(7) "Pharmacopoeia Helvetica," 5th ed., Bern, Switzerland, 1934.
(8) Berry, F. R., *Quart. J. Pharm. Pharmacol.*, **12**, 503(1939).
(9) Maney, P. V., and Kuever, R. A., THIS JOURNAL, **30**, 276(1941).
(10) Abbott, A. H. A., and Allport, N. L., *Quart. J. Pharm.*, **16**, 183(1943).
(11) Bandelin, F. J., *Am. J. Pharm.*, **117**, 124(1945).
(12) Filleborn, V. M., *ibid.*, **120**, 233(1948).
(13) "British Pharmacopoeia," 7th ed., the Pharmaceutical Press, London, England, 1945.
(14) Evanson, R. V., and DeKay, H. G., *Bull. Natl. Formulary Commun.*, **18**, 45(1950).
(15) Gershberg, S., and Stoll, F. D., THIS JOURNAL, **35**, 284(1946).
(16) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960.
(17) Office Consolidation of the Food and Drugs Act and of the Food and Drug Regulations, Queen's Printer, Ottawa, Ontario, Canada, 1954.
(18) Chapman, D. G., Crisafio, R., and Campbell, J. A., THIS JOURNAL, **43**, 297(1954).
(19) Noyes, A. A., and Whitney, W. R., *J. Am. Chem. Soc.*, **19**, 930(1897).
(20) Edwards, L. J., *Trans. Faraday Soc.*, **47**, 1191(1951).
(21) Nelson, E., THIS JOURNAL, **48**, 96(1959).
(22) Nelson, E., and Schaldemose, I., *ibid.*, **48**, 489(1959).
(23) Parott, E. L., Wurster, D. E., and Higuchi, T., *ibid.*, **44**, 269(1955).
(24) Niebergall, P. J., and Goyan, J. E., *ibid.*, **52**, 29 (1963).
(25) Hamlin, W. E., *et al.*, *ibid.*, **51**, 432(1962).
(26) Nelson, E., *ibid.*, **47**, 297(1958).
(27) Souder, J. C., and Ellenbogen, W. C., DRUG STANDARDS, **26**, 77(1958).
(28) Levy, G., THIS JOURNAL, **50**, 388(1961).
(29) Levy, G., and Hayes, B., *New Engl. J. Med.*, **262**, 1053(1960).
(30) Truitt, E. B., Jr., and Morgan, A. M., *Federation Proc.*, **18**, 453(1959).
(31) Batterman, R. C., *New Engl. J. Med.*, **258**, 213(1958).
(32) Levy, G., in "Salicylates An International Symposium," Churchill, London, England, 1963.
(33) Schroeter, L. C., *et al.*, THIS JOURNAL, **51**, 865(1962).
(34) Middleton, E. J., Davies, J., and Morrison, A. B., *ibid.*, **53**, 1378(1964).
(35) Melnick, D., Hochberg, M., and Oser, B. L., *J. Nutr.*, **30**, 233(1945).
(36) *Ibid.*, **30**, 67(1945).
(37) Morrison, A. B., Chapman, D. G., and Campbell, J. A., THIS JOURNAL, **48**, 634(1959).
(38) Chapman, D. G., Crisafio, R., and Campbell, J. A., *ibid.*, **45**, 374(1956).
(39) Morrison, A. B., Perusse, C. B., and Campbell, J. A., *ibid.*, **51**, 623(1962).
(40) Swintosky, J. V., *et al.*, *ibid.*, **66**, 399(1957).
(41) Juncher, H., and Raaschov, F., *Antibiot. Med.*, **4**, 497(1957).
(42) Chulski, T., *et al.*, *Nature*, **198**, 450(1963).
(43) Modell, W., and Houde, R. W., *J. Am. Med. Assoc.*, **167**, 2190(1958).
(44) Mainland, D. B., *J. Chronic Diseases*, **11**, 484(1960).
(45) Loranger, A. W., Prout, C. T., and White, M. A., *J. Am. Med. Assoc.*, **176**, 920(1961).
(46) Campbell, J. A., and Morrison, A. B., *Practitioner*, **183**, 758(1959).
(47) Morrison, A. B., and Campbell, J. A., *Indian J. Pharm.*, **25**, 209(1963).
(48) Endicott, C. J., and Kirchmeyer, F. J., DRUG STANDARDS, **24**, 193(1956).
(49) Nair, A. D., and Bhatia, V. N., THIS JOURNAL, **46**, 131(1957).
(50) Campagna, F., *et al.*, *ibid.*, **52**, 605(1963).
(51) Carter, A. K., *Can. Med. Assoc. J.*, **88**, 98(1963).
(52) Caminetsky, S., *ibid.*, **88**, 950(1963).
(53) Levy, G., *ibid.*, **90**, 978(1964).
(54) McKendry, J. B. R., *et al.*, *ibid.*, in press.
(55) Lu, F. C., Rice, W. B., and Mainville, C. W., *ibid.*, in press.
(56) Brudney, N., Stewart, D. J., and Eustace, B. T., *ibid.*, **90**, 980(1964).
(57) Levy, G., *et al.*, THIS JOURNAL, **52**, 1047(1963).
(58) Miller, L. C., *Drug Cosmetic Ind.*, **94**, 668(1964).

Research Articles

Dissolution Kinetics of a Weak Acid, 1,1-Hexamethylene *p*-Tolylsulfonylsemicarbazide, and Its Sodium Salt

By W. I. HIGUCHI, N. A. MIR, A. P. PARKER, and W. E. HAMLIN*

The dissolution behavior of the acid and the sodium salt of this drug in phosphate buffers has been investigated. Data have been analyzed by relationships derived from the diffusion controlled model for dissolution of solids in reactive media. The results of this study show that surface conversion of the sodium salt to the acid occurs in the lower pH range of these studies. Calculations suggest that appreciable conversion takes place only after initial surface supersaturation ratios of about 20 or greater are achieved. Under conditions of much greater initial surface supersaturation ratios, a relatively impermeable acid surface coating is formed, and the dissolution rate is governed by this acid phase.

IN MOST CASES the diffusion-controlled dissolution behavior of monophase solids in reactive media may be predicted by knowledge of the appropriate solubility equilibria and the effective diffusion coefficients of the species in solution (1–4). However, in those situations involving more than one phase, the problem is more difficult to describe. Cases in point are the recent studies (5, 6) on dissolving disks that exhibit simultaneous surface deposition of new phases and the experiments with prior mixed phases (7, 8).

In this report an analysis of the incongruent

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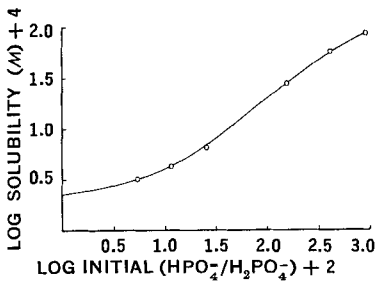

Fig. 1.—Solubility of tolazamide acid at 30°C. as a function of the buffer salt-to-acid ratio. Total buffer concentration is 0.10 *M*. Smooth curve is theoretical curve based on $(HA)_o = 2.1 \times 10^{-4}$ *M* and $K = 9.0$.

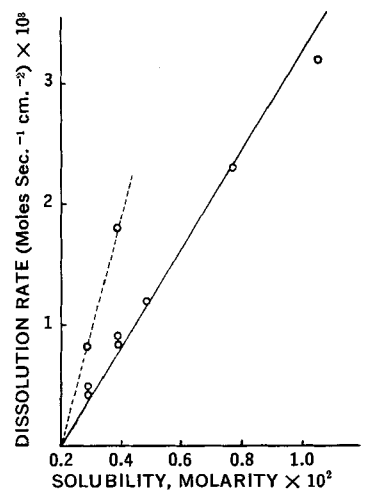

Fig. 2.—The dissolution rates of tolazamide acid (circles on solid line) as a function of the total solubility, C_s. The dissolution rates of sodium tolazamide in the same buffer following surface conversion to the acid are given by the circles on the broken line.

dissolution behavior of the sodium salt of a weak acid is presented. The results have bearing on the question of the relative availability of solid acidic drugs and their more soluble sodium salts.

EXPERIMENTAL

General Considerations.—Preliminary studies with the Wruble apparatus (9) had shown that 1,1-hexamethylene *p*-tolylsulfonylsemicarbazide (tolazamide)[1] would be a convenient compound for quantitative study. The dissolution rates for both the sodium salt and the free acid in phosphate buffers could be measured in the same apparatus under identical hydrodynamic conditions.

Materials and Procedure.—The sodium salt of tolazamide was prepared by Dr. W. Morozowich[2] by adding aqueous sodium chloride to an aqueous triethylamine solution of tolazamide acid, filtering the crystals, and washing with a mixture of 10 ml. of water in 90 ml. of acetone.

The procedure and apparatus for preparing and mounting the samples for the dissolution rate runs have been described by Milosovich (10). A machined aluminum sample holder die with a $^3/_8$-in. diameter was employed. Compression pressures of around 27,000 p.s.i. were used to form the surfaces. No variations of dissolution rates with pressure were observed in this pressure region.

All of the dissolution *versus* time determinations were recorded automatically as before (10, 11) with the Beckman DU spectrophotometer adapted for direct recording. The wavelength of 224.5 mμ, the $\lambda_{max.}$ for the anion form of tolazamide, was used throughout this study. The dissolution media were aqueous potassium phosphate solutions of different pH's and concentrations.

Solubility measurements also were carried out in the same phosphate buffers. Excess amounts of acid tolazamide or the sodium salt were placed in flasks and shaken at 30°. Filtered aliquots were spectrophotometrically assayed in 0.10 *M* K_2HPO_4 at 12 and 24 hours.

EXPERIMENTAL RESULTS

Solubility Determinations.—The solubility results for tolazamide acid in phosphate buffers are presented in Fig. 1 as a function of the initial $(HPO_4^=)/(H_2PO_4^-)$ ratio. The smooth curve is theory based on values of $(HA)_o = 2.1 \times 10^{-4}$ *M* and $K = 9.0$, where $(HA)_o$ is the solution concentration of the unionized acid tolazamide in equilibrium with the solid and K is defined by

$$HA + HPO_4^= \overset{K}{\rightleftarrows} H_2PO_4^- + A^-$$

The solubility of the sodium salt of tolazamide was found to be 0.17 *M* in 0.10 M K_2HPO_4. This gives a K_{sp} value of 2.9×10^{-2} for sodium tolazamide.

Dissolution Rate Experiments.—As expected, the amount dissolved *versus* time plots for tolazamide acid were linear with zero intercept. From the slopes, the rates were calculated. These are given in Fig. 2 as a function of their equilibrium solubilities in the same buffers. The rates are approximately proportional to the solubilities, as expected from previous considerations (3).

In Figs. 3–5 the dissolution–time plots from the

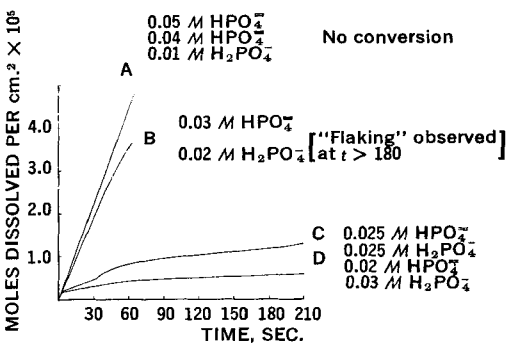

Fig. 3.—Dissolution behavior of sodium tolazamide in phosphate buffers at 30°. Total phosphate is 0.05 *M*.

[1] Trademarked as Tolinase by The Upjohn Co.

[2] The authors are grateful to Dr. Morozowich for his help in this connection and for discussions on the chemistry of tolazamide.

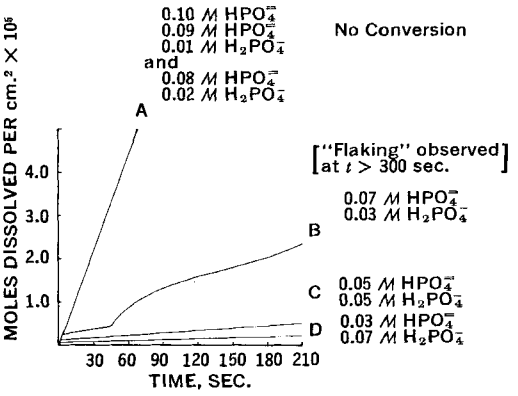

Fig. 4.—Dissolution behavior of sodium tolazamide in phosphate buffers at 30°. Total phosphate is 0.10 *M*.

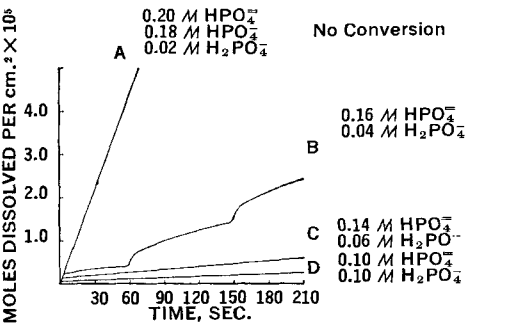

Fig. 5.—Dissolution behavior of sodium tolazamide in phosphate buffers at 30°. Total phosphate is 0.20 *M*.

sodium salt in phosphate buffers are presented. These results were remarkably reproducible up to those times included in the plots. Variations were the order of the thickness of the ink lines on the recorder chart paper. In certain instances beyond these times, greater variations in rates accompanied by flaking were observed.

THEORETICAL ANALYSIS OF DATA

Tolazamide Acid.—When tolazamide acid is dissolving in phosphate buffer, the following theoretical equation (1, 3) is expected to give the initial dissolution rate:

$$G = \frac{D_{HA}(HA)_o}{h} - \frac{D_{HB}(HB)_h}{2h} - \frac{D_{HB}D_A K(HA)_o}{2D_B h} + \frac{1}{2D_B h}\left[D^2_{HB}D^2_A K^2(HA)_o^2 + 4D^2_B D_{HB} D_A K(HA)_o(B^-)_h + D^2_B D^2_{HB}(HB)^2_h + 2D_A D_B D^2_{HB} K(HB)_h(HA)_o\right]^{1/2} \quad \text{(Eq. 1)}$$

Here G is the dissolution rate, h is the diffusion layer thickness, $(HA)_o = 2.1 \times 10^{-4}$ *M* is the equilibrium unionized tolazamide acid concentration, $K = 9.0$ is the equilibrium constant from the reaction

$$HA + B \rightleftarrows HB + A$$

HB and *B* are the dihydrogen and the monohydrogen phosphate species in the present case, and the *D*'s are the diffusion coefficients.

It has been shown (3) that Eq. 1 reduces to the Noyes-Whitney relation when all the diffusion coefficients are equal, *i.e.*,

$$G = DC_s/h \quad \text{(Eq. 2)}$$

when all *D*'s = *D*. Here C_s is the total solubility of the weak acid solid in the same buffer. In the case of tolazamide acid dissolving in phosphate buffers, the largest and the smallest diffusion coefficients should not differ by more than about a factor of 2. It can be shown easily by means of Eq. 1 that, if $D_{HB} = D_B = 2D_{HA} = 2D_A$, the dissolution rate solubility curve in Fig. 2 would have a slight curvature toward the *x* axis. A curvature of the estimated order of magnitude is suggested by the data, but it is within the experimental uncertainty.

The slope of the straight line in Fig. 2 is then equal to D/h, if Eq. 2 may be assumed to be essentially correct, and it has the value 4.1×10^{-6}.

Sodium Tolazamide with No Apparent Conversion to Acid.—The equation for the dissolution rate of sodium tolazamide may be obtained in a manner analogous to that for the dissolution rate of the weak acid. In this case, it is assumed that the solid–solution interface is governed by the K_{sp} for the salt instead of by the solubility of the weak acid. Consideration of simultaneous diffusion and chemical equilibria in the diffusion layer then leads to the following set of equations for the steady-state initial dissolution rate:

$$G = \frac{D_A(A)_o + D_{HA}(HA)_o}{h} \quad \text{(Eq. 3)}$$

$$G = \frac{D_{Na}(Na)_o}{h} \quad \text{(Eq. 4)}$$

$$G = \frac{D_A(A)_o + D_{HB}(HB)_h - D_{HB}(HB)_o}{h} \quad \text{(Eq. 5)}$$

$$D_B(B)_o - D_B(B)_h = D_{HB}(HB)_h - D_{HB}(HB)_o \quad \text{(Eq. 6)}$$

$$K = \frac{(A)(HB)}{(HA)(B)} = 9.0 \quad \text{(Eq. 7)}$$

and

$$K_{sp} = (Na)_o(A)_o = 2.9 \times 10^{-2} \quad \text{(Eq. 8)}$$

Most of the symbols have been defined. The subscripts *o* and *h* refer to the solid–solution interface and the bulk solution, respectively, as explained before (1, 3).

Equations 3–8 may be solved for G in terms of the knowns, $(HA)_o$, $(HB)_h$, $(B)_h$, K, and the *D*'s. The resulting general equation, which is relatively unwieldy, will not be presented here. However, it can be shown as before (3) that the final equation will reduce to

$$G = DC_s/h \quad \text{(Eq. 2)}$$

if again all the *D*'s are assumed to be equal. Here C_s is the total solubility of the sodium salt in the same buffer. This last point may be illustrated by noting that, at the high pH region, $(HA) \ll (A)$; and therefore Eqs. 3, 4, and 8 may be combined to give

$$G = \frac{K_{sp}^{1/2}(D_A D_{NA})^{1/2}}{h} \quad \text{(Eq. 9)}$$

which is identical to Eq. 2 when $D_A = D_{Na}$.

The dissolution rate of the sodium salt was $G = 7.3 \times 10^{-7}$ moles cm.$^{-2}$ second^{-1} (see Figs. 3–5) when conversion to the acid was not involved. Since the solubility, C_s, was found to be $C_s = 0.17\ M$, we find that according to Eq. 2 (or Eq. 3)

$$(D/h) = 4.3 \times 10^{-6}$$

in good agreement with the 4.1×10^{-6} observed in the case of the acid tolazamide dissolution.

Sodium Tolazamide with Conversion to Acid.—In the time ranges studied, there appeared to be two kinds of dissolution behavior for the sodium salt. When the buffer concentration was high and the pH was low, an acid coat formed after a brief period, and the dissolution rate was close to the dissolution rate of the acid phase itself. In Fig. 2 the rates taken from curves C and D of Fig. 4 are plotted (on dashed circles line) and compared with the data from the tolazamide acid experiments. These values are within about a factor of 2 of the rates for tolazamide acid. Thus, the coat which formed over the sodium salt phase must have been relatively impermeable to diffusion; to some extent, the coat must have been "self-healing" as it dissolved away.

The other kind of behavior occurred in the intermediate region (curves B in Figs. 3–5 and C in Fig. 3). Here the initial plateau regions, when they occur, probably corresponded to the dissolution of the relatively impermeable initial acid coat. However, when the coat dissolved, the conditions did not permit recoating without some appreciable dissolution of the exposed sodium salt itself. Eventually, in these cases, dissolution appeared to occur simultaneously from both phases, and flaking became noticeable.

Let us now attempt to consider some of the quantitative aspects of these results. First of all, let us examine the conditions at the high pH region where conversion to the free acid is incipient. Assuming that Eq. 2 (or Eq. 9) is applicable, we may calculate the effective supersaturations with respect to acid tolazamide at the solid–solution interface by using Eq. 7. We find that when the sodium salt dissolves in the 0.08 M HPO_4^-–0.02 M $H_2PO_4^-$ buffer, $(HA)_o$ must be $3.7 \times 10^{-3}\ M$. When the buffer is 0.07 M HPO_4^-–0.03 M $H_2PO_4^-$, $(HA)_o = 5.9 \times 10^{-3}\ M$.

Thus, according to these calculations, the solid–solution interface is effectively supersaturated with respect to acid tolazamide by more than *20 times* the equilibrium solubility just at the point where the effects of conversion to the acid become appreciable. The significance of this is that here the kinetic availability of sodium tolazamide may be more than 20 times that of the acid tolazamide which is the thermodynamically favored phase under these conditions.

We find that if the sodium salt dissolves in 0.05 M HPO_4^-–0.05 M $H_2PO_4^-$, $(HA)_o = 1.2 \times 10^{-2}\ M$. If the buffer is 0.03 M HPO_4^-–0.07 M $H_2PO_4^-$, then $(HA)_o = 1.8 \times 10^{-2}\ M$. Therefore, it appears that maximum possible initial supersaturation values of about 50 to 100 times greater than the acid tolazamide solubility were necessary to form an acid coat that would be essentially impermeable to the influences of the sodium salt beneath it. It is assumed in these latter estimations that initially the sodium salt is permitted to dissolve long enough so that steady state, as described by Eqs. 3–6, is attained before appreciable precipitation of the acid occurs. Actually, in these cases (curves C and D of Fig. 3) appreciable conversion probably takes place before such high supersaturation values are reached, *i.e.*, before steady-state diffusion conditions with the sodium salt phase are established. That this is probably true is consistent with the smaller Y-axis intercept values of the initial linear plateau portions (Fig. 3, curves B, C, D) for the lower pH runs. The smaller intercept values mean that effectively less sodium salt dissolved before the coat was essentially complete.

The following mechanism is consistent with the curves in Figs. 3–5. Because of the high initial supersaturation, rapid nucleation of the acid occurs on and in the vicinity of the surface greatly reducing the diffusional pathways between the solution and the sodium salt. The rate and amount of coating will depend on (*a*) the initial supersaturation with respect to HA at the surface, (*b*) on the concentration of A^- because A^- could be converted to more HA depending on how rapidly $H_2PO_4^-$ can diffuse to the surface from the bulk, and (*c*) on the concentration of $H_2PO_4^-$ in the bulk (or at constant pH, the total buffer concentration) because this would be proportional to the driving force for diffusion of $H_2PO_4^-$ to the surface.

Because the coating process itself may cut off the supply of A^- and because A^- is being removed from the vicinity of the surface both by conversion to HA and by diffusion away from the surface, this time-dependent phenomenon may last for a short period. Then the situation may tend to reverse, and the acid may begin to dissolve. When nearly all of this initial coat has dissolved, the sodium salt phase again becomes exposed and will dissolve until the critical supersaturation level is reached again. Thus, a repetitive cycle may be established (see curve B, Fig. 5). However, eventually a roughened condition may develop where the acid layer thickness becomes nonuniform, and spotty exposure of the sodium salt occurs. At these break points, if the local supersaturation levels are not high enough, dissolution of the sodium salt may continue without appreciable conversion. This may then lead to subsurface dissolution and eventually flaking of the acid.

REFERENCES

(1) Higuchi, W. I., *et al.*, THIS JOURNAL, **47**, 376(1958).
(2) Nelson, E., *ibid.*, **46**, 607(1957); **47**, 297(1958).
(3) Higuchi, W. I., Nelson, E., and Wagner, J. G., *ibid.*, **53**, 333(1964).
(4) Higuchi, W. I., *ibid.*, **53**, 532(1964).
(5) Levy, G., and Procknal, J. A., *ibid.*, **51**, 294(1962).
(6) Higuchi, W. I., and Hamlin, W. E., *ibid.*, **52**, 575 (1963).
(7) Levy, G., *ibid.*, **52**, 1139(1963).
(8) Nelson, E., *ibid.*, **47**, 300(1958).
(9) Wruble, M. S., *Am. J. Pharm.*, **102**, 318(1930).
(10) Milosovich, G., THIS JOURNAL, **53**, 484(1964).
(11) Niebergall, P. J., Milosovich, G., and Goyan, J. E., *ibid.*, **52**, 236(1963).