

Effect of Temperature on Solubilization and Hydrolytic Degradation of Solubilized Benzocaine and Homatropine

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Abstract □ The solubilization of benzocaine with polyoxyethylene (23) lauryl ether and polysorbate 80 was determined as a function of temperature. The enhancement of the stability of benzocaine and homatropine solubilized with from 3 to 15% polyoxyethylene (23) lauryl ether and polysorbate 80 was quantitatively determined at 30, 50, and 70°. For the alkaline hydrolysis of benzocaine and homatropine, the logarithm of the specific rate constant is linearly related to the percent of the surface-active agent. The specific rate constant for the hydrolysis of benzocaine is linearly related to the reciprocal of the apparent solubility of benzocaine in polyoxyethylene (23) lauryl ether and polysorbate 80.

Keyphrases □ Benzocaine, solubilization, hydrolysis—temperature effect □ Surfactants, nonionic, effect—solubilized benzocaine, homatropine hydrolysis □ Solubility, apparent—specific rate constant, benzocaine, homatropine □ Temperature effect—solubilized benzocaine, homatropine hydrolysis □ Homatropine, solubilization, hydrolysis—temperature effect

In a previous investigation, it was reported that in a 3% concentration four nonionic surface-active agents reduced the rate of hydrolysis of benzocaine and homatropine (1). The present study was undertaken to determine at several temperatures the effectiveness of polyoxyethylene (23) lauryl ether and polysorbate 80 in solubilizing and in retarding the alkaline hydrolysis of benzocaine and homatropine. It was assumed that concentrations as great as 15% of the nonionic surface-active agents would be acceptable in cosmetics and pharmaceuticals. The concentration of surface-active agent ranged from 3 to 15%. This investigation was carried out to determine if these concentrations of surface-active agents would slow the rate of hydrolysis of benzocaine and homatropine to an extent that would increase the shelflife significantly.

EXPERIMENTAL

Analysis and Solubility of Benzocaine—The method of analysis and the method for the determination of the solubility of benzocaine NF in various concentrations of polyoxyethylene (23) lauryl ether¹ and polysorbate 80² were reported previously (1, 2). The surface-active agents were commercial lots used without further purification. The apparent solubility was determined at 30, 50, and 70° and is given in Tables I and II.

Hydrolysis of Benzocaine—The rate of hydrolysis of benzocaine was determined in various concentrations of polyoxyethylene (23) lauryl ether and polysorbate 80 in 0.04 *N* hydroxyl-ion concentration at 30, 50, and 70° as previously described (1). At each temperature with each concentration of the surface-active agent, a standard absorbance-concentration curve was prepared, and the coefficients of the simultaneous equations were evaluated.

Hydrolysis of Homatropine—The method of analysis and the method for the determination of the rate of hydrolysis of homatropine³ in various concentrations of polyoxyethylene (23) lauryl ether and polysorbate 80 were reported (1, 3). The rate of hydrolysis

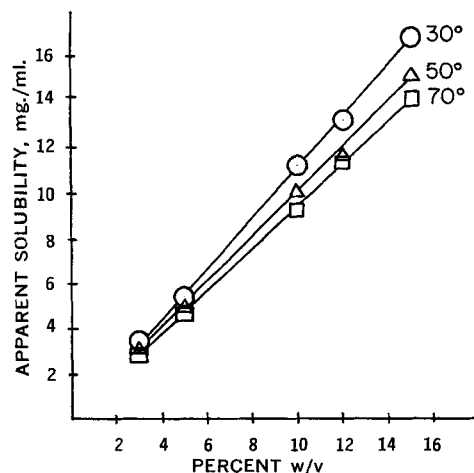


Figure 1—Apparent solubility of benzocaine at 30, 50, and 70° in solutions of polyoxyethylene (23) lauryl ether.

was determined in a borate buffer at pH 8 at 30, 50, and 70°. At 30°, the borate buffer consisted of 658 ml. of 0.4 *M* boric acid solution and 342 ml. of 0.1 *M* sodium borate solution. At higher temperatures, the buffer was adjusted by the addition of 0.4 *M* boric acid solution to pH 8, as measured by a Beckman model 72 pH meter.

RESULTS AND DISCUSSION

It is well known that surface-active agents in concentrations exceeding their CMC will solubilize or increase the apparent solubility of compounds of low water solubility. As shown in Figs. 1 and 2, the total or apparent solubility of benzocaine is linearly dependent on the concentration of polyoxyethylene (23) lauryl ether and polysorbate 80, respectively.

The influence of temperature on solubilization is complex, because both the structure of the micelle and the solubility of the solute may change with a change of temperature (4). This change in structure of the micelle and solubility of the solute may or may not be in the same direction. As the temperature of a solubilized system is increased, the extent of aggregation of the surface-active agent or the formation of micelles tends to be lessened due to the increased thermal activity. This phenomenon would tend to decrease the

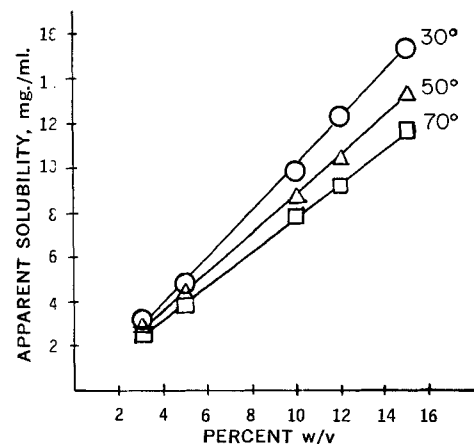


Figure 2—Apparent solubility of benzocaine at 30, 50, and 70° in solutions of polysorbate 80.

¹ Brij 35 SP, Atlas Chemical Industries, Inc., Wilmington, Del.

² Tween 80, Atlas Chemical Industries, Inc.

³ Obtained from K & K Laboratories, Inc., Plainview, N. Y.

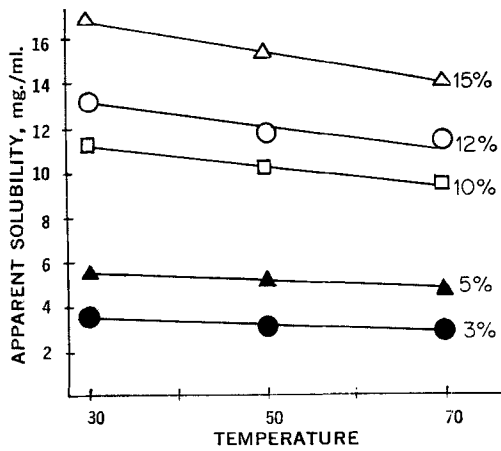


Figure 3—Influence of temperature on apparent solubility of benzocaine solubilized with polyoxyethylene (23) lauryl ether.

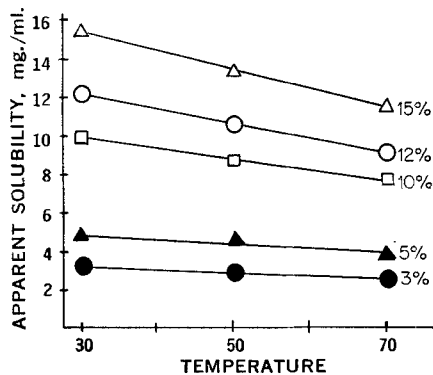


Figure 4—Influence of temperature on apparent solubility of benzocaine solubilized with polysorbate 80.

amount of solute solubilized. If the intrinsic solubility of the solute is decreased with an increase in temperature, the apparent solubility of the solute would be markedly lowered as both the intrinsic and micellar solubility are lessened with an increase in temperature.

If the intrinsic solubility of the solute is increased with an increase in temperature, the apparent solubility may be lowered or raised, depending on which of the opposing phenomena is predominant.

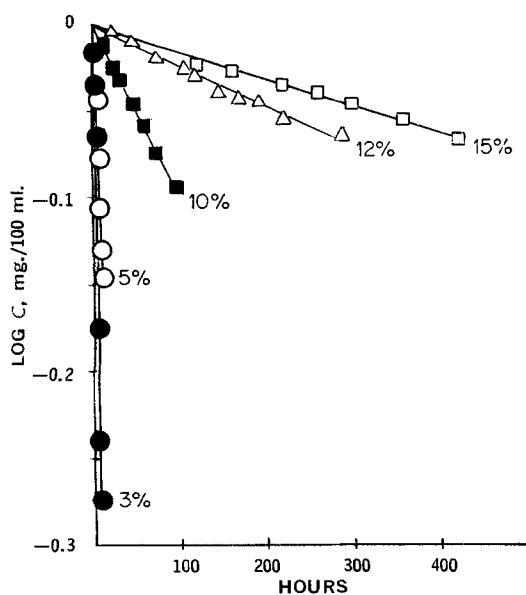


Figure 5—Hydrolysis of benzocaine at 30° in polyoxyethylene (23) lauryl ether at 0.04 N hydroxyl-ion concentration.

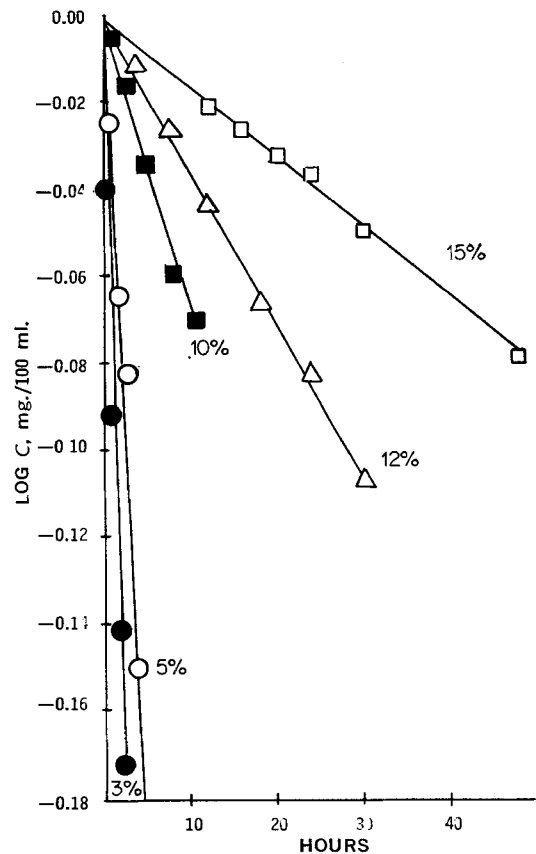


Figure 6—Hydrolysis of benzocaine at 30° in polysorbate 80 at 0.04 N hydroxyl-ion concentration.

The influence of temperature on the apparent solubility of benzocaine in various concentrations of polyoxyethylene (23) lauryl ether and polysorbate 80 is shown in Figs. 3 and 4, respectively. Within the temperature range from 30 to 70° for a given concentration of polyoxyethylene (23) lauryl ether and polysorbate 80, the apparent solubility is decreased as the temperature is increased. Thus, it appears that although an increase in temperature increases the intrinsic solubility of benzocaine, the apparent solubility is due less to micellar disruption.

At high concentrations of surface-active agents, it is possible that the degree of change in the structure of the micelle is greater than the degree of change in solubility of the solute. Thus, for a given in-

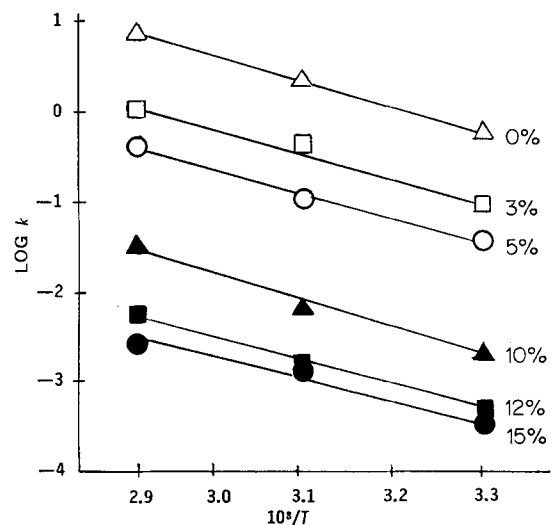


Figure 7—Arrhenius plot showing temperature dependence of hydrolysis of benzocaine in various concentrations of polyoxyethylene (23) lauryl ether.

Table I—Apparent Solubility, Specific Rate Constant, and Half-Life Period for the Hydrolysis of Benzocaine in 0.04 N Hydroxyl-Ion Concentration at 30, 50, and 70° in Various Concentrations of Polyoxyethylene (23) Lauryl Ether

Percent w/v of Polyoxyethylene (23) Lauryl Ether	k , hr. ⁻¹	$t_{1/2}$, hr.	Apparent Solubility, mg./ml.	Reciprocal of Solubility
30°				
0	0.63000	1.1	—	—
3	0.09840	7.0	3.56	0.280
5	0.03828	18.1	5.48	0.182
10	0.00230	301.6	11.26	0.088
12	0.00054	1283.3	13.20	0.075
15	0.00034	2008.7	16.85	0.059
50°				
0	2.49600	0.3	—	—
3	0.45960	1.5	3.04	0.328
5	0.11220	6.2	5.12	0.195
10	0.00690	100.4	10.22	0.097
12	0.00167	415.5	11.69	0.085
15	0.00135	513.3	15.26	0.065
70°				
0	7.88400	0.1	—	—
3	1.05600	0.6	2.84	0.352
5	0.45960	1.5	4.68	0.213
10	0.03282	21.1	9.32	0.107
12	0.00612	113.2	11.36	0.088
15	0.00276	251.1	14.10	0.070

crease in temperature the effect of diminution of micellar structure is greater than the effect of increased intrinsic solubility of the solute, and there is a marked decrease in apparent solubility. For example, in Fig. 3 with 15% polyoxyethylene (23) lauryl ether, the slope of the line obtained by plotting the apparent solubility of benzocaine against the temperature is -0.070 mg./ml./deg.

At lower concentrations of surface-active agents, the extent of aggregation and the change in intrinsic solubility of the solute are involved to a similar degree. As the temperature is increased, micellar

Table II—Apparent Solubility, Specific Rate Constant, and Half-Life Period for the Hydrolysis of Benzocaine in 0.04 N Hydroxyl-Ion Concentration at 30, 50, and 70° in Various Concentrations of Polysorbate 80

Percent w/v of Polysorbate 80	k , hr. ⁻¹	$t_{1/2}$, hr.	Apparent Solubility, mg./ml.	Reciprocal of Solubility
30°				
0	0.6300	1.1	—	—
3	0.1476	4.7	3.24	0.308
5	0.0900	7.7	4.67	0.214
10	0.0145	47.8	9.90	0.101
12	0.0076	90.9	12.28	0.081
15	0.0034	200.9	15.48	0.064
50°				
0	2.496	0.3	—	—
3	1.254	0.5	2.92	0.342
5	0.612	1.1	4.55	0.219
10	0.138	5.0	8.72	0.114
12	0.092	7.5	10.60	0.094
15	0.048	14.3	13.40	0.074
70°				
0	7.884	0.1	—	—
3	4.140	0.2	2.56	0.390
5	2.364	0.3	3.74	0.267
10	0.762	0.9	7.84	0.127
12	0.552	1.2	9.24	0.108
15	0.243	2.8	11.62	0.086

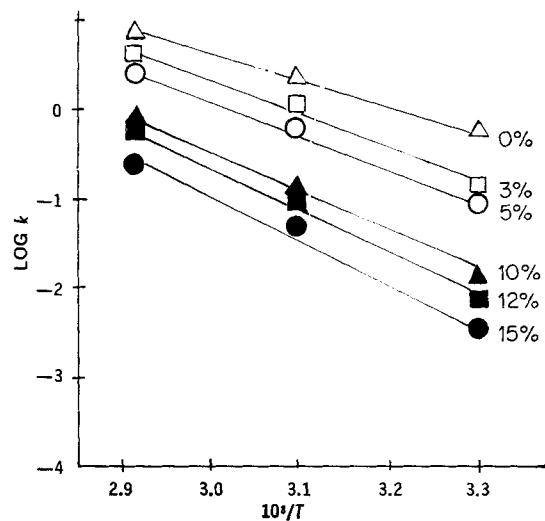


Figure 8—Arrhenius plot showing temperature dependence of hydrolysis of benzocaine in various concentrations of polysorbate 80.

solubilization is decreased and the intrinsic solubility of the solute is increased. Since at low concentrations of the surface-active agent these opposing effects are of a similar magnitude, the apparent solubility of the solute is not as greatly affected by a change in temperature as a solubilized system with a higher concentration of the surface-active agent. For example, in Fig. 3 with 3% polyoxyethylene (23) lauryl ether, the slope of the line is -0.018 mg./ml./deg., whereas with 15% polyoxyethylene (23) lauryl ether the slope is four times as great.

Similarly, for benzocaine solubilized with polysorbate 80, an increase in temperature results in a decrease of apparent solubility. For example, in Fig. 4 with 15% polysorbate 80, the slope of the line is -0.096 mg./ml./deg., while with 3% polysorbate 80 the slope is -0.017 mg./ml./deg.

For systems of benzocaine solubilized with polyoxyethylene (23) lauryl ether and polysorbate 80, the rate of change of apparent solubility with temperature is less at low concentrations than at high concentrations of surface-active agent.

Hydrolysis of Benzocaine in Presence of Polyoxyethylene (23) Lauryl Ether and Polysorbate 80—The rate of hydrolysis of benzocaine in 0.04 N hydroxyl-ion concentration was followed at 30, 50, and 70° in the presence of various concentrations of polyoxyethylene (23) lauryl ether and polysorbate 80. As demonstrated previously (1) and as shown in Figs. 5 and 6 for a given temperature and concentration of a surface-active agent, a plot of the logarithm of concentration of benzocaine against time was linear. The specific rate constant (k) for the pseudo-first-order reaction was determined

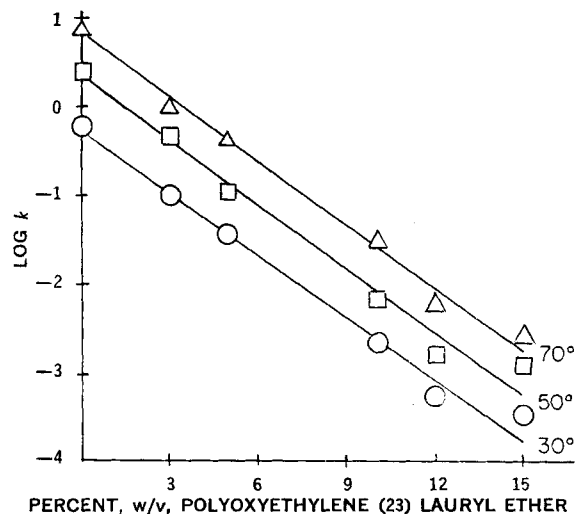


Figure 9—Relationship of $\log k$ for hydrolysis of benzocaine at 30, 50, and 70° to concentrations of polyoxyethylene (23) lauryl ether.

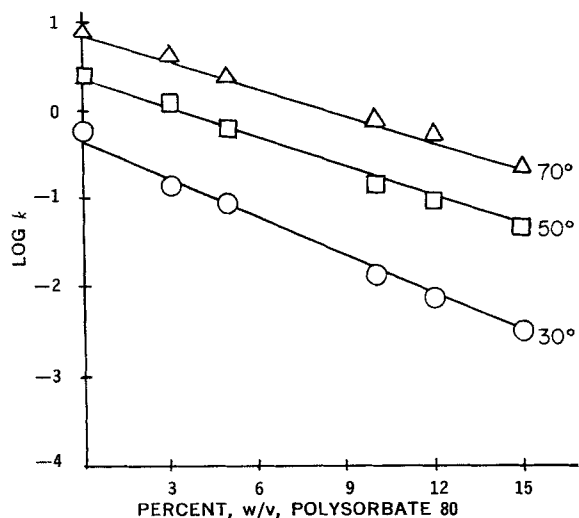


Figure 10—Relationship of $\log k$ for hydrolysis of benzocaine at 30, 50, and 70° to concentrations of polysorbate 80.

by multiplying the slope of the curve by 2.303; the half-life period ($t_{1/2}$) was calculated from the relationship: $t_{1/2} = 0.693/k$. The experimental values of k and $t_{1/2}$ at 30, 50, and 70° in the presence of various concentrations of polyoxyethylene (23) lauryl ether and polysorbate 80 are given in Tables I and II.

The dependence of k on temperature is described by an Arrhenius plot in Fig. 7 for various concentrations of polyoxyethylene (23) lauryl ether. The activation energy for the alkaline hydrolysis of benzocaine as calculated from this plot ranged from 12 to 15 kcal./mole. A similar influence of temperature on the hydrolysis of benzocaine in the presence of polysorbate 80 is shown in Fig. 8.

As shown in Table I, the $t_{1/2}$ is increased as the concentration of surface-active agent is increased. For example, at 30° the $t_{1/2}$ of benzocaine solubilized with 15% polyoxyethylene (23) lauryl ether is 1825-fold as great as that without the surface-active agent. As shown in Fig. 9, the logarithm of the rate constant is linearly related to the concentration of polyoxyethylene (23) lauryl ether. This relationship may be expressed:

$$\log k_{30^\circ} = -0.25C - 0.201 \quad (\text{Eq. 1})$$

$$\log k_{50^\circ} = -0.25C + 0.398 \quad (\text{Eq. 2})$$

$$\log k_{70^\circ} = -0.25C + 0.892 \quad (\text{Eq. 3})$$

where C is the percent of polyoxyethylene (23) lauryl ether. Since the slopes of the lines in Fig. 9 are the same, for the range of temperature investigated $d(\log k)/dC = -0.25$.

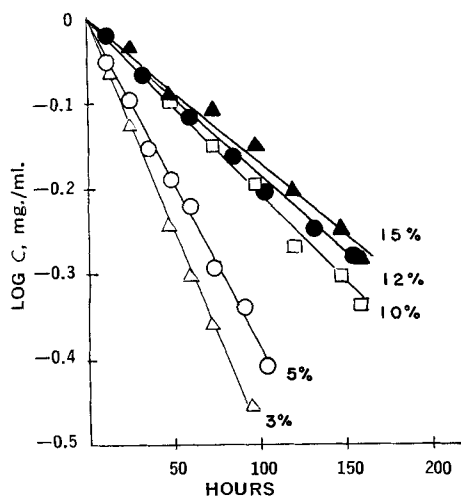


Figure 11—Hydrolysis of homatropine at 30° and pH 8 in various concentrations of polyoxyethylene (23) lauryl ether.

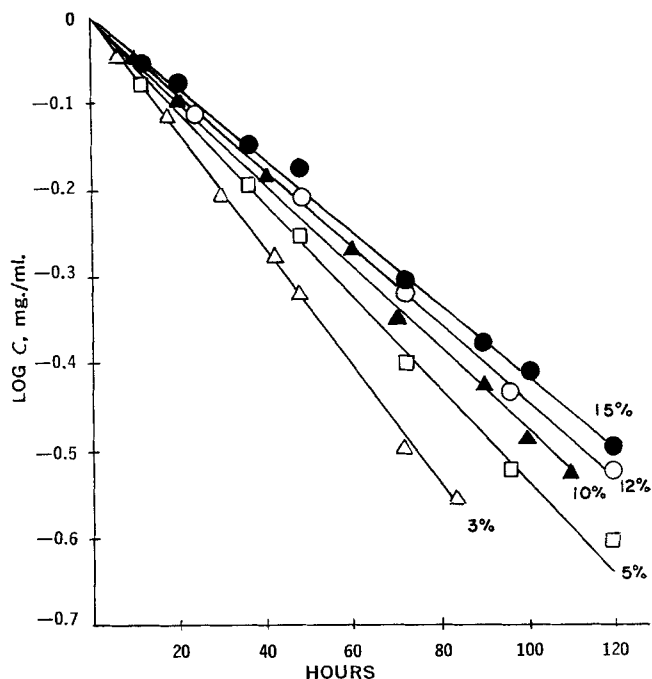


Figure 12—Hydrolysis of homatropine at 30° and pH 8 in various concentrations of polysorbate 80.

Inspection of Table II shows that the $t_{1/2}$ of benzocaine solubilized with 15% polysorbate 80 is increased 180-, 50-, and 30-fold at 30, 50, and 70°, respectively. The linear relationship shown in Fig. 10 between $\log k$ and the concentration of polysorbate 80 may be expressed:

$$\log k_{30^\circ} = -0.1C - 0.2 \quad (\text{Eq. 4})$$

$$\log k_{50^\circ} = -0.1C + 0.4 \quad (\text{Eq. 5})$$

$$\log k_{70^\circ} = -0.1C + 0.9 \quad (\text{Eq. 6})$$

Thus, the influence of concentration of polysorbate 80 on the hydrolysis of benzocaine may be expressed as $d(\log k)/dC = -0.1$.

Table III—Specific Rate Constant and Half-Life Period for the Hydrolysis of Homatropine at pH 8 at 30, 50, and 70° in Various Concentrations of Polyoxyethylene (23) Lauryl Ether

Percent w/v of Polyoxyethylene (23) Lauryl Ether	k , hr. ⁻¹	$t_{1/2}$, hr.
30°		
0	0.0160	43.2
3	0.0113	61.5
5	0.0091	75.9
10	0.0048	144.6
12	0.0043	162.7
15	0.0037	188.1
50°		
0	0.0958	7.4
3	0.0828	8.4
5	0.0690	10.0
10	0.0593	11.7
12	0.0566	12.2
15	0.0531	13.1
70°		
0	0.3162	2.2
3	0.3067	2.3
5	0.2629	2.6
10	0.2300	3.0
12	0.2156	3.2
15	0.2044	3.4

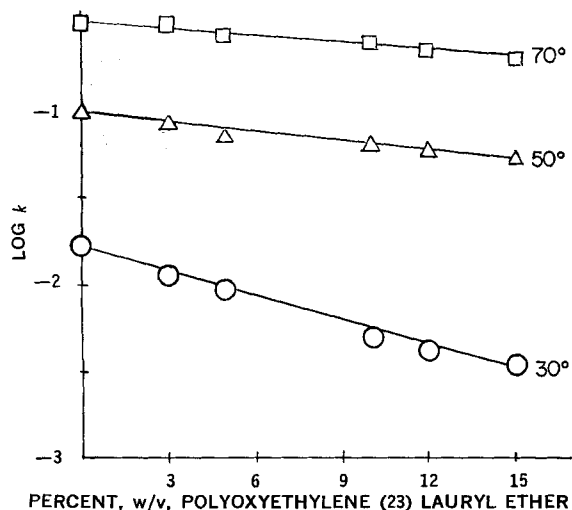


Figure 13—Relationship of $\log k$ for hydrolysis of homatropine at 30, 50, and 70° to concentrations of polyoxyethylene (23) lauryl ether.

The ratio of $d(\log k)/dC$ for polyoxyethylene (23) lauryl ether to that of polysorbate 80 is approximately 2.5. On a percentage basis, polyoxyethylene (23) lauryl ether is more effective than polysorbate 80 in retarding the hydrolytic degradation of benzocaine in the solubilized systems under the conditions studied.

Hydrolysis of Homatropine in Presence of Polyoxyethylene (23) Lauryl Ether and Polysorbate 80—The rate of hydrolysis of homatropine at pH 8 was followed at 30, 50, and 70° in the presence of various concentrations of polyoxyethylene (23) lauryl ether and polysorbate 80. Typical results for the first-order hydrolysis of homatropine are given in Figs. 11 and 12. From such plots the experimental values of k and $t_{1/2}$, as given in Tables III and IV, were determined. Plots (not shown) of $\log k$ against $1/T$ showed that the influence of temperature on the hydrolysis of homatropine in the presence of polyoxyethylene (23) lauryl ether and polysorbate 80 is described by the Arrhenius equation.

As shown in Tables III and IV, the $t_{1/2}$ is increased as the concentration of the surface-active agent is increased. For example, at 30° the $t_{1/2}$ of homatropine solubilized with 15% polyoxyethylene (23) lauryl ether is four times as great as that without the surface-active agent. The fourfold increase of the $t_{1/2}$ for homatropine is much less than the 1825-fold increase for benzocaine under the same conditions. This indicates that the solubilization technique may be used to increase stability significantly only with very slightly soluble compounds. In this case, a greater fraction of the moderately water-soluble homatropine remains in the aqueous phase, where it is readily attacked by the hydroxyl ion, than the less water-soluble

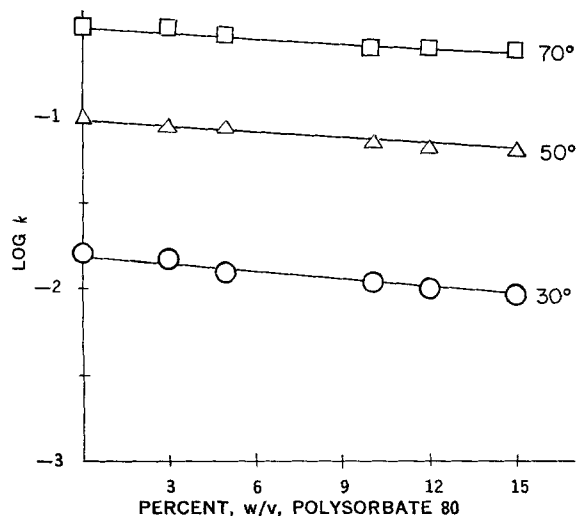


Figure 14—Relationship of $\log k$ for hydrolysis of homatropine at 30, 50, and 70° to concentrations of polysorbate 80.

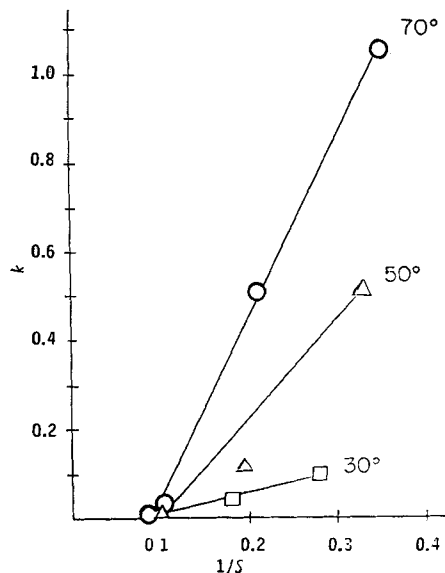


Figure 15—Reciprocal relationship between apparent solubility of benzocaine and k in the presence of polyoxyethylene (23) lauryl ether at 30, 50, and 70°.

benzocaine, which is associated with the micelle where it is not appreciably attacked by the hydroxyl ion, and enhanced stability is exhibited.

As shown in Fig. 13, the $\log k$ is linearly related to the concentration of polyoxyethylene (23) lauryl ether. This may be expressed:

$$\log k_{30^\circ} = -0.042C - 1.8 \quad (\text{Eq. 7})$$

$$\log k_{50^\circ} = -0.025C - 1.0 \quad (\text{Eq. 8})$$

$$\log k_{70^\circ} = -0.025C - 0.5 \quad (\text{Eq. 9})$$

where C is the percent of polyoxyethylene (23) lauryl ether.

Inspection of Table IV shows that the $t_{1/2}$ of homatropine solubilized with 15% polysorbate 80 is only slightly lengthened, *i.e.*, 50%. The linear relationship shown in Fig. 14 between the $\log k$ and concentration of polysorbate 80 may be expressed:

$$\log k_{30^\circ} = -0.017C - 1.8 \quad (\text{Eq. 10})$$

Table IV—Specific Rate Constant and Half-Life Period for the Hydrolysis of Homatropine at pH 8 at 30, 50, and 70° in Various Concentrations of Polysorbate 80

Percent w/v of Polysorbate 80	k , hr. ⁻¹	$t_{1/2}$, hr.
30°		
0	0.0160	43.2
3	0.0149	46.3
5	0.0126	54.8
10	0.0108	63.9
12	0.0102	67.8
15	0.0094	73.6
50°		
0	0.0958	7.4
3	0.0885	7.8
5	0.0852	8.1
10	0.0700	9.9
12	0.0657	10.5
15	0.0639	10.8
70°		
0	0.3162	2.2
3	0.3136	2.2
5	0.2875	2.4
10	0.2421	2.9
12	0.2400	2.9
15	0.2300	3.0

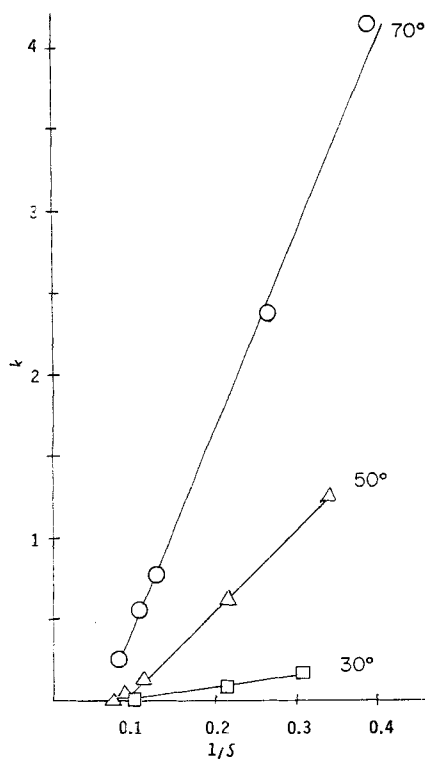


Figure 16—Reciprocal relationship between apparent solubility of benzocaine and k in the presence of polysorbate 80 at 30, 50, and 70°.

$$\log k_{30^\circ} = -0.017C - 1.0 \quad (\text{Eq. 11})$$

$$\log k_{70^\circ} = -0.017C - 0.5 \quad (\text{Eq. 12})$$

Thus, the influence of concentration of polysorbate 80 on the hydrolysis of homatropine may be expressed as $d(\log k)/dC = -0.017$.

The ratio of $d(\log k)/dC$ for polyoxyethylene (23) lauryl ester to that of polysorbate 80 is approximately 1.5. On a percentage basis, polyoxyethylene (23) lauryl ether is more effective than polysorbate 80 in retarding the hydrolytic degradation of homatropine in the solubilized systems under the conditions studied.

Apparent Solubility and k —Solubilization occurs by association with, adsorption on, and/or solution within the micelle (2). Presumably, a solubilized molecule is more stable because the attacking species cannot as readily contact the solubilized compound. The rate of hydrolysis of benzocaine in aqueous solutions is increased with an elevation of temperature. An elevation of temperature in a solubilized system, however, may affect also the degree of aggregation of the micelle, and the rate of change of diffusivity of the attacking species with temperature may be different from that in the aqueous solution. An examination of Tables I and II indicates that the apparent solubility is related to the stability. The correlation between the reciprocal ($1/S$) of apparent solubility and k is shown in Figs. 15 and 16 for benzocaine at 30, 50, and 70° in polyoxyethylene (23) lauryl ether and polysorbate 80, respectively. Thus, in the formulation of a solubilized product of benzocaine, its stability as expressed in terms of k would be anticipated to be linearly dependent on the reciprocal of the apparent solubility.

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