excretion was approached by the 1/2 *n*-butyl PVM/MA and the 1/2 cyclopentyl PVM/MA coated tablets in 18 and 24 hr., respectively. The excretion study was conducted through 48 hr. indicating complete availability for all enteric tablets except for the 1/2 cyclopentyl PVM/MA coated tablet which was 87% available. The deposition of an enteric tablet at a lower absorption site than the latter tablet would be expected to result in slower and less complete absorption with a lower plasma peak and lower degree of availability.

The variation of the tested products was considered by examination of the distribution of peak times for individuals. This parameter is a reflection of the combined variables of gastric emptying time, pH, and intestinal transit time. The distribution patterns for the control, the 1/2 ethyl PVM/MA, and the 1/2 isopropyl PVM/MA coated tablets were equivalent. The 1/2 *n*-butyl PVM/MA coated tablet indicated increased variation, and the 1/2 cyclopentyl PVM/MA coated tablet exhibited the greatest variation. In these fasting ambulatory subjects the absorption reproducibility of the enteric tablets was greatly dependent upon the absorption site of the intestine, *i.e.*, the upper part of the intestine exhibited significantly less variation in absorption than the lower part of the intestine.

These data reveal that the gradation in coating dissolution pH is significant in permitting some control over the absorption of acetylsalicylic acid. Many other drugs are absorbed at various rates throughout the intestinal tract. Therefore, each drug should be considered an individual problem in formulating enteric-release products to effect optimal absorption.

REFERENCES

(1) Schanker, L. S., *Ann. Rev. Pharmacol.*, **1**, 29(1961).
(2) Lappas, L. C., and McKeehan, W., *J. Pharm. Sci.*, **54**, 176(1965).
(3) *Ibid.*, **51**, 808(1962).
(4) Kleber, J. W., Nash, J. F., and Lee, C.-C., *ibid.*, **53**, 1519(1964).
(5) Nessel, R. J., DeKay, H. G., and Banker, G. S., *ibid.*, **53**, 882(1964).
(6) Hogben, C. A. M., Schanker, L. S., Tocco, D. J., and Brodie, B. B., *J. Pharmacol. Expil. Therap.*, **120**, 540 (1957).
(7) Schanker, L. S., Shore, P. A., Brodie, B. B., and Hogben, C. A. M., *ibid.*, **120**, 528(1957).
(8) Schanker, L. S., Tocco, D. J., Brodie, B. B., and Hogben, C. A. M., *ibid.*, **123**, 81(1958).
(9) Schanker, L. S., *ibid.*, **126**, 283(1959).
(10) James, A. N., and Pickering, G. W., *Clin. Sci.*, **49**, 181(1949).
(11) Rovelstad, R. A., *Gastroenterology*, **31**, 530(1956).
(12) Garrett, E. R., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 584(1957).
(13) Edwards, L. J., *Trans. Faraday Soc.*, **47**, 1191(1951).
(14) Weikel, J. H., Jr., and Lish, P. M., *Arch. Intern. Pharmacodyn.*, **119**, 398(1959).
(15) Eriksen, S. P., Swintosky, J. V., Serfass, E. J., Lin, T. H., Abrams, J., and Sturtevant, F. M., *J. Pharm. Sci.*, **50**, 151(1961).
(16) Levy, G., Gumtow, R. H., and Rutowski, J. M., *Can. Med. Assoc. J.*, **85**, 414(1961).
(17) Blythe, R. H., Grass, G. M., and MacDonnell, D. R., *Am. J. Pharm.*, **131**, 206(1959).
(18) Lappas, L. C., unpublished data.
(19) Schachter, D., and Manis, J. G., *J. Clin. Invest.*, **37**, 800(1958).
(20) Cummings, A. J., and Martin, B. K., *Biochem. Pharmacol.*, **13**, 767(1964).
(21) Brodie, B. B., Burns, J. J., and Weiner, M., *Med. Exptl.*, **1**, 290(1959); through *Chem. Abstr.*, **54**, 25254 (1960).
(22) Swintosky, J. V., *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 395(1956).
(23) Levy, G., *J. Pharm. Sci.*, **54**, 959(1965).
(24) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 20.
(25) *Ibid.*, p. 934.
(26) *Ibid.*, pp. 1072, 1073.

Hydrolysis of Solubilized Aspirin

By A. G. MITCHELL* and J. F. BROADHEAD

The hydrolysis of aspirin in buffered solutions of the nonionic surfactant, cetomacrogol, has been studied at 37° over the pH range 1 through 7. Cetomacrogol reduces the hydrolysis rate of unionized aspirin but not that of ionized aspirin. The reaction occurs mainly in the aqueous phase but at low pH the contribution of a hydrogen ion catalyzed reaction within the micelles becomes significant. A kinetic expression has been derived to account for reaction both in the aqueous phase and in the micelles.

THE HYDROLYSIS of aspirin in aqueous solution has been investigated extensively by Edwards (1, 2) and Garrett (3, 4). They determined overall first-order rate constants as a function of pH and proposed various reaction mechanisms.

The effect of anionic, cationic, and nonionic surfactants on the stability of solubilized aspirin has been studied by Nogami *et al.* (5). It was shown that each surfactant suppressed the hydrolysis of unionized aspirin, while the hydrolysis of the anionic form of aspirin was suppressed only by cationic surfactants.

In this work, a detailed study has been made of the stability of aspirin at 37° in several concentrations of the nonionic surfactant, cetomacrogol, over the pH range 1 through 7. A kinetic expression has been derived to account for the hydrolysis of the solubilized drug.

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EXPERIMENTAL

Reagents and Solutions—Aspirin was recrystallized from acetone, m.p. 134–136°. Salicylic acid was recrystallized from alcohol and then water,

m.p. 159–161°. Cetomacrogol 1000 B.P.C.[1] has the general formula $CH_3 \cdot (CH_2)_m [O \cdot CH_2 \cdot CH_2]_n \cdot OH$, where m may be 15 or 17 and n may be 19 to 23. The molecular weight was taken as 1300. Solutions of cetomacrogol were passed through a column of mixed bed ion-exchange resins to remove alkaline impurities (6). Using a Zeiss laboratory interferometer the refractive index of the effluent was measured as an instrument scale reading and the concentration of cetomacrogol determined from a standard curve of instrument scale reading *versus* molar concentration.

Cetomacrogol solutions were buffered as follows: pH 1.0–2.2 HCl–KCl buffer (7), pH 2.2–2.9 glycine–HCl buffer (7), pH 2.9–4.6 acetate buffer (8), and pH 6.8–7.1 phthalate buffer (8). Ferric chloride reagent (1% $FeCl_3 \cdot 6H_2O$ in 0.05 N HCl). All solutions were made using freshly boiled and cooled glass-distilled water.

Apparatus—Beckman research pH meter (relative precision ± 0.001 under optimum conditions). The glass-saturated calomel electrode system was standardized, using 0.05 M potassium hydrogen phthalate, and the electrode response was checked on this buffer after each reading. The pH/E.M.F. relationship of the electrode was checked periodically using 0.05 M sodium borate. pH measurements were made at 37 ± 0.1° in a constant-temperature jacketed beaker.

Colorimetric analyses were made using a Unicam SP 1300 colorimeter and an Ilford No. 624 bright spectrum green filter (495–575 mμ).

Analytical Method—Solutions were analyzed for salicylic acid, using the blue color developed on reaction with ferric chloride (9).

Solubility of Aspirin—Excess aspirin was equilibrated with aqueous buffer or buffered cetomacrogol solutions by rotation in sealed cylinders in a water bath thermostatically controlled at 37 ± 0.1°. After filtration through a jacketed filter-funnel, aliquots of filtrate were assayed for salicylic acid present due to hydrolysis. Further samples were made alkaline with 0.5 N KOH, heated on a steam bath for 60 min., reacidified with 0.5 N HCl, and assayed for total salicylic acid. The solubility of aspirin was calculated from the difference between the amount of salicylic acid present initially and the amount found after complete hydrolysis.

Kinetic Procedure—An accurately weighed amount of aspirin was dissolved in aqueous buffer or buffered cetomacrogol solution maintained at 37 ± 0.1° in a thermostatically controlled water bath. Duplicate samples were withdrawn at zero time and then at suitable time intervals. One sample was assayed immediately for salicylic acid and the other for salicylic acid after complete hydrolysis. The concentration of aspirin remaining at each sampling time was calculated.

Density Measurements—A pycnometer of approximately 10-ml. capacity was used to measure the density of the cetomacrogol solutions at 37° (10). Each density was the mean of at least two determinations.

RESULTS AND DISCUSSION

Hydrolysis—The hydrolysis of aspirin proceeds as a first-order reaction both in aqueous buffer and in buffered cetomacrogol solutions (Fig. 1). Reaction rate constants were determined over the pH range 1 through 7 and the pH profiles in various surfactant concentrations are shown in Fig. 2. (Table I.) At the pH of maximum stability, pH 2.27, where aspirin exists largely in the unionized form, the half-life increases with cetomacrogol concentration and in 0.07 M cetomacrogol is approximately twice that in aqueous buffer. In the plateau region where aspirin is largely ionized, the rate of hyrolysis is independent of cetomacrogol concentration.

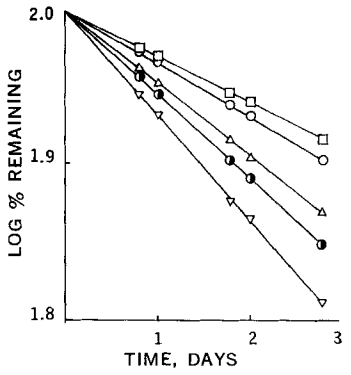

Fig. 1—First-order plots for the hydrolysis of aspirin solubilized in cetomacrogol solutions at 37°, pH 2.27. Key: cetomacrogol, moles L.$^{-1}$—▽, 0.00; ◑, 0.01; △, 0.02; ○, 0.05; □, 0.07.

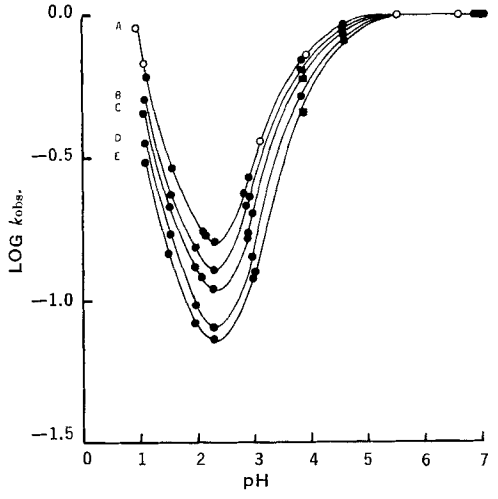

Fig. 2—Variation of observed first-order rate constant with pH for hydrolysis of aspirin solubilized in cetomacrogol solutions at 37°. Key: cetomacrogol, moles L.$^{-1}$—A, 0.00; B, 0.01; C, 0.02; D, 0.05; E, 0.07; ●, present study; ■, calculated; ○, Nogami (5).

On the two-phase model of micelle formation, solute will partition between the aqueous phase and the micellar phase. Using the two-phase model for a first-order process in surfactant solution, Yamada and Yamamoto (11) derived Eq. 1:[2]

$$k_{obs.} = \frac{1 - v}{Kv + (1 - v)} k_w \qquad \text{(Eq. 1)}$$

[1] Texofor A24, Glovers Chemicals Ltd., Leeds, England.

[2] See the *Appendix*.

TABLE I—RATE CONSTANTS FOR DECOMPOSITION OF ASPIRIN IN AQUEOUS BUFFER AND BUFFERED CETOMACROGOL SOLUTIONS

pH	Cetomacrogol, moles L.$^{-1}$	$k_{obs.}$ Day^{-1}
1.11	0	0.600
1.56	0	0.290
1.96	0	0.190
2.08	0	0.173
2.16	0	0.165
2.27	0	0.160
2.83	0	0.234
2.87	0	0.271
2.95	0	0.300
3.84	0	0.691
4.60	0	0.918
6.88	0	0.981
1.11	0.01	0.507
1.54	0.01	0.232
1.95	0.01	0.155
2.27	0.01	0.123
2.86	0.01	0.213
2.94	0.01	0.231
4.60	0.01	0.894
1.11	0.02	0.460
1.54	0.02	0.213
1.95	0.02	0.130
2.05	0.02	0.120
2.27	0.02	0.109
2.85	0.02	0.165
2.90	0.02	0.171
2.96	0.02	0.203
4.61	0.02	0.868
7.05	0.02	0.984
1.11	0.05	0.356
1.55	0.05	0.165
1.96	0.05	0.0953
2.28	0.05	0.0804
2.95	0.05	0.140
3.86	0.05	0.486
4.61	0.05	0.830
7.10	0.05	1.000
1.11	0.07	0.308
1.54	0.07	0.143
1.96	0.07	0.0828
2.28	0.07	0.0726
2.96	0.07	0.119
3.02	0.07	0.126
4.62	0.07	0.780
6.98	0.07	0.981

where $k_{obs.}$ is the observed rate constant in surfactant solutions at a given pH, k_w is the rate constant in aqueous solution at the same pH, K is the apparent partition coefficient for the distribution of solute between the micelles and aqueous phase, v is the volume fraction of micellar phase, and $1-v$ is the volume fraction of aqueous phase.

To test the applicability of Eq. 1 to the hydrolysis of aspirin in surfactant solutions, it was first necessary to estimate v and K.

Partial Molar Volume—The partial molar volume of cetomacrogol at 37° calculated from the density measurements shown in Fig. 3 was 1170 ml. mole^{-1}. Florence (12) has reported a value of 1099 ml. mole^{-1} at 30°. The partial molar volume was used to calculate v at each cetomacrogol concentration. The CMC of cetomacrogol is sufficiently low (13) for the concentration of monomeric surfactant to be neglected at the cetomacrogol concentrations under consideration.

Apparent Distribution Coefficient—The pH-dependent apparent distribution coefficient, K, is given by:

$$K = \frac{D_m}{v} \cdot \frac{(1 - v)}{D_w} \qquad \text{(Eq. 2)}$$

where D_m is the amount of solute in the micellar phase and D_w is the amount of solute in the aqueous phase. The total amount of solute, D, is given by:

$$D = D_w + D_m \qquad \text{(Eq. 3)}$$

In a given volume of a saturated solution the total amount of solute is equal to the solubility, C_s, and Eq. 3 becomes:

$$C_s = D_w + D_m \qquad \text{(Eq. 4)}$$

D_w was calculated from:

$$D_w = C_{sw}(1 - v) \qquad \text{(Eq. 5)}$$

where C_{sw}, the total solubility of aspirin in aqueous solution, is given by Eq. 6 (14):

$$C_{sw} = C'_{sw}[1 + \text{antilog (pH–pKa)}] \qquad \text{(Eq. 6)}$$

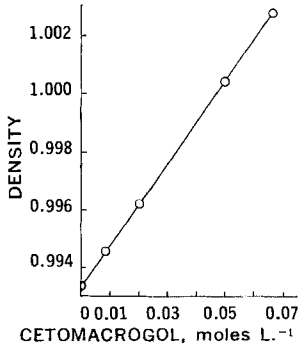

Fig. 3—Densities of cetomacrogol solutions at 37°.

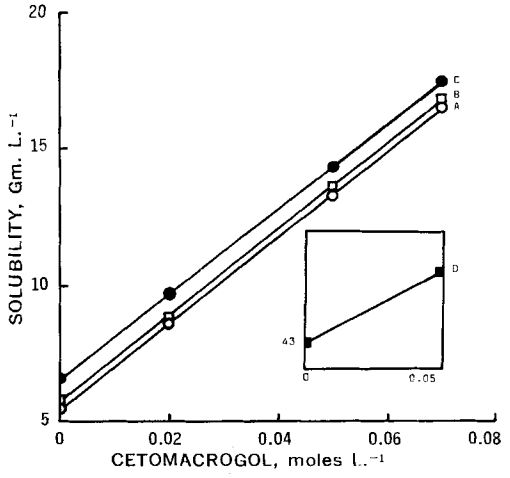

Fig. 4—Solubility of aspirin in aqueous buffer and buffered cetomacrogol solutions at 37°. Key: ○, pH 1.11; □, pH 2.04; ●, pH 2.75; ■, pH 4.36. Curves B–D calculated from solubilities at pH 1.11, and Eqs. 4–7; all points determined by experiment.

TABLE II—DISTRIBUTION OF ASPIRIN BETWEEN MICELLES AND AQUEOUS PHASE OF CETOMACROGOL SOLUTIONS AT VARIOUS pH VALUES

	Aspirin, mg. ml.$^{-1}$								
	Cetomacrogol, 0.02 *M*			Cetomacrogol, 0.05 *M*			Cetomacrogol, 0.07 *M*		
pH	*Dw*	*Dm*	*K*[a]	*Dw*	*Dm*	*K*[a]	*Dw*	*Dm*	*K*[a]
1.11	5.40	3.30	25.5	5.14	8.15	25.7	5.00	11.50	25.9
2.04	5.63	3.29	24.4	5.40	8.30	24.5	5.20	11.65	24.9
2.76	6.35	3.37	21.7	6.12	8.23	21.6	5.97	11.53	21.7
4.37				42.20	8.20	3.1			

[a] *K* calculated from the mean value of *Dm* at each cetomacrogol concentration.

C'_{sw}, the aqueous solubility of unionized aspirin at 37°, is 5.46 Gm. L.$^{-1}$, and the pKa for aspirin calculated by the solubility method (14) is 3.5 ± 0.03.

The solubility of aspirin at various pH values is shown as a function of cetomacrogol concentration in Fig. 4. The amount of aspirin in the micelles, D_m, at each cetomacrogol concentration is constant and from Eqs. 4 and 5 is given by:

$$D_m = C_s - C_{sw}(1 - v) \qquad \text{(Eq. 7)}$$

Table II shows some of the values for D_w, D_m, and K.

Agreement between the theoretical solubility curves shown in Fig. 4 (calculated from solubilities measured at pH 1.11 and Eqs. 4–7) and solubility values determined experimentally over the pH range where direct estimations were possible confirms the validity of this approach. Apparent distribution coefficients at any required pH can be determined from the plot of *K versus* $1/1 + k_a/[H^+]$, shown in Fig. 5.

Kinetics—One of the assumptions implicit in Eq. 1 is that only drug in the aqueous phase undergoes hydrolysis. It has been shown recently (15) that this assumption is valid for the hydrolysis of chlorobutol in nonionic surfactants at pH 8.7 and pH 9.2. If Eq. 1 is applicable to the hydrolysis of aspirin in cetomacrogol solutions, then a plot of the observed rate constant, $k_{obs.}$, for each pH against $(1-v)/Kv+(1-v)$ should be a line of slope k_w passing through the origin. Figure 6 shows that the equation holds at pH 2.95 and above, but at lower pH values the lines intercept the ordinate above the origin. The occurrence of an intercept indicates that at pH < 2.95 a reaction additional to that in the aqueous phase is making a significant contribution toward the over-all reaction.

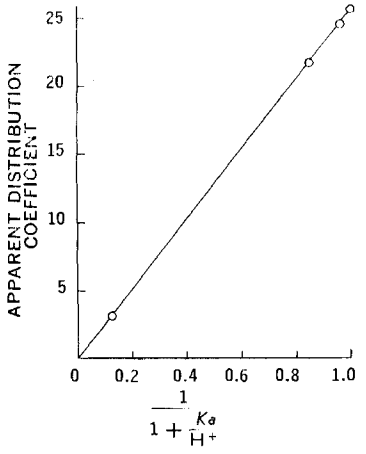

Fig. 5—Apparent distribution coefficients for the partition of aspirin between the micelles and aqueous phase of cetomacrogol solutions at 37°, plotted as a function of the ionization constant and hydrogen ion concentration.

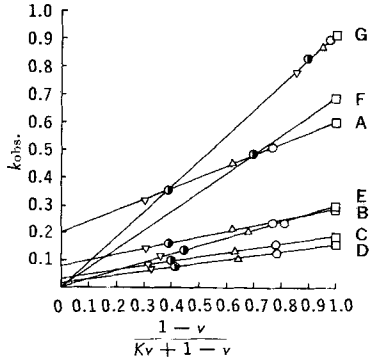

Fig. 6—Plot of observed rate constant against (1 − v)/Kv + (1 − v) in accordance with Eq. 1. Key: cetomacrogol, moles L.$^{-1}$— □, 0.00; ○, 0.01; Δ, 0.02; ◑, 0.05; ▽, 0.07; A, pH 1.11; B, pH 1.55; C, pH 1.95; D, pH 2.27; E, pH 2.95; F, pH 3.84; G, pH 4.60

When the term $(1-v)/Kv + (1-v) = 0$, the volume of the micellar phase, v, is equal to 1. Hence the additional reaction must be taking place in the micellar phase and has a rate constant, k_m, equal to the intercept. It is apparent from Fig. 7 that k_m is directly proportional to the hydrogen-ion concentration which suggests that the reaction is due to hydrogen-ion attack on unionized aspirin within the micelles. To account for the reaction in the micelles, Eq. 8[3] was derived in a manner similar to the derivation of Eq. 1.

$$k'_m = \frac{Kv}{Kv + (1 - v)} \cdot k_m \qquad \text{(Eq. 8)}$$

where k'_m is the contribution of the micellar rate constant to the observed rate constant in the solubilized system. If k'_w is the corresponding contribution of the aqueous rate constant then the over-all rate constant is given by:

$$k_{obs.} = k'_m + k'_w \qquad \text{(Eq. 9)}$$

Equation 1 can now be rewritten to account for the micellar reaction:

$$k'_w = \frac{1 - v}{Kv + (1 - v)} \cdot k_w \qquad \text{(Eq. 10)}$$

where from Eqs. 9 and 8:

[3] See the *Appendix*.

$$k'_w = k_{obs.} - k'_m = k_{obs.} - \frac{Kv}{Kv + (1 - v)} \cdot k_m$$

At pH > 2.95, the reaction within the micelles is negligible and $k'_w = k_{obs.}$. Hence at any pH, a plot of k'_w, the contribution of the aqueous rate constant to the observed rate constant, *versus* the term $(1 - v)/Kv + (1 - v)$ should be a straight line

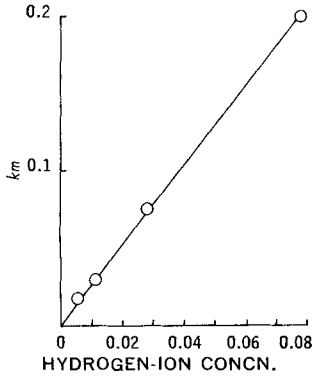

Fig. 7—Influence of hydrogen-ion concentration on the micellar rate constant.

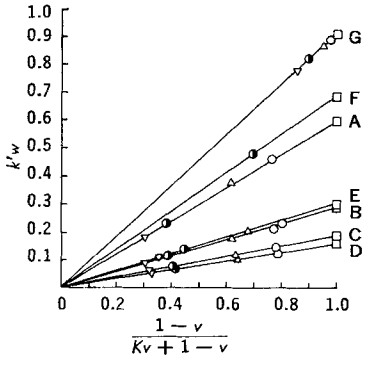

Fig. 8—Plot of contribution of the aqueous rate constant to the observed rate constant against (1 − v)/Kv + (1 − v) *in accordance with Eq. 10. Key: cetomacrogol, moles L.$^{-1}$— □, 0.00; ○, 0.01; △, 0.02; ◑, 0.05; ▽, 0.07; A, pH 1.11; B, pH 1.55; C, pH 1.95; D, pH 2.27; E, pH 2.95; F, pH 3.84; G, pH 4.60*

TABLE III—INFLUENCE OF ASPIRIN CONCENTRATION AND IONIC STRENGTH ON THE OBSERVED RATE CONSTANT

pH	Ionic Strength	Cetomacrogol, moles L.$^{-1}$	K	Aspirin— mg. ml.$^{-1}$	$k_{obs.}$ Day^{-1}
1.11	0.147	0.00		2.48	0.600
1.11	0.147	0.00		3.00	0.605
1.11	0.400	0.00		2.12	0.600
1.11	0.147	0.02	25.7	2.52	0.460
1.11	0.147	0.02	25.7	6.06	0.460
1.11	0.147	0.05	25.7	2.26	0.354
1.11	0.147	0.05	25.7	6.06	0.360
1.96	0.060	0.05	24.9	4.00	0.0950
1.95	0.060	0.05	24.9	8.48	0.0956
1.95	0.200	0.05	24.9	4.88	0.0953
1.96	0.400	0.05	24.9	4.40	0.0956
2.78	0.012[a]	0.00		2.78	0.239
2.78	0.100[a]	0.00		2.50	0.242

[a] Different strength glycine–HCl buffer, all other ionic strengths adjusted with KCl.

of slope k_w, which passes through the origin. Such a plot is shown in Fig. 8. Equation 10 therefore separates the contributions of the aqueous and micellar rate constants toward the observed rate constant and is essentially the same as an equation derived by Winters and Grunwald (16) for the reaction of methyl bromide with cyanide ions in anionic and cationic surfactants.

Both Eqs. 1 and 10 are derived on the assumption that the distribution of aspirin between the micelles and aqueous phase obeys the simple partition law. This appears to be true for some solutes, but for others Mitchell and Brown (17) have shown that the distribution coefficient depends on the degree of saturation of the system with solute. In the present work direct estimation of the apparent distribution coefficient was difficult because of the unstable nature of aspirin. The apparent distribution coefficients therefore were calculated using solubility data and Eqs. 2–7. This procedure is open to criticism since the method is limited to measurements at saturation below which it cannot be assumed that the calculated distribution coefficients will be valid. If, however, the apparent distribution coefficient varies with the degree of saturation of the system with aspirin, then $k_{obs.}$ should also vary. Results in Table III show that, at each pH for a given cetomacrogol concentration, values of $k_{obs.}$ are independent of aspirin concentration. It is reasonable to conclude therefore that the apparent distribution coefficients are independent of aspirin and cetomacrogol concentrations. Table III also includes values of $k_{obs.}$ determined at the same pH but different ionic strengths to show that the reaction is independent of ionic strength.

APPENDIX

Derivation of Eq. 1—Let C = initial reactant concentration (moles L.$^{-1}$ total system), C_w = initial reactant concentration in the aqueous phase (moles L.$^{-1}$ aqueous phase), and x = concentration reacting in time t (moles L.$^{-1}$ total system). Then, on the assumption that hydrolysis in a solubilized system takes place only in the aqueous phase, the concentration of reactant remaining after time t, is $C_w(C - x)/C$ moles L.$^{-1}$ aqueous phase or $C_w(1 - v)(C - x)/C$ moles L.$^{-1}$ total system. The differential rate equation for the concentration change with respect to the total system is:

$$\frac{dx}{dt} = k_w C_w (1 - v) \frac{(C - x)}{C} \qquad \text{(Eq. 11)}$$

which on integration and rearrangement gives:

$$k_w = \frac{C}{C_w(1 - v)} \frac{1}{t} \ln \frac{C}{C - x} \qquad \text{(Eq. 12)}$$

From Eq. 2, the distribution coefficient:

$$K = \frac{C - C_w(1 - v)}{C_w v} \qquad \text{(Eq. 13)}$$

which on rearrangement becomes:

$$\frac{C}{C_w} = Kv + (1 - v) \qquad \text{(Eq. 14)}$$

Substitution into Eq. 12 gives:

$$k_w = \frac{Kv + (1 - v)}{1 - v} \cdot \frac{1}{t} \ln \frac{C}{C - x} \quad \text{(Eq. 15)}$$

where $1/t \ln C/(C - x)$ is the observed rate constant $k_{obs.}$, assuming that hydrolysis takes place only in the aqueous phase. Substitution of $k_{obs.}$ into Eq. 15 and rearrangement leads to Eq. 1:

$$k_{obs.} = \frac{1 - v}{Kv + (1 - v)} k_w \quad \text{(Eq. 1)}$$

Derivation of Eq. 8—On the assumption that decomposition in solubilized systems takes place only in the micelles, the differential rate equation is given by:

$$\frac{dx}{dt} = k_m C_m v \frac{(C - x)}{C} \quad \text{(Eq. 16)}$$

where C_m is the intiial reactant concentration in the micelles (moles L.$^{-1}$ micellar phase). Integration and rearrangement gives:

$$k_m = \frac{C}{C_m v} \frac{1}{t} \ln \frac{C}{C - x} \quad \text{(Eq. 17)}$$

From Eq. 2, the distribution coefficient:

$$K = \frac{C_m (1 - v)}{C - C_m v} \quad \text{(Eq. 18)}$$

which on rearrangement becomes:

$$\frac{C}{C_m} = \frac{K_v + (1 - v)}{K} \quad \text{(Eq. 19)}$$

Substitution into Eq. 17 gives:

$$k_m = \frac{Kv + (1 - v)}{Kv} \frac{1}{t} \ln \frac{C}{C - x} \quad \text{(Eq. 20)}$$

where the term $1/t \ln C/(C - x)$ is the observed rate constant, assuming that hydrolysis takes place only in the micelles. In a system where reaction takes place in both micelles and aqueous phase this term is equal to k'_m, the contribution of the micellar rate constant to $k_{obs.}$, where $k_{obs.}$ is now the over-all observed rate constant defined in Eq. 9. Substitution of k'_m into Eq. 20 and rearrangement leads to Eq. 8:

$$k'_m = \frac{Kv}{Kv + (1 - v)} \cdot k_m \quad \text{(Eq. 8)}$$

REFERENCES

(1) Edwards, L. J., *Trans. Faraday Soc.*, **46**, 723(1950).
(2) *Ibid.*, **48**, 696(1952).
(3) Garrett, E. R., *J. Am. Chem. Soc.*, **79**, 3401(1957).
(4) Garrett, E. R., *J. Org. Chem.*, **26**, 3660(1961).
(5) Nogami, H., Awazu, S., and Nakajima, N., *Chem. Pharm. Bull. Tokyo*, **10**, 503(1962).
(6) Ginn, M. E., and Church, C. L., *Anal. Chem.*, **31**, 551 (1959).
(7) Colowick, S. P., and Kaplan, N. O., "Methods in Enzymology," vol. I, Academic Press Inc., New York, N. Y., 1955, pp. 138–140.
(8) Long, C., "Biochemists Handbook," E. and F. N. Spon, Ltd., London, England, 1961, p. 30.
(9) De Marco, J. D., and Marcus, A. D., *J. Pharm. Sci.*, **51**, 1010(1962).
(10) Bauer, N., and Lewin, S. Z., "Physical Methods of Organic Chemistry," vol. I, 3rd ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 142–162.
(11) Yamada, H., and Yamamoto, R., *Chem. Pharm. Bull. Tokyo*, **13**, 1279(1965).
(12) Florence, A. T., *J. Pharm. Pharmacol.*, **18**, 384(1966).
(13) Mitchell, A. G., and Wan, L. S. C., *J. Pharm. Sci.*, **53**, 1467(1964).
(14) Albert, A., and Serjeant, E. P., "Ionization Constants of Acids and Bases," Methuen & Co., Ltd., London, England, 1962, pp. 106–112.
(15) Anderson, R. A., and Slade, A. H., *J. Pharm. Pharmacol.*, **18**, 640(1967).
(16) Winters, L. J., and Grunwald, E., *J. Am. Chem. Soc.*, **87**, 4608(1965).
(17) Mitchell, A. G., and Brown, K. F., *J. Pharm. Pharmacol.*, **18**, 115(1966).