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DISSOLUTION MODEL FOR A WEAK CARBOXYLIC ACID

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ABSTRACT

A chemical reaction, diffusion, and ionization model is presented for the dissolution of solid, weak acids in reactive media. The model assumes an equilibrium plane, which is located within the diffusion layer and in which ionization equilibrium is established. The model, which proposes that the aqueous diffusion layer is divided into three zones, is tested by use of experimental dissolution rates of p-aminobenzoic acid and is compared to a two-zone model.

INTRODUCTION

In early studies (1,2) of the dissolution kinetics of solid weak acids into basic medium, the kinetics were explained by the Nernst-Brunner two-zone model, which assumes instantaneous chemical equilibria. The two-zone model as shown in Figure 1 introduced the concept of a reaction plane (3,4). Molecules of the

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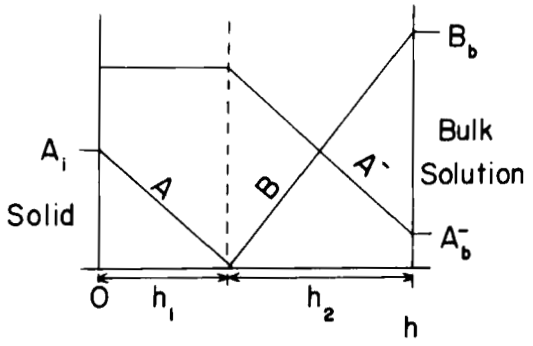

FIGURE 1

Concentration profiles during the dissolution of a carboxylic acid in aqueous sodium hydroxide solutions according to the Nernst-Brunner double film model.

dissolved solid A diffuse from the interface toward the bulk while molecules of the dissolved reactant B diffuse from the bulk liquid toward the interface. Both species meet and react at the reaction plane. Dissolution rate (amount dissolved per unit surface per unit time) is expressed as

$$R = \frac{1}{V} \quad \frac{D_A C_A + D_B C_B}{h_1 + h_2} \qquad \text{(Eq. 1)}$$

in which V is the volume of the dissolution medium, D_A and D_B are the diffusion coefficients of the acid and base, respectively, C_A and C_B are the concentrations of acid and base, respectively, and h_1 and h_2 are the distances the acid and base, respectively, must travel to reach the reaction plane.

Factors that influence the dissolution of solids into reactive medium, in which simultaneous diffusion and chemical

reaction with the reactive species from the bulk solution occur, have been modeled for solid acids (5-7) and a basic compound (8).

The simultaneous chemical reaction and diffusion model as shown in Figure 2 proposes that the reaction of a weak acid dissolving in an alkaline medium occurs not only at the reaction plane but elsewhere in the diffusion layer (5). The concentration gradients are nonlinear, and the the slope of the gradient at any distance is dependent on the reaction of the species at that position in the diffusion layer. Thus, concave gradients indicate an increased concentration of the species due to chemical reaction compared to the concentration of the same species in systems with no chemical reaction. The dissolution rate is

$$R = \frac{D_{HA}[HA]_i}{h} + \frac{D_B^2[B^-]_b}{h} + \frac{[HA]_i D_A K}{D_B^2 + D_B[HA]_i D_A K} \qquad \text{(Eq. 2)}$$

in which D is the diffusion coefficient of species x, [X] is the concentration of species x at position z (subscripts i and b indicate interface and bulk, respectively), $K = K_{HA}/K_w$ where K_{HA} and K_w are the ionization equilibrium constants for the weak acid and water, respectively, and h is the thickness of the diffusion layer. In cases in which the equilibria are rapid compared to diffusion, ionization of the acid may be ignored or assumed to be instantaneous at the solid-liquid interface. If ionization is only moderate, dissolution kinetics may deviate appreciably from the models.

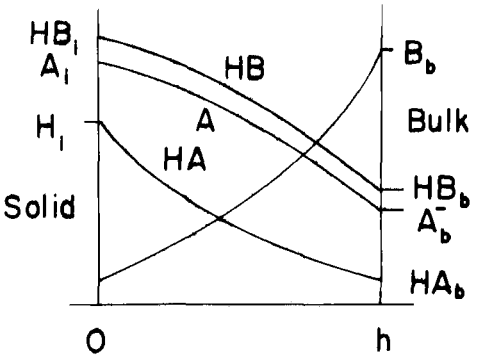

FIGURE 2

Concentration profiles during the dissolution of a carboxylic acid in aqueous sodium hydroxide solutions according to the simultaneous chemical reaction and dissolution model (5).

This study compares the experimental dissolution rates of p-aminobenzoic acid in alkaline media in terms of the two-zone (surface ionization) model and a three-zone model, which assumes an equilibrium plane for dissolution accompanied by equilibrium and a very rapid, second-order, irreversible chemical reaction (9).

EXPERIMENTAL

Preparation of Spheres. By means of a hydraulic press fitted with a spherical punch and die set, analytical grade p-aminobenzoic acid was compressed at a force of 2,270 kg into spheres having a diameter of 0.9525 ± 0.005 cm.

Dissolution Methodology. Dissolution media from 0.0096 to 0.1895 molar sodium hydroxide were prepared using freshly distilled water, and their concentration was determined using

standard solutions of potassium hydrogen phthalate. The dissolution rate was determined in distilled water, pH 3.6 phosphate buffer and the various concentrations of sodium hydroxide at 25 ± 0.1°, as described previously (10,11) under conditions where the concentration of the solute did not exceed 5% of solubility. The dissolution apparatus and method were described previously (11,12). Solubility measurements were made at 25°, as reported earlier (13).

THEORY

According to the presentation of Carmichael and Chang (9) as shown in Figure 3, the distance to the equilibrium plane at which they assumed ionization occurred instantaneously is

$$h_1 = \sqrt{D_{HA}/k_f} \qquad \text{(Eq. 3)}$$

in which k_f is the forward rate constant of ionization. After equilibrium is established, the acid diffuses through zone 2 toward the bulk solution as B^- diffuses from the bulk solution through zone 3 in the direction of the interface. Zone 2 and 3 intersect at the reaction plane, which is at a distance $h_1 + h_2$ from the surface of the solid and where the acid and B^- react instantaneously. Species A^- and HB produced by the reaction then diffuse toward the bulk solution.

As ionization does not occur in zone 1, the dissolution rate is

$$R = \frac{D_{HA}}{h_1} \left([HA]_i - [HA]_{ep} \right) \qquad \text{(Eq. 4)}$$

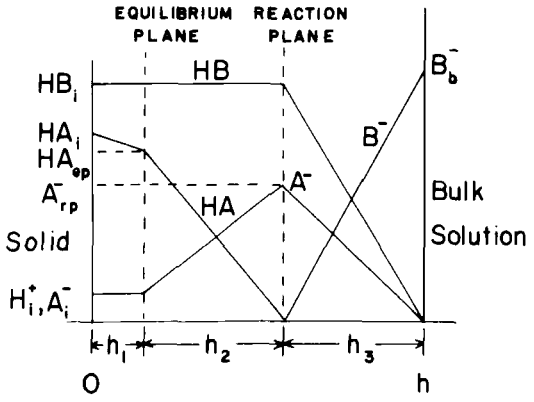

FIGURE 3

Concentration profiles during the dissolution of a carboxylic acid in aqueous sodium hydroxide solutions according to the chemical reaction, diffusion, and ionization model.

in which $[HA]_i$ and $[HA]_{ep}$ represent the concentration of acid at the interface and the equilibrium plane, respectively.

As one mole of HA reacts with one mole of B^-, at steady state the flux of HA through zone 2 is equal to the flux of B^- through zone 3. For each mole of B^- consumed, one mole of HB is produced. The flux of HB out of the film is equivalent to the flux of B^- into the film. Under sink conditions this may be expressed as

$$\frac{D_{HA}[HA]_{ep}}{h_2} = \frac{D_B[B^-]_b}{h_3} = \frac{D_{HB}[HB]_i}{h_3} \qquad \text{(Eq. 5)}$$

According to mass balance, all HA exiting zone 1 must appear in zone 2 as HA or A^-. Thus, the flux of HA through zone

1 is equal to the sum of the flux of HA and the flux of A^- in zone 2. Since the flux of A^- is opposite to the flux of HA in zone 2,

$$\frac{D_{HA}\left([HA]_i - [HA]_{ep}\right)}{h_1} = \frac{D_{HA}[HA]_i}{h_2} - \frac{D_A\left([A^-]_{rp} - (A^-)_{ep}\right)}{h_2} \qquad \text{(Eq. 6)}$$

When equilibrium is established at h_1,

$$K_{HA} = \frac{[H^+]_{ep}\,[A^-]_{ep}}{[HA]_{ep}} \qquad \text{(Eq. 7)}$$

Assuming that H^+ is obtained from the ionization of the weak acid, $[A^-]_{ep} = [H^+]_{ep}$. Thus,

$$[A^-]_{ep} = \sqrt{K_{HA}[HA]_{ep}} \qquad \text{(Eq. 8)}$$

Upon substituting Eq. 8 into Eq. 6

$$\frac{D_{HA}\left([HA]_i - [HA_{ep}]\right)}{h_1} = \frac{D_{HA}[HA]_i}{h_2} - \frac{D_A\left([A^-]_{rp} - \sqrt{K_{HA}[HA]_{ep}}\right)}{h_2} \qquad \text{(Eq. 9)}$$

Assuming equal fluxes of A^- through zones 2 and 3 at steady state,

$$\frac{D_A\left([A^-]_{rp} - \sqrt{K_{HA}[HA]_{ep}}\right)}{h_2} = \frac{D_A[A^-]_{rp}}{h_3} \qquad \text{(Eq. 10)}$$

If Eq. 10 is solved,

$$[A^-]_{rp} = \frac{K_{HA}[HA]_{ep}}{1 - (h_2/h_3)} \qquad \text{(Eq. 11)}$$

Substituting the term h_2/h_3 from Eq. 5 into Eq. 11,

$$[A^-]_{rp} = \frac{\sqrt{K_{HA}[HA]_{ep}}}{1 - \frac{D_{HA}[HA]_{ep}}{D_B[B^-]_b}} \qquad \text{(Eq. 12)}$$

Solving Eq. 9 and 5 for h_2/h_1 and h_3/h_2, respectively, and substituting

$$V = \frac{h_2}{h_1} = \frac{D_{HA}[HA]_{ep} - D_A\left([A^-]_{rp} - \sqrt{K_{HA}[HA]_{ep}}\right)}{D_{HA}\left([HA]_i - [HA]_{ep}\right)} \qquad \text{(Eq. 13)}$$

and

$$U = \frac{h_3}{h_2} = \frac{D_B[B^-]_b}{D_{HA}[HA]_{ep}} \qquad \text{(Eq. 14)}$$

In addition h_3/h_1 can be obtained

$$UV = \frac{h_3}{h_1} = \frac{h_2}{h_1}\,\frac{h_3}{h_2} \qquad \text{(Eq. 15)}$$

As the thickness of the entire diffusion layer is the sum of the thickness of each zone ($h = h_1 + h_2 + h_3$), then

$$\frac{h}{h_1} = 1 + \frac{h_2}{h_1} + \frac{h_3}{h_1} \qquad \text{(Eq. 16)}$$

Using Eq. 13 and 15

$$\frac{h}{h_1} = 1 + V + UV = 1 + V\,(1+U) \qquad \text{(Eq. 17)}$$

and

$$\frac{h}{h_1} = 1 + \left\{ \frac{D_{HA}[HA]_{ep} - D_A\left[[A^-]_{rp} - \sqrt{K_{HA}[HA]_{ep}} \right]}{D_{HA}\left[[HA]_i - [HA]_{ep} \right]} \right\} \left\{ 1 + \frac{D_B[B^-]_b}{D_{HA}[HA]_{ep}} \right\} \quad \text{Eq. (18)}$$

The two unknown terms in Eq. 12 and 18 are $[A^-]_{rp}$ and $[HA]_{ep}$. As $[HA]_{ep}$ must be evaluated to calculate the three-zone dissolution rate, Eq. 11 is substituted into Eq. 18. With algebraic manipulations, the following third degree polynomial is extracted.

$$A[HA]_{ep}^{3.0} + B[HA]_{ep}^{2.5} + C[HA]_{ep}^{2.0} + D[HA]_{ep}^{1.5} + E[HA]_{ep} = 0 \quad \text{(Eq. 19)}$$

in which

$$A = \frac{D_{HA}^3 h}{D_B[B^-]_b h_1} \quad \text{(Eq. 20)}$$

$$B = \frac{D_{HA}^2 D_A K_{HA}}{D_B[B^-]_b} \quad \text{(Eq. 21)}$$

$$C = D_{HA}^2 \left[1 + \frac{[HA]_i D_{HA}}{D_B[B^-]_b} \right] \left[1 + \frac{h}{h_1} \right] \quad \text{(Eq. 22)}$$

$$D = D_{HA} D_A K_{HA}^{0.5} \quad \text{(Eq. 23)}$$

$$E = [HA]_i D_{HA}^2 \left[\frac{h}{h_1} - 1 \right] - D_{HA} D_B [B^-]_b \quad \text{(Eq. 24)}$$

RESULTS AND DISCUSSION

Simultaneous Chemical Reaction, Diffusion, and Ionization Model. The parameters used to test the validity of the 3-zone model were obtained from the literature as shown in Table 1 or experimentally determined. The thickness of the entire diffusion layer under the hydrodynamics of the system was calculated by using the Noyes-Whitney equation, $h = D_{HA}C_s/R$ (11). As $[HA]_i$ is defined as the concentration of HA at the solid-liquid interface, it is equivalent to the intrinsic solubility of the acid. Thus, the experimental dissolution rate, when ionization is suppressed, may be used in the Noyes-Whitney equation to calculate $[HA]_i$. Before Eq. 4 was used to calculate a theoretical dissolution rate, HA_{ep} was determined by using the iterative method of Newton (15) and a computer program. Then Eq. 4 was used to calculate the dissolution rate at each concentration of base as summarized in Table 2. The relative dissolution rate is the ratio of the dissolution rate in reactive medium to the dissolution rate R_o in unreactive medium. As the isoelectric point of p-aminobenzoic acid is at pH 3.6 (16), the R_o was experimentally measured at pH 3.6 and was used to calculate the relative dissolution rate since it represented minimal ionization.

In the three-zone model the flux of HA across zone 1 is not constant but varies with HA_{ep}. The concentration of HA at the equilibrium plane is dependent on the concentration $[B^-]_b$ of base in the bulk solution. As the bulk concentration of OH^- is

TABLE 1. Parameters of p-Aminobenzoic Acid

Literature and Calculated Values		
k_f, reciprocal sec	4 X 4 10^5	(18)*
D, cm^2/sec	8.425 X 10^{-6}	(19)
C_{s,H_2O}, M/L	4.29 X 10^{-2}	(20)
$C_{s,pH\ 3.6}$, M/L	4.226 X 10^{-2}	
K	1.26 X 10^{-5}	(18)
MW, g/M	137.14	(20)
h_1, cm	4.3758 X 10^{-6}	
Experimental Values		
h, cm	2.64 X 10^{-3}	
R_{o,H_2O}, $mg/cm^2/hr$	67.65	
$R_{o,pH\ 3.6}$, $mg/cm^2/hr$	66.63	

*reference

increased, the concentration of HA at the equilibrium plane is decreased with a resulting increase in concentration gradient across zone 1 and a consequential enhancement of dissolution rate. As the concentration of A^- at the equilibrium plane is increased by increases in the bulk concentration of OH^-, a limiting concentration of HA is not attained, and equilibrium is maintained at the equilibrium plane.

TABLE 2. Concentration at Equilibrium Plane and Calculated and Experimental Dissolution of p-Aminobenzoic Acid in Various Media

Medium	$(HA)_{ep}$, M/L	Calculated		Experimental	
		Rate, $mg/cm^2/hr$	R/R_o	Rate, $mg/cm^2/hr$	R/R_o
pH 3.6 buffer				66.6 ± 1.6	1.00
0.0096 M NaOH	4.214×10^{-2}	114.1	1.71	96.6 ± 0.4	1.45
0.0382	4.201×10^{-2}	237.1	3.56	241.8 ± 4.2	3.63
0.0722	4.185×10^{-2}	392.0	5.88	397.3 ± 3.8	5.96
0.0827	4.180×10^{-2}	439.6	6.60	478.1 ± 14.9	7.18
0.0933	4.175×10^{-2}	487.7	7.32	506.2 ± 16.5	7.60
0.1006	4.171×10^{-2}	520.8	7.81	564.7 ± 6.2	8.48
0.1442	4.150×10^{-2}	718.4	10.78	712.7 ± 10.2	10.70
0.1895	4.129×10^{-2}	923.7	13.86	950.6 ± 14.3	14.27

A comparison of the experimental relative dissolution rates given in Table 2 and theoretical relative rates is shown in Figure 4. In accord with the model there is a substantial increase in dissolution rate as the concentration of base is increased due to the formation of a greater concentration of acid anion with a decrease of HA at the equilibrium plane, and a consequential increase in concentration gradient across zone 1, which enhances the dissolution rate.

2-Zone Models. To challenge the concept of ionization within the aqueous diffusion layer, two models based on the assumption of surface ionization may be considered. In the Nernst-Brunner double film model of Figure 1 the flux of A in reactive medium, the flux of B in reactive medium, and the flux of A in unreactive medium are

$$R_A = \frac{D_A[A]_i}{h_1} \qquad \text{(Eq. 25)}$$

$$R_B = \frac{D_B[B]_b}{h_2} \qquad \text{(Eq. 26)}$$

and

$$R_o = \frac{D_A[A]_i}{h} \qquad \text{(Eq. 27)}$$

respectively. The relative dissolution rate is

$$\frac{R}{R_o} = \frac{D_A[A]_i/h_1}{D_A[A]_i/h} = \frac{h}{h_1} \qquad \text{(Eq. 28)}$$

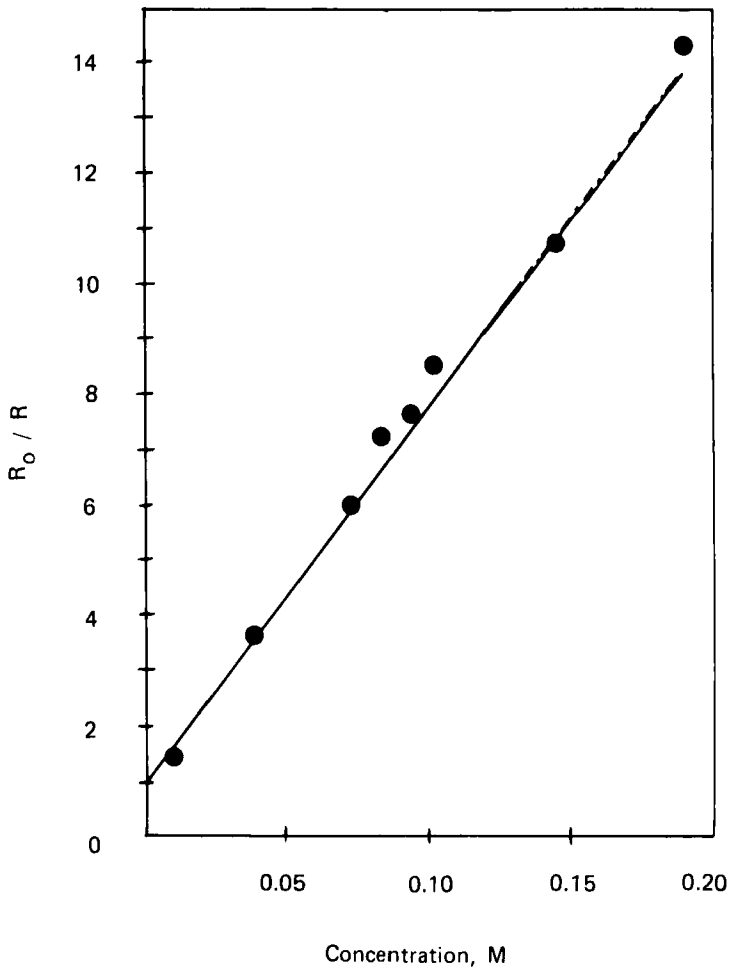

FIGURE 4

Comparison of the experimental and theoretical relative dissolution rate of p-aminobenzoic acid in various concentrations of sodium hydroxide solution as predicted by several models. Key: ●, experimental; _____, 3-zone; - - -, Nernst-Brunner; and.-.-., Mooney model.

Utilizing Eq. 1 and 2

$$h = h_1 + h_2 = \frac{D_A[A]_i}{R} + \frac{D_B[B]_i}{R_B} \qquad \text{(Eq. 29)}$$

Utilizing the equation for ionization of the acid and equating the characteristic time of diffusion to time of reaction (9,14) yields

$$\frac{R}{R_o} = \frac{\frac{D_A[A]_i}{R} + \frac{D_B[B]_i}{R_B}}{\frac{D_A[A]_i}{R}} \qquad \text{(Eq. 30)}$$

In a system in which one mole of A reacts with one mole of B, as the flux of A is equivalent to the flux of B, the relative dissolution rate is

$$\frac{R}{R_o} = \frac{D_A[A]_i + D_B[B]_b}{D_A[A]_i} \qquad \text{(Eq. 31)}$$

$$= 1 + \frac{D_B[B]_b}{D_A[A]_i}$$

Where A and B represent HA and B^-, Eq. 31 in the form

$$\frac{R}{R_o} = 1 + \frac{D_B[B^-]_b}{D_{HA}[HA]_i} \qquad \text{(Eq. 32)}$$

permits the calcuation of the theoretical relative dissolution rates as given in Table 3.

TABLE 3. Experimental and Theoretical Relative Dissolution Rates of p-Aminobenzoic Acid in Various Concentrations of Sodium Hydroxide Solution as Predicted by Three Models

Molarity of NaOH	Relative Dissolution Rate			
	Experimental	3-Zone	Nernst-Brunner	Mooney
0.0096	1.45	1.71	1.65	1.65 (4.72)*
0.0382	3.63	3.56	3.60	3.59 (5.31)
0.0722	5.96	5.88	5.91	5.92 (5.59)
0.0827	7.18	6.60	6.62	6.65 (5.65)
0.0933	7.60	7.32	7.34	7.34 (5.70)
0.1006	8.48	7.81	7.84	7.80 (5.73)
0.1442	10.70	10.78	10.80	10.82 (5.89)
0.1895	14.27	13.86	13.88	13.95 (6.01)

*interfacial pH

In the model proposed by Mooney et al. (17) surface ionization is assumed and chemical reaction and diffusion are assumed to occur simultaneously throughout the film with nonlinear concentration gradients similar Figure 2. The relative dissolution rate according to this model is

$$\frac{R}{R_o} = \frac{D_{HA}[HA]_i + D_H\left([H^+]_i - [H^+]_h\right) + D_{OH}\left([OH^-]_h - [OH^-]_i\right)}{D_{HA}[HA]_i} \qquad \text{(Eq. 33)}$$

To use Eq. 33 requires an evaluation of concentration of H^+ at the interface because in strong alkaline media the pH of the

TABLE 4. Ratio of Experimental Relative Dissolution Rate to the Theoretical Relative Dissolution Rate of p-Aminobenzoic Acid for Several Models in Various Concentrations of Sodium Hydroxide Solution

Malority	Ratio		
	3-Zone	Nernst-Brunner	Mooney
0.0096	0.848	0.879	0.879
0.0382	1.020	1.008	1.011
0.0722	1.014	1.009	1.007
0.0827	1.088	1.085	1.080
0.0933	1.038	1.035	1.035
0.1006	1.086	1.082	1.087
0.1442	0.993	0.991	0.989
0.1895	1.030	1.028	1.023

interface is significantly lower than the pH of the bulk solution. The concentration of H^+ at the interface was calculated by use of

$$-D_H[H^+]_i^2 + [H^+]_i \left(D_H[H^+]_h - D_{OH}[OH^-]_h \right) + K_w \left(D_{OH} + D_A K [HA]_i \right) = 0 \qquad \text{Eq. 34}$$

The interfacial pH and relative dissolution rate are tabulated in Table 3. Visual comparison in Figure 4 of the data from Table 3 shows that the three models are essentially coincident.

The accuracy of each model at each concentration of base is compared in Table 4.

CONCLUSION

The dissolution rate calculated by the chemical reaction, diffusion, and ionization model adequately describes the dissolution of p-aminobenzoic acid in alkaline media. With p-aminobenzoic acid ionization is rapid, and zone 1 comprises only an insignificant fraction ($h_1/h = 0.00166$) of the entire diffusion layer. Thus, the 3-zone model is practically reduced to a 2-zone model.

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REFERENCES

1. C.V. King and S.S. Brodie, J. Am. Chem. Soc., 59, 1375 (1937).
2. A.W. Hixson and S.J. Baum, J. Ind. Eng. Chem., 36, 528 (1944).
3. E. Brunner, Z. Physik. Chem., 47, 56 (1904).
4. W. Nernst, ibid, 47, 52 (1904).
5. W.I. Higuchi, Eugene L. Parrott, Dale E. Wurster and T. Higuchi, J. Am. Pharm. Assoc., Sci. Ed., 47, 376 (1958).
6. W.I. Higuchi, N.A. Mir, A.P. Parker and W.E. Hamlin, J. Pharm. Sci., 54, 8 (1965).

7. K.G. Mooney, M.A. Mintun, K.J. Himmelstein and V.J. Stella, ibid., 70, 13 (1981).

8. W.E. Hamlin and W.I. Higuchi, ibid., 55, 205 (1966).

9. Gregory R. Carmichael and Shuh-Chih Chang, Chem. Engr. Sci., 35, 2463 (1980).

10. E.L. Parrott, D.E. Wurster and T. Higuchi, J. Am. Pharm. Assoc. Sci. Ed., 44, 269 (1955).

11. R.J. Bruan and E.L. Parrott, J. Pharm. Sci., 61, 175 (1972).

12. S.A. Shah and E.L. Parrott, ibid., 65, 1874 (1976).

13. E.L. Parrott and V.K. Sharma, ibid., 56, 1341 (1967).

14. D.L. Roberts and S.K. Friedlanger, A. I. Ch. E. J., 25, 593 (1980).

15. W. Cheney and D. Kincaid, "Numberical Mathematics and Computing," Brooks/Cole, Monterey, Calif., 1980, p. 45.

16. A. Adamson, "A Textbook of Physical Chemistry," 2nd ed., Academic Press, New York, N.Y., 1973, p. 479.

17. K.G. Mooney, M.A. Mintun, K.J. Himmelstein and V.J. Stella, J. Pharm. Sci., 70, 13 (1981).

18. G. Porter, Ed., "Progress in Reaction Kinetics," MacMillan, New York, N.Y., 1964, pp. 306-307.

19. L.C. Longsworth, J. Am. Chem. Soc., 75, 5705 (1953).

20. M. Windholz, Ed., "The Merck Index," Prentice-Hall, Englewood Cliffs, N.J., 1962.