This investigation was supported by grant T-337B from the American Cancer Society, by a Public Health Service research grant 5-RO1-GM-09775-05, by a research career program award 5-K3-CA-18718-05 fom the National Cancer Institute, and a training grant 5-T1-GM-555-05 from the Division of Medical Sciences, Bethesda, Md.

Keyphrases

Enzyme inhibitors
9-(1-Hydroxy-2-alkyl)adenines—synthesis
Adenosine deaminase—inhibitor binding site identified

Apparent Nonsteady-State Dissolution Phenomenon in Solutions of Colloidal Solubilizers

Sir:

It has been demonstrated in recent reports (1–3) that the dissolution rate of solids in solutions of surfactant above the critical micelle concentration cannot be predicted by the Noyes-Whitney equation (4). Higuchi (1) has suggested that the dissolution process in solutions of colloidal solubilizers may be quantitated by the diffusion layer theory. In a previous report (3) we have found reasonable agreement of diffusion layer theory with initial dissolution rate data obtained under well-stirred conditions. We have recently observed, however, that the initial dissolution rates of salicylic acid in micellar solutions of a nonionic polyoxyethylene surfactant represent presteady-state values. Accordingly, the enhancement of apparent steady-state dissolution rate by the colloidal solubilizer is significantly greater than predicted by diffusion layer theory.

Details of the experimental procedure will be presented in a subsequent report. Briefly, in each dissolution experiment nondisintegrating disks of salicylic acid were used which provided a constant surface area over the entire experimental time period. Dissolution was followed at 37° at a 50 r.p.m. agitation rate (provided by an overhead blade) in either 0.1 *N* HCl or in various concentrations of polyoxyethylene (23) lauryl ether[1] dissolved in 0.1 *N* HCl. The amount of salicylic acid in solution at various intervals of time was determined spectrophotometrically at 304 mμ.

A kinetic method has been devised to ascertain steady-state dissolution rates which introduces the concept of an *excess dissolution rate, i.e.,* $(DR_c - DR_w)$ where DR_c is the dissolution rate per unit area in the colloid system and DR_w is the dissolution rate per unit area in an aqueous system under equivalent hydrodynamic conditions. Both the Dankwerts theory (1, 5) and the diffusion layer theory (1) predict a first-order dependence of excess dissolution rate on $(C_M - C')$, the micellar phase concentration gradient.

According to Gibaldi and Feldman (6), dissolution in a simple aqueous system under constant-surface and nonsink conditions follows first-order kinetics and a plot of log $(C_S - C)$ *versus* time is linear (where C_S is the solubility of the drug in the dissolution medium and C is the concentration of drug in solution at time t). Since the excess dissolution rate is proportional to a concentration gradient term, it follows that a plot of log $(DR_c - DR_w)$ *versus* time should be linear.

A representative plot of the log of excess dissolution rate as a function of time is shown in the figure. As noted in the plot a significant time lag occurs before apparent linearity (attainment of steady state) is observed. A similar plot of log dissolution rate in 0.1 *N* HCl *versus* time shows

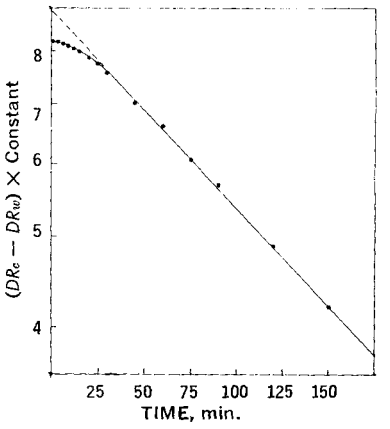

Fig. 1—Plot of the difference in dissolution rates of salicylic acid in 3% polyoxyethylene (23) lauryl ether solution, DR_c, *and 0.1 N HCl,* DR_w, *(on log scale)* versus *time under stirred conditions.*

[1] Brij 35 SP, Atlas Chemical, Wilmington, Del.

excellent linearity with no evident time lag. Extrapolation of this plot to $t = 0$ yields the value of the solubility of the drug in 0.1 N HCl as predicted by theory.

The presteady-state phenomenon indicates that the apparent initial contribution of the micellar phase to the dissolution process is much less than its contribution at steady state. This disparity is evident when the ratios of dissolution rates in 3% polyoxyethylene (23) lauryl ether solution and in 0.1 N HCl are compared. The initial dissolution data suggest a 50% increase in dissolution rate while a comparison of steady-state data indicates a 90% increase in the apparent first-order rate constant for dissolution.

The present findings suggest the possibility of a more general phenomenon. Initial dissolution rate data (obtained from apparent zero-order rate plots) in systems of colloidal solubilizers may represent presteady-state conditions and must, therefore, be used cautiously in attempting to explain dissolution phenomena.

(1) Higuchi, W. I., *J. Pharm. Sci.*, **56**, 315(1967).
(2) Parrott, E. L., and Sharma, V. K., *ibid.*, **56**, 1341 (1967).
(3) Gibaldi, M., Feldman, S., Wynn, R., and Weiner, N. D., *ibid.*, **57**, 787(1968).
(4) Noyes, A. A., and Whitney, W. R., *J. Am. Chem. Soc.*, **19**, 930(1897).
(5) Dankwerts, P. V., *Ind. Eng. Chem.*, **43**, 1460(1951).
(6) Gibaldi, M., and Feldman, S., *J. Pharm. Sci.*, **56**, 1238(1967).

Milo Gibaldi
Stuart Feldman
Norman D. Weiner*

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

Received February 12, 1968.
Accepted for publication April 1, 1968.
* College of Pharmaceutical Sciences, Columbia University, New York, NY 19923

Keyphrases

Colloidal solubilizer solutions—dissolution
Dissolution—apparent nonsteady state
Salicylic acid disks—dissolution rates

Observations on the Instability of Cyclamate in Hydroalcoholic Solution

Sir:

Cyclamic acid, widely used as such and as its sodium and calcium salts for sweetening pharmaceuticals and other products, is generally conceded to be extremely stable in solution (1, 2). Hydrolysis of cyclamic acid has been reported to occur only under very rigorous conditions (3–5). Studies in our laboratories have affirmed that aqueous solutions of cyclamate degrade to sulfuric acid and cyclohexylamine at very slow rates, which are proportional to hydrogen ion concentration. The half-life for a solution at 25° buffered at pH 2.0 is calculated to be 60 years!

Stability studies on experimental formulations led to the discovery that cyclamate sweeteners degrade at markedly faster rates in hydroalcoholic vehicles than would be predicted by their behavior in aqueous systems. In one instance, samples of an antibacterial amine formulation stored 24 months at room temperature were found to assay substantially higher than the initial value for total amine by nonaqueous titration. The formulation contained 0.1% amine in a hydroalcoholic vehicle sweetened with 0.6% sodium cyclamate and buffered at an apparent pH of 4.0. The increased titer was found to be due to cyclohexylamine formed from the cyclamate, and a material balance was obtained by gas-liquid chromatographic (GLC) assay of cyclohexylamine content. In a second case, formulations in 85% alcohol sweetened with calcium cyclamate and sodium saccharin were found unchanged after several weeks of storage, while similar formulations sweetened with calcium cyclamate and saccharin *acid* were found to have increased in apparent pH and deposited a precipitate, identified as calcium sulfate after isolation and the usual tests for the ions. Again, degradation of cyclamate was confirmed by GLC assay of the cyclohexylamine produced. The apparent pH of the stable formulations was about 6.5, while that of the labile ones was 3.7.

Unbuffered 1% (w/v) solutions of cyclamic acid[1] were made up in distilled water, absolute alcohol, and alcohol–water mixtures of graded composition. Portions of the solutions were heated in flint glass screw-capped bottles at 80°

[1] Hexamic acid, Abbott Laboratories, North Chicago, Ill.