Acetylsalicylic Acid Hydrolysis in Aqueous Solutions of Polysorbate 80

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The hydrolysis of acetylsalicylic acid (ASA) has been shown to occur at a measurable rate within polysorbate 80 micelles in an aqueous environment at pH 1.8. An estimate of the apparent pseudo first-order rate constant for the micellar degradation is made on the basis of the distribution of the undissociated ASA between the aqueous and the micellar pseudophase.

HYDROLYTIC SUSCEPTIBILITY of various drug species, in aqueous systems containing surfactants at concentrations above their CMC, has been the subject of several studies. Generally, it has been found that hydrolysis occurs within the micellar pseudophase as well as in the aqueous phase. Riegelman (1) demonstrated that benzocaine, solubilized in the polyoxyethylene palisade layer of certain cetyl alcohol polyoxyethylene ethers, is subject to hydroxyl-ion catalyzed hydrolysis. However, recent studies (2) indicate that no hydroxyl-ion catalyzed hydrolysis of chlorobutanol occurs within micelles formed by lauromacrogal or polysorbate 20. It has been suggested by Nogami (3) that the observed suppression by surfactants of the hydrolysis, below pH 5, of undissociated acetylsalicylic acid is due to partitioning of a part of the ASA into the micelles, where it becomes less hydrolyzable. The present study was undertaken to determine quantitatively the degree of protection afforded by polysorbate 80 to aqueous solutions of ASA.

EXPERIMENTAL

Reagents—Acetylsalicylic acid U.S.P. (Mallinckrodt) and polysorbate 80 (Atlas Chemical Industries, Inc.) were used as received. All other chemicals used were reagent grade.

Apparatus—All studies were performed using a Sargent constant-temperature water bath held at 30° ± 0.01°, Burrell wrist action shaker, Beckman model GS pH meter, and Beckman model DU spectrophotometer.

Experimental Procedure—Since solutions of relatively high buffer capacity were required in many cases, all solutions were adjusted to an ionic strength of 1.00. Analysis of salicylic acid and ASA was accomplished spectrophotometrically by the method of Edwards (4).

Solubility studies were conducted in vials of 20-ml. capacity. Excess solid ASA was added to vials containing 20 ml. of 0, 1, 2.5, and 4% solutions of polysorbate 80 at various pH's in the range 2.63–4.43. The solutions were agitated until successive assays indicated a state of equilibration. In general, three separate equilibrations were run at each combination of pH and polysorbate 80 concentration. Samples were forced through Millipore G.S. 0.22-μ filters prior to assay and the pH of the filtrate noted at this time. Buffers were as follows: pH 2.63, phosphate; pH 3.63, 4.10, 4.21, and 4.43, citrate.

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Kinetic studies were carried out with saturated suspensions as well as with saturated and half-saturated solutions of ASA at a pH of 1.8. The suspensions and solutions were sampled periodically, and the samples filtered and analyzed as before. Kinetics were followed at 0, 2, and 4% polysorbate 80 levels for periods of 48 hr. Phosphate buffer (1.69 *M*) was used, and duplicate runs were conducted at each polysorbate concentration.

RESULTS AND DISCUSSION

The apparent pKa of acetylsalicylic acid under the conditions of these studies was obtained from

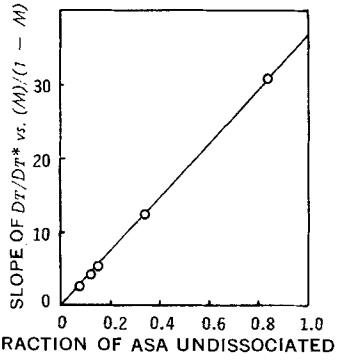

Fig. 1—Graph showing the slopes of $(D)_t/(D)_t^*$ vs. $(M)/(1 - M)$ *plotted* vs. *the fraction of ASA undissociated. The intercepts are the partition coefficients of the undissociated and dissociated acid.*

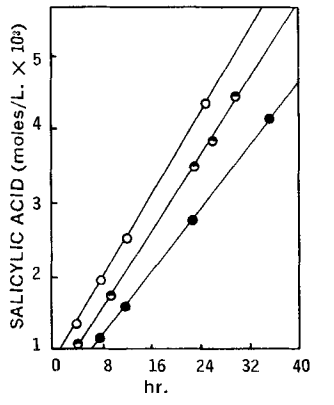

Fig. 2—Graph showing the rate of appearance of salicylic acid in aqueous suspensions of ASA at pH = 1.8 and 30°. Polysorbate 80 concentrations: ○, *4%;* ◓, *2%;* ●, *0%.*

TABLE I—ZERO-ORDER RATE CONSTANTS OF ASA HYDROLYSIS IN AQUEOUS SUSPENSIONS[a]

Polysorbate 80, % w/v	Over-All Zero-Order Rate Constants (moles-L.$^{-1}$ hr.$^{-1}$ × 10^4)
0	1.10
2	1.23
4	1.40

[a] Conditions: pH = 1.80; ionic strength = 1.00; temperature = 30° C.

TABLE II—FIRST-ORDER RATE CONSTANTS OF ASA HYDROLYSIS IN AQUEOUS SOLUTIONS[a]

Polysorbate 80, % w/v	Over-All First-Order Rate Constants[b] (hr.$^{-1}$ × 10^2)	Micellar First-Order Rate Constants[b] (hr.$^{-1}$ × 10^2)
0[c]	9.2	...
2[c]	5.4	1.8
4[c]	4.5	2.2
0[d]	9.6	...
2[d]	5.7	1.9
4[d]	4.4	1.8

[a] Conditions: pH = 1.80; ionic strength = 1.00; temperature = 30° C. [b] Constants are calculated on the basis of the micellar pseudophase, assuming its volume in ml. is equal to the weight of polysorbate 80 in Gm., and assuming a partition coefficient of 51.9. [c] Saturated solutions of ASA. [d] Half-saturated solutions of ASA.

solubility data and found to be 3.35. The usual literature value cited is 3.49.

Hydrolysis of polysorbate 80 at pH 1.8 and unit ionic strength was found to be approximately 3% after an elapsed time of 48 hr. This degree of degradation did not have a measurable effect on either the solubility or the stability of ASA.

Partitioning of ASA into the Micellar Pseudophase—Results of the solubility determinations were interpreted assuming a linear partition isotherm, as described previously (5). In the present studies, however, the volume occupied by the micelles was not assumed to be negligible. Figure 1 represents a plot of the slope of the ratio $(D)_t/(D)_t^*$ *versus* $(M)/(1 - M)$, against the mole fraction of undissociated ASA. $(D)_t$ and $(D)_t^*$ are the total concentration of ASA in solution, and the concentration of ASA exclusive of that present in the micelles, respectively; (M) is the volume fraction of micellar pseudophase in the system, assuming the micellar volume in ml. is equal to the weight of surfactant in Gm. The curve passes through the origin, indicating the absence of dissociated ASA in the micellar pseudophase of the polysorbate 80 solutions. These findings are in agreement with those of Nogami (3).

The apparent partition coefficient of undissociated ASA, under the conditions of the kinetics studies, was found to be 52. This differs from that (about 37) predicted by Fig. 1. In this case, the high percentage of phosphoric acid (6.7%) present in the medium would change the polarity of the solvent so as to increase the activity coefficient of the undissociated ASA. This was confirmed by solubility determinations of ASA at pH 1.55 and unit ionic strength in aqueous solutions at various phosphoric acid concentrations.

Kinetic Studies—Since from the solubility studies it is inferred that the dissociated form of ASA exists only in the aqueous phase, the observed increase in degradation rate constants in suspensions (pseudo zero-order rate constants) with added polysorbate 80 is due to instability of undissociated ASA in the micellar phase. These constants were calculated from the rate of appearance of salicylic acid in the suspensions as illustrated in Fig. 2. Results are given in Table I.

Rates of hydrolysis were also determined in homogeneous solutions at saturation and half-saturation under conditions similar to the suspensions. The results are presented in Table II, where it can be seen that the rate of hydrolysis of ASA in polysorbate 80 micelles, while lower than in the aqueous phase, is not negligible. The reaction occurring within the micellar pseudophase is presumably hydrogen-ion catalyzed since the hydroxyl and water catalyzed reactions do not occur to a measurable extent at this pH (4).

Salicylic acid, produced during the hydrolysis, has been shown (6) to have no significant effect on the apparent solubility of ASA in aqueous systems.

SUMMARY AND CONCLUSIONS

Hydrolysis of ASA occurs to a significant extent within polysorbate 80 micelles in an aqueous medium at a pH of 1.8. An estimate of the pseudo first-order rate constants for the micellar degradation indicates a rate approximately one fifth that in the corresponding aqueous phase. For this reason, the addition of polysorbate 80 to aqueous suspensions of ASA can be expected to accelerate hydrolytic degradation at pH's below approximately 5.

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