

skin irritation produced by europium chloride were of the same magnitude and duration reported for the other members of the rare earth series (19-23). Moreover, the skin lesion from intradermal administration was the same (24). Europium chloride produced the same type and degree of depression as the other rare earths (19-23) did on the various biological systems studied. Also, the mechanism of death, cardiovascular collapse coupled with respiratory paralysis, was identical to that of the other elements of the series. Although this element has a relatively low toxicity, care should be exercised to prevent skin lesions with nodule formation by using appropriate clothing.

REFERENCES

- (1) Savitskiy, Y. M., *Vestn. Akad. Nauk SSSR*, **6**, 81(1960).
- (2) Spiller, R., *Atom Ind.*, **9**, 13(1960).
- (3) Spedding, F. H., and Daane, A. H., "The Rare Earths," John Wiley & Sons, Inc., New York, N. Y., 1961, p. 641.
- (4) Anderson, W. K., and Dunning, D. D., *Proc. Nucl. Eng. Sci. Conf.* 2nd Philadelphia, 1957, 53-59.

- (5) Ransohoff, J. A., *Nucleonics*, **17**, 80(1959).
- (6) Muroma, A. P., *Ann. Med. Exptl. Biol. Fenniae Helsinki*, **31**, 432(1953).
- (7) Bruce, D. W., Hietbrink, B. E., and DuBois, K. P., *Toxicol. Appl. Pharmacol.*, **5**, 750(1963).
- (8) Gehrcke, E., Law, E., and Meinhardt, O., *Z. Ges. Naturw.*, **5**, 106(1939).
- (9) Schepers, G. W. H., Delahant, A. B., and Redlin, A. J., *A.M.A. Arch. Ind. Health*, **12**, 297(1955).
- (10) Schepers, G. W. H., *ibid.*, **12**, 301(1955).
- (11) *Ibid.*, **12**, 306(1955).
- (12) Van Cleave, C. D., AECU-218 (1949).
- (13) Durbin, P. W., *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **91**, 78(1956).
- (14) Draize, J. H., Woodward, G., and Calvery, H. O., *J. Pharmacol. Exptl. Therap.*, **82**, 377(1944).
- (15) Trendelenburg, P., *Arch. Exptl. Pathol. Pharmacol.*, **81**, 55(1917).
- (16) Shipley, R. E., and Wilson, C., *Proc. Soc. Exptl. Biol. Med.*, **78**, 724(1951).
- (17) Litchfield, J. T., Jr., and Wilcoxon, F., *J. Pharmacol. Exptl. Therap.*, **96**, 99(1949).
- (18) Gardner, M. V., *J. Franklin Inst.*, **243**, 77(1947).
- (19) Haley, T. J., *et al.*, *Brit. J. Pharmacol.*, **17**, 526(1961).
- (20) Haley, T. J., *et al.*, *THIS JOURNAL*, **51**, 1043(1962).
- (21) Haley, T. J., *et al.*, *Toxicol. Appl. Pharmacol.*, **5**, 227(1963).
- (22) Haley, T. J., *et al.*, *ibid.*, **6**, 614(1964).
- (23) Haley, T. J., *et al.*, *THIS JOURNAL*, **53**, 1186(1964).
- (24) Haley, T. J., and Upham, H. C., *Nature*, **200**, 271(1963).

Dissolution Rate Studies III. Penetration Model for Describing Dissolution of a Multiparticulate System

By JERE E. GOYAN

Danckwerts' penetration model is used to derive equations for the dissolution of solids in a multiparticulate system. The equations obtained are capable of explaining the deviations from linearity of cube-root plots. The loss of sensitivity in distinguishing differences between polymorph dissolution rates at high agitation intensities also may be rationalized from these equations.

IT HAS BEEN shown in a previous publication (1) that the Hixon-Crowell cube-root law (2) does not appear to hold for rapidly stirred systems. The data showed that a square-root law described the system more accurately.

The cube-root law is derived using the diffusion layer model proposed by Nernst (3). It is of interest to derive an equation using the penetration theory described by Danckwerts (4). This model (derived for dissolution of a gas in a liquid) assumes that a turbulent liquid is a mass of eddies which are being exposed continuously to fresh surfaces of a gas and then returned to the bulk of the liquid. It is proposed further that free diffusion takes place into each of the packets during the short period of time in which the packet is in contact with the surface. The rationality of such a model is supported strongly by the work of Fage and Townend (5) who found evidence of turbulent flow in a tube as close as 6μ from the interface. The validity of the model has been discussed by Danckwerts (4) and Hanratty (6). This model should be equally valid for the dissolution of a solid into a liquid and has been demonstrated for the case of dissolution from a flat surface (7).

Danckwerts defines the surface having ages be-

tween t and $t + dt$ as $\phi(t)dt$. Hence the flux per unit area, R , ($\text{Gm. sec.}^{-1} \text{ cm.}^{-2}$) from a spherical surface would be

$$R = \int_0^{\infty} \psi(t)\phi(t) dt \quad (\text{Eq. 1})$$

where $\psi(t)$ is the rate of diffusion into a stagnant liquid of infinite depth defined by

$$\psi(t) = -D \left. \frac{dC}{dr} \right|_{r=a} \quad (\text{Eq. 2})$$

Here C is the concentration, r the radial distance from the center, and a the radius of the sphere. The usual formulation for Fick's second law in spherical coordinates is (8)

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \quad \text{or} \quad \frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial r^2} \quad (\text{Eq. 3})$$

where $u = rC$, and t is the time in seconds. The following boundary conditions are assumed:

$$\begin{aligned} r = a & \quad C = C_A \text{ at all } t > 0 \\ r = \infty & \quad C = 0 \\ t = 0 & \quad C = 0 \text{ for all } r \end{aligned}$$

The Laplace transform of Eq. 3 is

$$s\bar{u} = D \frac{d^2 \bar{u}}{dr^2} \quad (\text{Eq. 4})$$

Defining $q = \sqrt{s/D}$ the solution for Eq. 4 is

$$\bar{u} = c_1 e^{-qr} + c_2 e^{qr}$$

or

$$\bar{C} = \frac{c_1 e^{-qr}}{r} + \frac{c_2 e^{qr}}{r},$$

now $C \rightarrow 0$ as $r \rightarrow \infty$, therefore $c_2 = 0$, and

$$\bar{C} = \frac{c_1 e^{-qr}}{r} \quad (\text{Eq. 5})$$

Evaluating c_1 by use of the boundary conditions

$$\bar{C} = \frac{C_A}{s} \frac{a}{r} e^{-q(r-a)} \quad (\text{Eq. 6})$$

and

$$C = C_A \frac{a}{r} \operatorname{erfc} \frac{r-a}{2\sqrt{Dt}} \quad (\text{Eq. 7})$$

Then,

$$\frac{dC}{dr} = -\frac{C_A a}{r^2} \operatorname{erfc} \frac{r-a}{2\sqrt{Dt}} - \frac{C_A a}{r} \left\{ \frac{1}{\sqrt{\pi Dt}} \exp \left[-\left(\frac{r-a}{2\sqrt{Dt}} \right)^2 \right] \right\} \quad (\text{Eq. 8})$$

$$\left. \frac{dC}{dr} \right|_{r=a} = -\frac{C_A}{a} - \frac{C_A}{\sqrt{\pi Dt}}$$

and

$$\psi(t) = \frac{DC_A}{a} + \frac{DC_A}{\sqrt{\pi Dt}} \quad (\text{Eq. 9})$$

by Eq. 2.

The actual form of $\phi(t)$ may be assumed as various functions. First the slowly stirred laminar flow case will be considered. For a sphere falling slowly in a liquid, the contact time for each liquid layer could be assumed constant τ . (τ is the time needed to generate one unit area of new surface.) The surface contact time between t and $t + dt$ then would be

$$\phi dt = \frac{dt}{\tau}$$

and Eq. 1 becomes

$$R = \int_0^\tau \psi(t) \frac{dt}{\tau}$$

The model assumes a layer at $r = a$ which has a concentration C_A' (not necessarily saturated).

Now the total flux of solute into the layer at $r = a$, R' , would be

$$R' = k_1 - k_2 C_A' - R$$

where k_1 is the intrinsic dissolution rate constant, k_2 is the crystallization rate constant, and the other symbols have their previous meanings. The attainment of a steady-state concentration, C_A , would be extremely rapid, in which case $R' = 0$.

$$0 = k_1 - k_2 C_A - \int_0^\tau \left(\frac{DC_A}{a} + \frac{DC_A}{\sqrt{\pi Dt}} \right) \frac{dt}{\tau} \quad (\text{Eq. 10})$$

and

$$k_1 - k_2 C_A = \frac{DC_A}{a} + 2\sqrt{\frac{D}{\pi\tau}} C_A \quad (\text{Eq. 11})$$

and

$$R = \left(\frac{D}{a} + 2\sqrt{\frac{D}{\pi\tau}} \right) C_A \quad (\text{Eq. 12})$$

Next the rapidly stirred turbulent flow case will be considered. In a turbulent liquid, the layer at a is again assumed to have the concentration C_A' , and the form for $\phi(t)$ given by Danckwerts (4) is

$$\phi = p e^{-pt}$$

where p is the mean rate of production of fresh surface (proportional to stirring rate).

Use of this function gives a new equation analogous to Eq. 10

$$0 = k_1 - k_2 C_A - \int_0^\infty \frac{DC_A}{a} p e^{-pt} dt - \int_0^\infty \frac{DC_A}{\sqrt{\pi Dt}} p e^{-pt} dt$$

and again assumption of a steady-state concentration at a gives

$$C_A = \frac{k_1}{k_2 + (D/a) + \sqrt{Dp}} \quad (\text{Eq. 13})$$

and

$$R = [(D/a) + \sqrt{Dp}] C_A \quad (\text{Eq. 14})$$

Equations 11-14 are of interest since either model can explain the anomalous results shown by Hamlin *et al.* (9) for the dissolution of polymorphs. In either model as the intensity of agitation is increased (p increases or τ decreases), the term containing p or τ may become large compared with k_2 . If one assumes that the difference in solubility of the polymorphs is mainly due to differences in the crystallization rate constant k_2 [since $(k_1/k_2) = C_s$, the saturation solubility], the observation that differences in dissolution rate of polymorphs may decrease at high agitation intensities is explained. With more soluble polymorphs, k_2 could be large with respect to the other terms (k_1 also would be increased greatly), and the difference in dissolution rate would be maintained at higher agitation intensities, as found by Milosovich (10). Anomalies also might be expected at small values of a , but these are harder to explain since C_s also changes as a is reduced to very small values.

Returning to Eq. 14 [a reasonable model for the previous work (1)] and taking surface areas into account

$$\frac{-dW}{dt} = A[\sqrt{Dp} + (D/a)] C_A \quad (\text{Eq. 15})$$

where W is the weight and A the area of the particles. For monodisperse systems, this leads to the equation¹

¹ This equation now takes the change of a with time into account; this was unnecessary in the earlier portion, since the rate of change of a is negligible compared with the rate at which the liquid surface is being renewed. It also treats C_A as a constant which is equivalent to assuming $k_2 + \sqrt{Dp} \gg D/a$ (Ordinarily it is assumed to be C_s , the saturation solubility.)

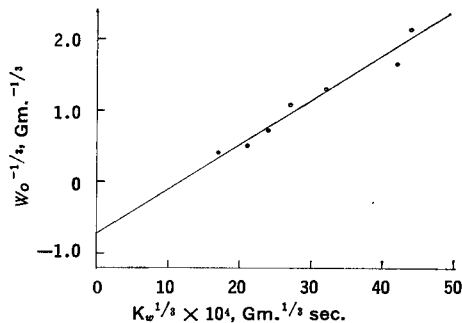


Fig. 1.—Hixon-Crowell rate constant vs. reciprocal of the cube root of initial sample weight.

$$\frac{dW}{bW^{2/3} + eW^{1/3}} = -dt \quad (\text{Eq. 16})$$

where

$$b = \sqrt{D\rho} C_A \alpha N^{1/3}$$

and

$$e = \frac{D \alpha N^{2/3} C_A}{\gamma}$$

N = number of particles; α , γ are constants containing density and geometric terms.

Solution of this differential equation yields

$$b[W^{1/3} - Wo^{1/3}] - e \log \frac{e + b W^{1/3}}{e + b Wo^{1/3}} = \frac{-b^2 t}{3} \quad (\text{Eq. 17})$$

where Wo is the original weight of the particles, and W is the weight at time t . Now Wo is always greater than W ; therefore the logarithmic argument is always equal to or less than 1. The series expansion

$$\log x = 2 \left[\frac{x-1}{x+1} + \frac{1}{3} \left(\frac{x-1}{x+1} \right)^3 + \dots \right]$$

was therefore utilized, dropping all but the first term.² The resulting equation is

$$Wo^{1/3} - W^{1/3} = \frac{2e + b(W^{1/3} + Wo^{1/3})}{3(W^{1/3} + Wo^{1/3})} t \quad (\text{Eq. 18})$$

This equation predicts that a cube-root plot should bend upwards with time, as it does (11). If initial dissolution rate is followed where only a small fraction has dissolved, $Wo \cong W$. Then let $Wo^{1/3} + W^{1/3} = 2Wo^{1/3}$, and take the derivative of $Wo^{1/3} - W^{1/3}$ with respect to time giving

$$\frac{d}{dt} (Wo^{1/3} - W^{1/3}) = K_w^{1/3} = \left[\frac{e + b Wo^{1/3}}{3 Wo^{1/3}} \right]$$

This is then rearranged to give

² For $e \geq 0.5 b$, the maximum error ($W \rightarrow 0$) would be about 3%.

$$1/Wo^{1/3} = \frac{3}{e} K_w^{1/3} - \frac{b}{e} \quad (\text{Eq. 19})$$

where $K_w^{1/3}$ is the Hixon-Crowell rate constant at $t = 0$. (The initial slope of a plot of $Wo^{1/3} - W^{1/3}$ versus time.)

A plot of the data (12) shows the expected linearity (Fig. 1). The value for e obtained from the plot is $4.76 \times 10^{-3} \text{ Gm.}^{2/3} \text{ sec.}^{-1}$ and b is $3.41 \times 10^{-3} \text{ Gm.}^{1/3} \text{ sec.}^{-1}$. Equation 18 predicts that the Hixon-Crowell constant $K_w^{1/3}$ at any time t should be equal to

$$\left[\frac{2e + b(W^{1/3} + Wo^{1/3})}{e + b(Wo^{1/3})} \cdot \frac{Wo^{1/3}}{W^{1/3} + Wo^{1/3}} \right] K_w^{1/3}$$

The data (12) (using values of b and e from above) predict that the rate at $Wo^{1/3} - W^{1/3} = 4$ should be 0.069. The measured slope is 0.067.

Multiplying both sides of Eq. 18 by $(Wo^{1/3} + W^{1/3})$ one obtains

$$Wo^{2/3} - W^{2/3} = \left[\frac{2e + b(W^{1/3} + Wo^{1/3})}{3} \right] t \quad (\text{Eq. 20})$$

This plot would bend down with increasing time. Since the cube-root plot bends up and this one down, it does not seem surprising that the square-root plot appears linear throughout most of the dissolution.

Returning to Eq. 12, it should be noted that for slow stirring and small a , the equation becomes

$$R = \frac{D}{a} C_A \quad (\text{Eq. 21})$$

which may be written

$$a^2 = a_0^2 - \frac{2DC_A}{\rho} t$$

An equation identical to that used by Higuchi and Hiestand (13) (when C_A would $\rightarrow C_s$) to describe their work on micronized powders under slow stirring conditions.

Thus it appears that a penetration type of model gives results consistent with present experimental data. The model may be visualized as a very thin layer having concentration C_A which is being exposed constantly to fresh surfaces of liquid having a concentration much less than C_A . The model seems at least as reasonable as the diffusion layer model and explains some of the anomalies which the diffusion layer model does not.

REFERENCES

- (1) Niebergall, P. J., Milosovich, G., and Goyan, J. E., *THIS JOURNAL*, **52**, 236(1963).
- (2) Hixon, A. W., and Crowell, J. H., *Ind. Eng. Chem.*, **23**, 923(1931).
- (3) Nernst, W., *Z. Physik. Chem. (Leipzig)*, **47**, 52(1904).
- (4) Danckwerts, P. V., *Ind. Eng. Chem.*, **43**, 1460(1951).
- (5) Page, A., and Townend, H. C. H., *Proc. Roy. Soc. (London)*, **135A**, 656(1932).
- (6) Hanratty, J. T., *A.I.C.E. J.*, **2**, 359(1956).
- (7) Johnson, A. I., and Huang, C. S., *ibid.*, **2**, 412(1956).
- (8) Crank, J., "The Mathematics of Diffusion," Oxford University Press, London, 1956, p. 84.
- (9) Hamlin, W. E., *et al.*, *THIS JOURNAL*, **51**, 432(1962).
- (10) Milosovich, G., *ibid.*, **53**, 484(1964).
- (11) Ref. 1, Fig. 7.
- (12) Ref. 1, Table 2.
- (13) Higuchi, W. I., and Hiestand, E. N., *THIS JOURNAL*, **52**, 67(1963).