Hydrolysis of Solubilized Esters

By P. B. SHETH* and E. L. PARROTT

The solubilizing ability of four nonionic surface-active agents is quantitatively compared. The critical micelle concentration (CMC) of the surface-active agents was evaluated from the solubility curves. The effect of the surface-active agents on the rate of hydrolysis of benzocaine and homatropine was investigated. At a concentration of surface-active agent less than the CMC, the surface-active agents do not significantly affect the rate of hydrolysis of the esters. At a concentration exceeding the CMC, the surface-active agents enhance the stability, due to micellar interaction.

THE PHENOMENON of micellar solubilization in aqueous systems and its applications to pharmaceuticals has received considerable attention (1–5). The nonionic surface-active agents have been most frequently used in the solubilization of drugs which possess a low water solubility (6, 7). Their use has been presumably due to their lower toxicity and irritation in comparison to ionic surface-active agents (8–10).

Studies of several readily oxidizable materials solubilized by ionic and nonionic surface-active agents have shown the solubilized preparation to be less easily oxidized than emulsions or simple aqueous dispersions (11–13). Riegelman reported that ionic and nonionic surface-active agents provide a different degree of protection from base hydrolysis (14).

This investigation was undertaken to determine the effectiveness of several nonionic surface-active agents in solubilizing and in retarding the alkaline hydrolysis of benzocaine and homatropine. As several mechanisms for increasing the stability of benzocaine to hydrolytic degradation have been studied, benzocaine was chosen for this investigation with the thought that a comparison with previous reports would be of interest (14–16). In pharmaceuticals, basic nitrogen-containing drugs, *i.e.*, amines and alkaloids, are generally used in the salt form in order to enhance the water solubility and/or stability of the drug. In product development it may occasionally be necessary to prepare a clear liquid pharmaceutical in a pH range at which these drugs exist in the base form. In such products the utilization of the phenomenon of micellar formation could possibly increase the apparent solubility and stability of the drug; to study this possibility homatropine was chosen.

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EXPERIMENTAL

Materials—The surface-active agents were commercial lots which were used without further purification: polyoxyethylene lauryl ether[1] (PLE); oxyethylene polymer containing 80% polyoxyethylene[2] (POE), approximate mol. wt. 8700; a product formed by the addition of propylene oxide to ethylenediamine followed by the addition of ethylene oxide[3] (POEEO); a condensation product of *tert*-octylphenol with ethylene oxide[4] (OPEO), average mol. wt. 2800; homatropine;[5] and benzocaine N.F.

Solubility Studies—An excess of benzocaine and aqueous solutions of the surface-active agents were rotated in 50-ml. amber bottles in a constant-temperature bath at 30 ± 0.1° for 24 hr. A portion was withdrawn from each bottle with a pipet fitted with a cotton filter. After dilution with distilled water, the absorbance was measured with a Beckman DU spectrophotometer, and the solubility of the benzocaine was determined by means of a calibration curve.

In the analysis of samples containing surface-active agents, with the exception of OPEO solutions, water was used as a blank, since the samples were diluted at least 500-fold and there was no absorption by the surface-active agents. OPEO absorbs strongly in the region of 280 mμ near the maximum for benzocaine. In the assay of solutions containing OPEO, a blank of the OPEO solution, diluted in the same manner as the sample, was used to compensate for absorption by the surface-active agent.

The concentration of a surface-active agent at which micelles are formed is known as the critical micelle concentration. As shown in Figs. 1–4, the apparent solubility of benzocaine was plotted against the concentration of the surface-active agent. The inflection in the solubility curve indicates micelle formation (17).

Hydrolysis of Benzocaine—For studies in 3% POE, 75 ml. of an aqueous 4% POE solution was pipeted into a 6-oz. bottle containing 1 mg. of benzocaine in 5 ml. of solution. For studies in 0.005% POE, 5 ml. of an aqueous 0.1% POE solution was pipeted into a 6-oz. bottle containing 70 ml. of distilled water and 5 ml. of a solution containing 1 mg. of benzocaine. The solution was placed in a 30° constant-temperature bath, and

[1] Marketed as Brij 35 by Atlas Chemical Industries, Inc., Wilmington, Del.

[2] Marketed as Pluronic F 68 by Wyandotte Chmeical Corp., Wyandotte, Mich.

[3] Marketed as Tetronic 908 by Wyandotte Chemical Corp., Wyandotte, Mich.

[4] Marketed as Triton WR-1339 by Winthrop Laboratories, New York, N. Y.

[5] Obtained from K & K Laboratories, Inc.

when thermal equilibrium was attained, 20 ml. of 0.2 *N* sodium hydroxide solution at 30° was added to give a 0.04 *N* hydroxyl ion concentration. At definite intervals of time, samples were withdrawn from the solution which was maintained at 30°. The absorbance of the sample was measured immediately at 284 and 265 mμ, and the concentration of benzocaine was determined by use of simultaneous equations obtained from standard absorption curves (14). With samples containing 3% POE, a blank of a solution of 3% POE and 0.04 *N* hydroxyl ion concentration was used; with samples containing 0.005% POE, a blank of a solution containing 0.005% POE and 0.04 *N* hydroxyl ion concentration was used.

The hydrolysis of benzocaine in water, PLE, and POEEO was followed in a similar manner. With OPEO, a direct ultraviolet method was not satisfactory due to strong absorbance of the surface-active agent at 284 mμ (6). A chloroform extraction procedure was used. The absorption maximum of benzocaine in chloroform was 279 mμ.

Hydrolysis of Homatropine—One hundred milligrams of homatropine was dissolved in 100 ml. of solvent medium, *i.e.*, water, 0.005 or 3% solution of surface-active agent, at 30°. The first 30-ml. sample was withdrawn, designated as the zero time, and analyzed for homatropine. The solution was maintained at 30°, and subsequent 10-ml. samples were withdrawn at definite intervals of time and were analyzed by the procedure of Patel and Lemberger (18).

RESULTS AND DISCUSSION

In dilute aqueous solutions in which the surface-active agent is molecularly dispersed, compounds of low water solubility, such as benzocaine, do not dissolve to a greater extent than they would in water; however, at concentrations of the surface-active agent in excess of the CMC, the apparent solubility is increased. When the CMC is exceeded, the apparent solubility of benzocaine is linearly dependent on the concentration of the surface-active agent. As shown in Figs. 1–4, the point of inflection in the solubility curve indicates the CMC.

The amount of benzocaine solubilized by micellar interaction is represented by the difference between the apparent solubility in a solution of a surface-active agent and the solubility of benzocaine in water. The difference between the concentration of the surface-active agent and its CMC represents the amount of surface-active agent in the micellar form. This relationship may be expressed by the equation:

$$S = S_0 + K\,(C_{\text{surfactant}} - C_{\text{CMC}}) \quad \text{(Eq. 1)}$$

in which S is the apparent solubility of a compound in the aqueous solution of a surface-active agent, S_0 is the solubility of the compound in water, $C_{\text{surfactant}}$ is the concentration of the surface-active agent, C_{CMC} is the critical micelle concentration, and K is a constant, *i.e.*, the slope of the solubility curve.

For the solubilization of benzocaine, the K values in Table I show the order of solubilizing ability of the surface-active agents to be OPEO > PLE > POEEO > POE.

The conditions of 30° and 0.04 *N* hydroxyl ion concentration for the hydrolysis of benzocaine were essentially the same as those used by previous investigators (14, 15). The initial concentration

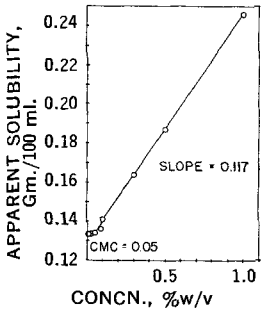

Fig. 1—Apparent solubility of benzocaine at 30° in aqueous solutions of PLE.

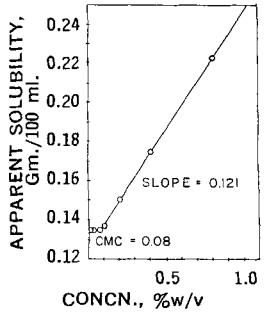

Fig. 2—Apparent solubility of benzocaine at 30° in aqueous solutions of OPEO.

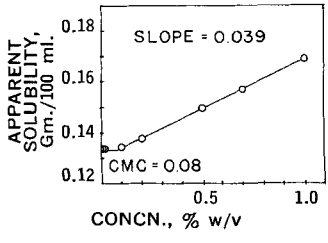

Fig. 3—Apparent solubility of benzocaine at 30° in aqueous solutions of POEEO.

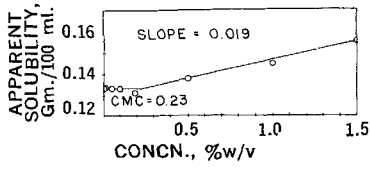

Fig. 4—Apparent solubility of benzocaine at 30° in aqueous solutions of POE.

TABLE I—SOLUBILIZING AND STABILIZING ABILITY OF SOME NONIONIC SURFACE-ACTIVE AGENTS FOR BENZOCAINE

Agent	*K*, Slope of Solubility Curve	$t_{1/2}$, in 3% Agent, min.
PLE	0.117	291
OPEO	0.121	295
POEEO	0.039	107
POE	0.019	91

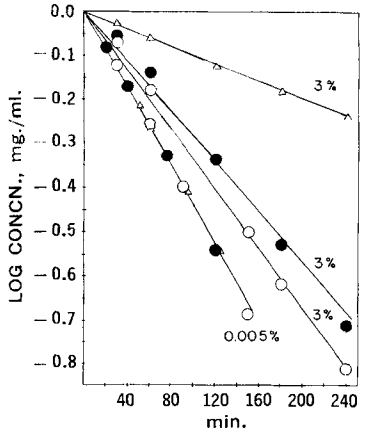

Fig. 5—A plot showing the effect of 3% concentration of surface-active agents on the rate of hydrolysis of benzocaine at 30° and 0.04 N hydroxyl ion concentration. The points on the 0.005% curve represent the hydrolysis in the presence of 0.005% surface-active agent; the line on which these points fall is drawn for the hydrolysis of benzocaine at 0.04 N hydroxyl ion concentration. Key: O, POE; ●, POEEO; △, PLE.

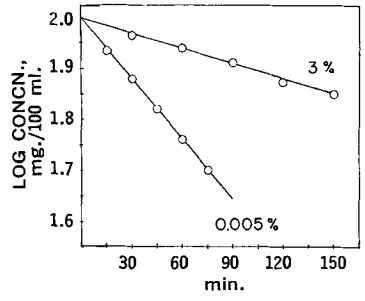

Fig. 6—A plot showing the effect of 3% OPEO on the rate of hydrolysis of benzocaine at 30° and 0.04 N hydroxyl ion concentration. The points on the 0.005% curve represent the hydrolysis in the presence of 0.005% OPEO; the line on which these points fall is drawn for the hydrolysis of benzocaine at 0.04 N hydroxyl ion concentration.

TABLE II—SPECIFIC RATE CONSTANTS AND HALF-LIFE PERIODS FOR HYDROLYSIS OF BENZOCAINE IN 0.04 *N* HYDROXYL ION CONCENTRATION AT 30° IN THE PRESENCE OF SOME NONIONIC SURFACE-ACTIVE AGENTS

Agent	% Agent	k (min.$^{-1}$)	$t_{1/2}$, min.
Water	...	0.01006	69
PLE	0.005	0.00996	70
	3.00	0.00238	291
OPEO	0.005	0.00908	76
	3.00	0.00234	295
POEEO	0.005	0.01012	69
	3.00	0.00644	107
POE	0.005	0.00989	70
	3.00	0.00759	91

of benzocaine was either 1 mg./100 ml. or 1 mg./ml. of solution. The hydrolysis of homatropine was carried out in distilled water at 30°. The experimental conditions for the hydrolysis of the esters produced an insignificant change in hydrogen ion concentration, and consequently the observed hydrolysis was pseudo first-order.

Hydrolysis of Benzocaine in the Presence of Nonionic Surface-Active Agents—The rate of hydrolysis of benzocaine was followed at 30° in the presence of four nonionic surface-active agents. As shown in Figs. 5 and 6, a plot of the logarithm of concentration of benzocaine against time is linear, designating a pseudo first-order reaction. The specific rate constant was determined by multiplying the slope of the curve by 2.303. As the hydrolysis is a pseudo first-order reaction, the half-life period was determined by dividing 0.693 by the specific rate constant (19). The specific rate constants and the half-life periods are given in Table II.

The alkaline hydrolysis was carried out in water and in a 0.005% solution of the surface-active agent, which was a concentration less than the CMC. A comparison of the half-life periods of benzocaine at 0.04 *N* hydroxyl ion concentration in water and in 0.005% surface-active agent shows that the surface-active agent *per se* does not significantly affect the stability. In Figs. 5 and 6 the points on the 0.005% curve are experimental values showing the rate of hydrolysis of benzocaine in the presence of 0.005% surface-active agent; the line upon which these points fall is drawn to show the rate of hydrolysis of benzocaine in water at 0.04 *N* hydroxyl ion concentration.

In 3% concentration of surface-active agents, the half-life periods were increased. For example, with PLE and OPEO the half-life of benzocaine was increased fourfold. As the surface-active agents exhibited no effect on the stability below their CMC, the increased stability at a concentration exceeding the CMC is attributed to micellar interaction.

This is further suggested by the stability of benzocaine in other surface-active agents. POE, which forms micelles of a low aggregation number, would theoretically provide less opportunity for micellar interaction with benzocaine; therefore, it would only slightly increase the stability of benzocaine. The experimental results concur, as the half-life of benzocaine in the presence of 3% POE is increased only 30%.

Hydrolysis of Homatropine in the Presence of Nonionic Surface-Active Agents—The rate of hydrolysis of homatropine was followed at 30° in the presence of four nonionic surface-active agents. As shown in Figs. 7 and 8 the rate of hydrolysis is first order with respect to homatropine. The observed specific rate constants and the half-life periods are given in Table III.

When the hydrolysis was carried out at a concentration of 0.005% surface-active agent, the rate of degradation was the same as that in distilled water. In Figs. 7 and 8, the points on the 0.005% curve are experimental values showing the rate of hydrolysis of homatropine in the presence of 0.005% surface-active agent; the line upon which these points fall is drawn to show the rate of hydrolysis of homatropine in water.

In 3% concentrations of OPEO and PLE, the half-life periods were increased approximately twofold. In 3% concentrations of POE and

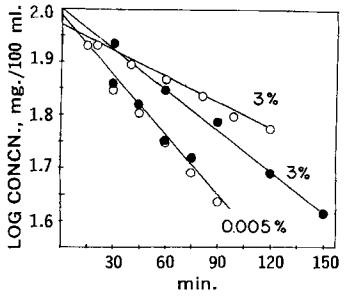

Fig. 7—A plot showing the effect of 3% of surface-active agents on the rate of hydrolysis of homatropine at 30°. The points on the 0.005% curve represent the hydrolysis in the presence of 0.005% surface-active agent; the line on which these points fall is drawn for the hydrolysis of homatropine in water. Key: ○, PLE; ●, POE.

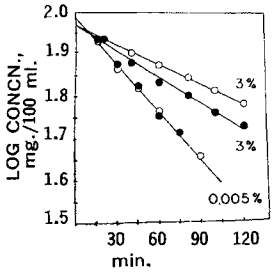

Fig. 8—A plot showing the effect of 3% of surface-active agent on the rate of hydrolysis of homatropine at 30°. The points on the 0.005% curve represent the hydrolysis in the presence of 0.005% surface-active agent; the line on which these points fall is drawn for the hydrolysis of homatropine in water. Key: ○, OPEO; ●, POEEO.

TABLE III—SPECIFIC RATE CONSTANTS AND HALF-LIFE PERIODS FOR HYDROLYSIS OF HOMATROPINE AT 30° IN THE PRESENCE OF SOME NONIONIC SURFACE-ACTIVE AGENTS

Agent	% Agent	k (min.$^{-1}$)	$t_{1/2}$, min.
Water	...	0.00897	77
OPEO	0.005	0.00885	78
	3.00	0.0046	150
PLE	0.005	0.00938	74
	3.00	0.00483	143
POEEO	0.005	0.00897	77
	3.00	0.00552	125
POE	0.005	0.0091	76
	3.00	0.00552	125

POEEO, the half-life periods are increased approximately 60%.

It has been suggested that solubilization occurs by (*a*) solution of the solubilizate within the interior of the micelle, (*b*) adsorption on the surface of the micelle, and (*c*) penetration into the palisade layer of the micelle (14). When a nonpolar compound is solubilized within the lipophilic interior of the micelle, the system is presumably more stable because the attacking species cannot readily contact the solubilized compound. If a compound is solubilized by penetration into the palisade layer of the micelle, it is generally susceptible to attack and degradation, although to a lesser extent than a compound solubilized by surface adsorption on the micelle.

In comparing the effect of the nonionic surface-active agents on the hydrolysis of benzocaine and homatropine, the greater stabilization of benzocaine may be attributed to the deeper penetration of the less polar benzocaine into the palisade layer of the micelles. The more polar homatropine only superficially penetrates the palisade layer, or is adsorbed onto the surface of the micelle; thus, homatropine is exposed to the hydroxyl ions and its stability is not markedly enhanced by solubilization.

A comparison of the effect of the four nonionic surface-active agents on the solubilization and the stability of benzocaine, as given in Table I, indicates that the stability increase by solubilization reflects the solubilizing ability of the surface-active agent. PLE and OPEO have the same solubilizing ability, and at 3% concentration both increase the half-life of benzocaine approximately fourfold. POE, which has the least solubilizing ability, only slightly increases the half-life of benzocaine. POEEO is intermediate in its solubilizing ability and enhancement of stability.

The limited solubilization of benzocaine by POE mirrors its low aggregation number and limited incorporation of benzocaine in the micelle. POE does not appreciably retard the hydrolysis of benzocaine, which is adsorbed on the surface of the micelle and is exposed to the attacking hydroxyl ions.

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