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.

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@~~~> *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°

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

TABLE I—RELATION OF ALCOHOL CONTENT, APPARENT pKa, AND EXTENT OF CYCLAMATE HYDROLYSIS

| Alcohol		pKa	% Intact Cyclamate	
% (v/v)	mol. %		2 hr./80°	22 hr./80°
0	0	2.28	99.5	91.7
20	7.16	2.48	98.8	77.0
40	17.06	2.60	94.7	47.0
60	31.65	2.90	70.7	23.0
80	53.30	3.22	25.0	0
100	100.0	3.45	12.0	0

for periods of 2 and 22 hr., and the extent of degradation was determined by GLC assay of cyclohexylamine. Aliquots of the solutions were basified, and chloroform extracts were injected into a Perkin-Elmer model 801 gas chromatograph fitted with dual-flame ionization detectors. The GLC operating parameters were: (*a*) column—9.1 M. (6 ft.), 0.63 cm. ($^1/_4$ in.) o.d. glass helix packed with 5% potassium hydroxide, 10% polyethylene glycol 4000 on Anakrom ABS,[2] 80/90 mesh. (*b*) helium flow—40 ml./min. (*c*) temperature—column, 75°, injector block, 150°, detector, 150°.

Dimethylformamide was used as the internal standard. Under these conditions, cyclohexylamine has a retention time of 3 min. and the internal standard 7 min. Cyclohexylamine content was determined by the peak-height ratio method. Apparent pKa values were determined for each of the solutions at room temperature by potentiometric titration of a 50-ml. sample with 1 *N* sodium hydroxide added from a 1-ml. microburet.

The correlation of increasing alcohol content, and the concomitant increase in the apparent pKa of cyclamic acid, with the extent of hydrolysis is evident in Table I.

The degradation of unbuffered solutions of cyclamate would be expected to be autocatalytic, for the release of sulfuric acid increases hydrogen

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[2] Analabs, Inc., Hamden, Conn.

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ion concentration. The results of these experiments are consistent with a mechanism involving attack by hydrogen ion on undissociated cyclamic acid, *viz.*;
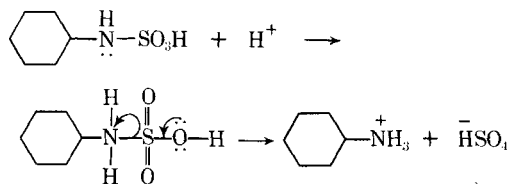
More comprehensive studies on the degradation of cyclamate in low dielectric media are in progress and will be reported at a later date. This communication is intended to alert formulators to the necessity for avoiding an acidic pH range in cyclamate sweetened solutions of low dielectric constant. Such solutions should be buffered to at least 2 pH units above the apparent pKa of cyclamate in the vehicle.

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