room temperature, which was shown not to follow either zero-order or first-order kinetics at any level of aspirin concentration. Comparison of Fig. 7 with the graphs obtained for the apparent solubilities of aspirin *versus* time (Figs. 2–6) shows that the onset of hydrolysis was approximately coincident with the time when about 90% of the apparent solubilities had been reached.

Figure 8 shows the extent of hydrolysis of aspirin due to either polysorbate 20 or polysorbate 80 when present above and below the CMC. A slightly reduced hydrolysis of aspirin occurred when these surfactants were present at concentrations above the CMC. This finding is in general agreement with the literature report (7) that nonionic surfactants suppressed hydrolysis of the undissociated form of aspirin. Data from the present study indicate that the presence of surfactants of any class, either above or below the CMC, did not show significant differences in the extent of hydrolysis of aspirin from the controls. This observation could well be attributed to the relatively low concentrations of surfactants involved in the study.

A statistical analysis for variance (8) developed by Fisher was performed on the apparent solubility measurements of aspirin after each solution had reached equilibrium. Following this, Fisher's least significant difference (LSD) test was applied to provide some quantitative concepts in the solubility changes of aspirin as influenced by the different surfactants. Statistically, all of the surfactants studied, except for dioctyl sodium sulfosuccinate, yielded significant differences from the controls in solubility (Table II). Both cationic surfactants, cetylpyridinium chloride and benzalkonium chloride, when present below the CMC showed significantly lower apparent solubilities compared to the controls. In contrast, cetylpyridinium chloride, above its CMC demonstrated in order of ranking the greatest significant increase in aspirin solubility. The apparent solubility of aspirin increased approximately 17% in the range above (0.2%) the CMC of this surfactant, while below the surfactant CMC the solubility of aspirin was actually lowered. Similarly, benzalkonium chloride when present above (0.1%) its CMC increased aspirin solubility but decreased the solubility when studied below its CMC.

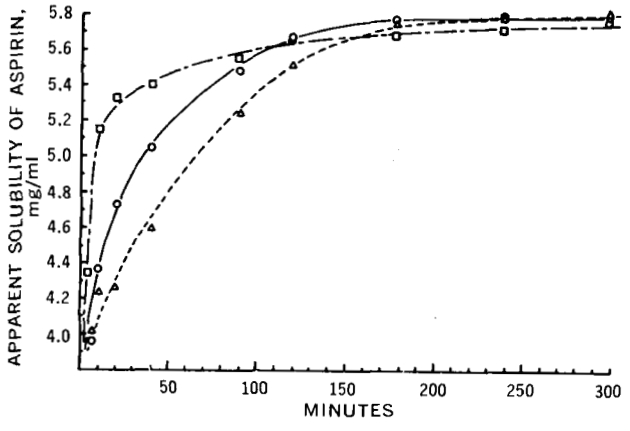

Figure 6—*Effect of dioctyl sodium sulfosuccinate on the apparent solubility of aspirin as a function of time at 37° in pH 2.4 buffer. Key: △, above CMC; ○, below CMC; and □, buffer control.*

SUMMARY

1. The solubilizing effect of the various classes of surfactants on the apparent solubility of aspirin as obtained under the experimental conditions described were, ranked in decreasing effective-

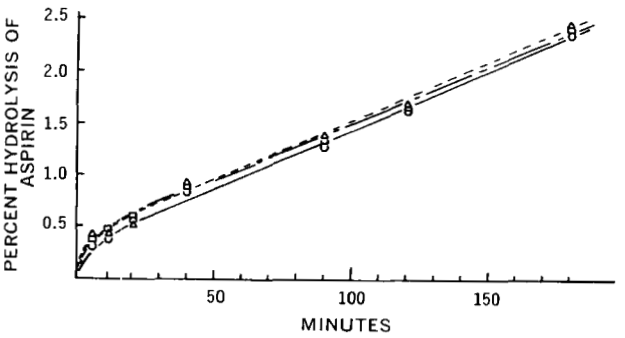

Figure 7—*Percentage hydrolysis found for aspirin as influenced by cetylpyridinium chloride strength in pH 2.4 Clark–Lubs buffer at 37°. Key: △, above CMC; ○, below CMC; and □, buffer control.*

Table II—Results of Fisher's Least-Significant Difference Test[a]

Groups[b]										
4[c]	5[c]	6	3[c]	3[d]	1[c]	1[d]	5[d]	2[c]	2[d]	4[d]
Mean Aspirin Solubility										
5.5467	5.5687	5.7527	5.7823	5.7960	5.8283	5.8448	5.8717	5.9693	5.9747	6.7223

[a] At the 0.05 level; LSD = 0.0448. [b] Group 1 = polysorbate 80, Group 2 = polysorbate 20, Group 3 = dioctyl sodium sulfosuccinate, Group 4 = cetylpyridinium chloride, Group 5 = benzalkonium chloride, and Group 6 = pH 2.4 buffer (control). [c] Below CMC. [d] Above CMC.

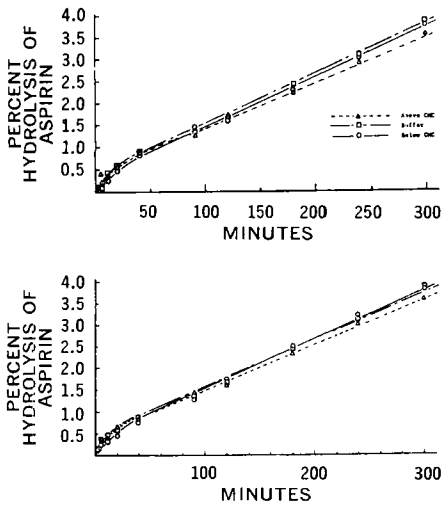

Figure 8—*Percentage hydrolysis found for aspirin as influenced by polysorbate 20 (top) and polysorbate 80 (bottom) in pH 2.4 buffer at 37°. Key: △, above CMC; ○, below CMC; and □, buffer control.*

ness, as follows: cetylpyridinium chloride (above CMC) > polysorbate 20 > benzalkonium chloride (above CMC) > polysorbate 80 > dioctyl sodium sulfosuccinate.

2. Both cationic surfactants, benzalkonium chloride and cetylpyridinium chloride, when present in concentrations less than their CMC failed to enhance the apparent solubility of aspirin. In contrast, cetylpyridinium chloride, above its CMC, showed the most significant increase in aspirin solubility.

3. The mechanism for the varying solubilizing effects of the surfactants on aspirin solubility cannot be fully explained at this time. It appears that the micellar size and shape formed with the different surfactant molecules may have played a prominent role in producing the observed solubilizing effects.

REFERENCES

(1) S. S. Ashan and S. M. Blaug, *Drug Stand.*, **28**, 95(1960).

(2) A. R. Cooke, *Dig. Dis.*, **18**, 225(1973).

(3) K. L. Mittal, *J. Pharm. Sci.*, **61**, 1334(1972).

(4) S. C. Wan and K. C. Poon, *ibid.*, **58**, 1562(1969).

(5) J. R. Bloor, J. C. Morrison, and C. T. Rhodes, *ibid.*, **59**, 387(1970).

(6) K. C. James, *J. Pharm. Pharmacol.*, **10**, 363(1958).

(7) H. Nogami, S. Awazu, and N. Nakajima, *Chem. Pharm. Bull.*, **10**, 503(1962).

(8) G. W. Snedecor and W. G. Cochran, "Statistical Methods," 6th ed., Iowa State University Press, Ames, Iowa, 1967, chap. 10.

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