

Mechanism of Dissolution I: Mathematical Interpretation of Concentration Gradients Developed during Dissolution of a Solid

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Abstract □ The dissolution of *m*-acetotoluide from fused disks was studied using a column dissolution model. This model allowed the study of dissolution under both ascending and descending conditions. Fick's second law of diffusion was solved for the case of $D = f(c)$ and theoretical concentrations calculated assuming the existence of a saturated layer at the solid-liquid interface. Excellent agreement between the theoretical and experimental values for dissolution and diffusion indicated that diffusion control of the dissolution process was obtained in the ascending model. The descending model produced mass transfer rates far in excess of any that could be predicted by molecular diffusion alone. An effective interfacial concentration, less than saturation, was developed in the descending model which could be determined experimentally and which, when used to calculate the total amount dissolved, gave excellent correlation with experimental results. A random-walk model with autocorrelation, which gives rise to the telegraph equation, was used to describe the concentration gradient developed in the descending model.

Keyphrases □ Concentration gradients, during dissolution of a solid—mathematical interpretation, analyzed, compared with diffusion layer theory □ Dissolution, mechanisms—concentration gradients, *m*-acetotoluide from fused disks, ascending and descending conditions, column model, mathematical interpretation □ *m*-Acetotoluide—concentration gradients developed during dissolution from fused disks, column model

The dissolution of solids in liquids is of considerable importance in the pharmaceutical sciences and has been reviewed in the pharmaceutical literature (1, 2). Theories describing the actual mechanism of dissolution or solvation of the solid have, by necessity, been derived from studies of solute mass transfer. Three basic theories of mass transfer at the solid-liquid interface have been developed: the film theory (3), the penetration theory (4), and the surface renewal theory (5). A combination film-penetration theory also has been proposed (6, 7). While the theories of mass transport differ somewhat, they all make the assumptions that solid-solution equilibrium or saturation concentration exists at the solid-liquid interface and that mass transfer is the slow step in the dissolution process and thereby controls the rate of dissolution.

However, as early as 1905, Brunner (8) introduced the idea that the solvation velocity at the interface was not infinitely fast as proposed by Nernst (3). Subsequently, Berthoud (9) postulated the existence of an intermediate concentration, less than saturation, at the interface. The existence of this intermediate concentration was later defended and the theory was expanded by other workers (10, 11). The role of the solvation mechanism has been deduced mainly from studies of dissolution as a function of solubility. Roller (12, 13) measured the solubilities and rates of solution of calcium sulfate in the anhydrous and hydrate forms and attributed the

anomalies in his results to the relative rates of release at the interface of the crystalline forms. Wurster and Taylor (14), working with polymorphs of prednisolone, observed differences in the dissolution rates which were not proportional to the solubility difference and postulated an interface-controlling step. Wurster and Kildsig (15), using complex formation to increase the apparent solubility of the solid, determined an effective interfacial concentration for the solid *m*-aminobenzoic acid. The same effective interfacial concentration was obtained by decreasing the solubility of *m*-aminobenzoic acid, thus supporting the validity of the experimental determination (16).

A review of the literature indicates that while diffusion is assumed to play a vital role in the dissolution process as described by the mass transfer theories, little has been accomplished in the correlation of existing dissolution theory with the laws of diffusion. This study investigates the concentration gradients developed during static dissolution for two cases: (a) dissolution from the solid in an ascending direction, and (b) dissolution from the solid in a descending direction. The concentration gradients developed are analyzed mathematically and compared with diffusion layer theory.

THEORY

When the dissolution of a solid is assumed to be diffusion controlled, Fick's second law of diffusion:

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left[D(c) \frac{\partial c}{\partial x} \right] \quad (\text{Eq. 1})$$

may be utilized to calculate the concentration profile for a static system. Therefore, solving Eq. 1 under suitable initial and boundary conditions allows the calculation of the theoretical concentration at any time and point in space. For the dissolution column model employed in this study, these conditions were:

$$\text{boundary conditions} \quad C = C_s \quad x = 0, t > 0 \quad (\text{Eq. 2})$$

$$\text{initial conditions} \quad C = 0 \quad x > 0, t = 0 \quad (\text{Eq. 3})$$

where C_s is the concentration of a saturated solution and equal to 6.10×10^{-3} g. ml.⁻¹ at 30°.

The solution of Eq. 1 under the conditions of Eqs. 2 and 3 was given by Boltaks (17) as:

$$C_{(x,t)} = C_s \left[1 - \frac{\int_0^x \frac{1}{D} e^{-\frac{1}{2t}} \int_0^x \frac{1}{D} x dx dx}{\int_0^\infty \frac{1}{D} e^{-\frac{1}{2t}} \int_0^x \frac{1}{D} x dx dx} \right] \quad (\text{Eq. 4})$$

Equation 4 may be evaluated by the iterative procedure of Cranic (18) using the solution of Eq. 1 for constant D :

$$C = C_s \left[1 - \text{erf} \frac{x}{2(Dt)^{1/2}} \right] \quad (\text{Eq. 5})$$

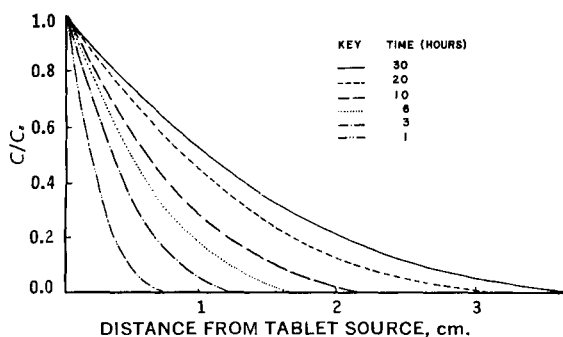


Figure 1—Theoretical concentration profiles for concentration-dependent diffusion.

as an initial approximation. The theoretical concentration profiles predicted by Eq. 4 are shown in Fig. 1.

Dissolution can be considered a complex process composed of the solvent-solid interaction leading to solvation of the molecule and the movement of this solvated molecule to the bulk of the dissolution medium. In general, dissolution may be described by two rate processes: the rate of the interfacial or solid-solvent reaction and the rate associated with the diffusional or transport process. The solution concentration at any point in the dissolution column then depends upon which of the two rates is faster. For the ascending dissolution model, the experimental concentration obtained is much less than the theoretical concentration predicted by Fick's equation based on a saturated layer model if the interfacial rate is slow compared to the rate of diffusion. If, however, the interfacial rate is fast compared to the diffusional rate, the experimental concentration is equal to the theoretical concentration predicted by the presence of a saturation concentration at the interface.

EXPERIMENTAL

The dissolution of *m*-acetotoluide was evaluated in this study. Its solubility at $30 \pm 0.02^\circ$ was determined to be 6.10×10^{-3} g. ml.⁻¹. The diffusion coefficient was determined as a function of concentration by the method of Goldberg and Higuchi (19) using a silver membrane filter¹ having a 1.2- μ pore size. This membrane was approximately 50 μ thick; the area exposed, and thus available for transport, was 0.785 cm.². Both solutions were stirred at 450 r.p.m. using magnetic stirrers and 5-cm. Teflon-coated magnetic stirring bars. The appearance of a black silver oxide on the silver membrane greatly affected the rate of transport and, hence, the calculated value of the diffusion coefficient. This condition required the use of a new membrane with subsequent recalibration of the diffusion cell. All diffusion coefficients were determined at $30 \pm 0.02^\circ$.

The cell constant was determined using KCl as the diffusing solute. To obtain a temperature and diffusion equilibrium, a 4-hr. lag time was used before the first sample. Subsequent samples were removed at 30-min. intervals for a 3-hr. period. The sample volume

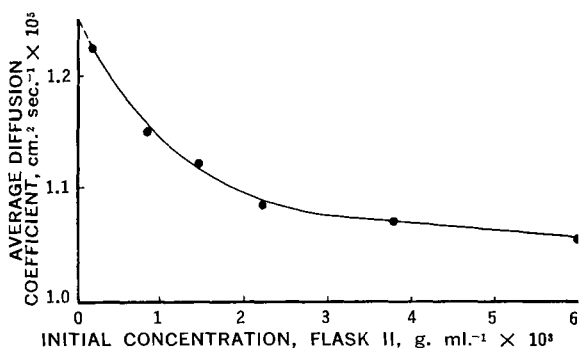


Figure 2—Diffusion coefficient of *m*-acetotoluide as a function of concentration.

¹ Flotronics Metal Membrane Filter, Selas Flotronics, Spring House, Pa.

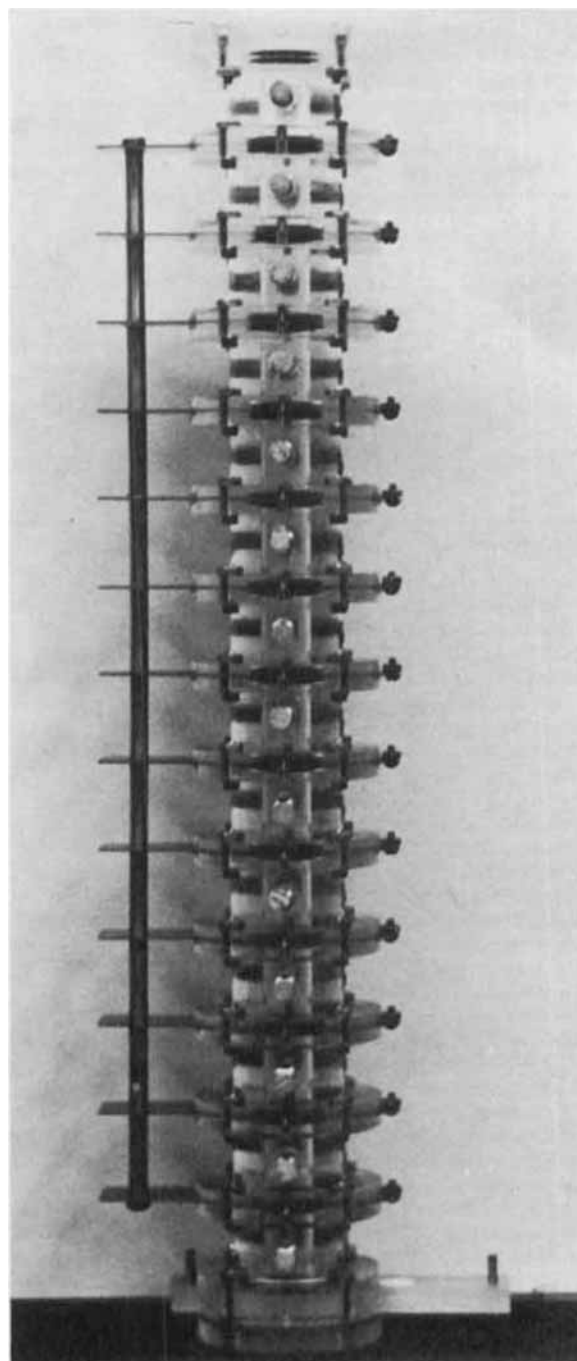


Figure 3—Dissolution column used to study dissolution from a solid in both ascending and descending directions.

was replaced after each sample was withdrawn, and corrections were made for the KCl concentration withdrawn. An atomic absorption spectrophotometer² was used to assay the K⁺ ion present in each solution. The concentration of the KCl solution in the receiving flask was determined before and after each experimental run to establish the initial equilibrium time period and to ensure that the equilibrium concentration between the two flasks had not been reached. The cell constant was determined from the relationship:

$$L = \frac{\Delta C / \Delta t_{\text{KCl}}}{D_{\text{KCl}} \Delta C} \quad (\text{Eq. 6})$$

where L is the cell constant, $\Delta C / \Delta t_{\text{KCl}}$ is the rate of transport for 0.10 M KCl in grams per second, and D_{KCl} is the diffusion coeffi-

² Perkin-Elmer model 290, Perkin-Elmer Corp., Norwalk, Conn.

Table I—Comparison of Theoretical and Experimental *m*-Acetotoluide Total Concentrations for Data Based on the Dissolution Column Using the Ascending Method

Hours	Theoretical Concentration, g. × 10 ³	Experimental Concentration, g. × 10 ³	Percent Deviation ^a
0.250	0.7095	0.6925	-2.4
0.500	0.9640	1.0634	+10.3
0.750	1.164	1.1666	+0.2
0.875	1.252	1.2747	+1.8
1	1.335	1.3087	-2.0
2	1.867	1.7524	-6.1
3	2.278	2.1391	-6.1
4	2.626	2.4715	-5.9
6	3.208	3.0704	-4.3
10	4.094	3.8853	-5.1
15	5.064	5.3905	+6.4
20	5.845	6.3233	+8.2
25	6.533	6.6051	+1.1
30	7.151	7.1234	-0.4

^a Deviation of experimental concentration from theoretical.

cient for 0.10 *M* KCl at 30° and equals 2.093×10^{-5} cm.²/sec. (20). The term ΔC is the difference in initial concentrations between the two flasks. The diffusion coefficients of *m*-acetotoluide were determined by rearrangement of Eq. 6 for varying values of *C* (Fig. 2). The diffusion coefficient at infinite dilution was determined, by extrapolation, to be 1.250×10^{-5} cm.² sec.⁻¹.

The dissolution column (Fig. 3) consisted of a series of 14 Plexiglas compartments, each of which was 3 cm. in height and contained a volume of 2.89 ml. The internal bore of the column was 1.1 cm. ($7/16$ in.). The compartments, labeled 1 through 14 beginning with the source compartment adjacent to the solid tablet, were separated by glass-epoxy slides which could be closed by an aluminum draw rod to seal the compartments at the end of an experimental determination. These slides were coated with a silicone lubricant to prevent twisting of the O-rings sealing the compartments. Each compartment contained two 28-gauge syringe needles (Luer-Lok) for sample withdrawal using 5-ml. syringes (Luer-Loc). Prewashed "000" corks were used to seal the syringe needles during an experimental run. The tablet-holding slide (constructed of Kel-F) contained a 1.1-cm. ($7/16$ -in.) diameter countersink into which a fused tablet could be inserted. Paraffin was painted around the periphery of this recess to seal the sides of the tablet since the study involved dissolution from only one face of the solid. Dowel pins allowed correct positioning of the tablet within the column.

The dissolution column was filled with distilled water, taking care to avoid any air bubbles, and placed in an environmental chamber consisting of an oven³ converted to a glove box. The temperature in the glove box was set at $30 \pm 0.05^\circ$ using a certified thermometer (NBS) and was maintained at $\pm 0.003^\circ$ by using a 250-w. heater connected to an actuated proportional temperature controller⁴ through a rheostat. The fan motor responsible for air

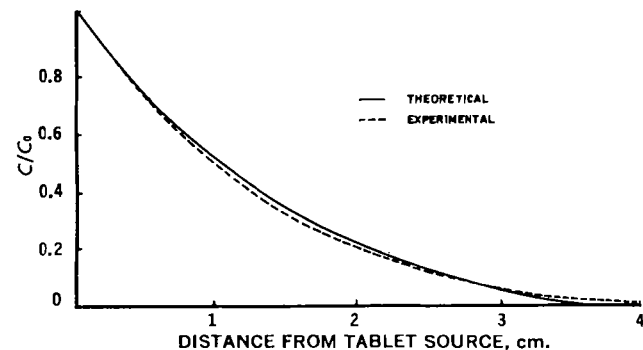


Figure 4—Comparison of experimental diffusion profile with that predicted by Eq. 4 for the 30-hr. time period.

³ Hotpack model 1206.

⁴ Thermonitor model St., Sargent Welch Scientific Co., Skokie, Ill.

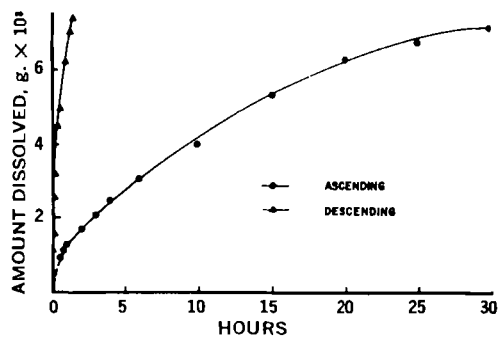


Figure 5—Comparison of the amount of *m*-acetotoluide dissolved in ascending and descending dissolutions.

circulation was mounted externally to the chamber to eliminate vibration.

At time $t = 0$, the tablet in the slide was moved into contact with the solvent. After the desired time period, the compartments were closed and the contents of each compartment were assayed spectrophotometrically for *m*-acetotoluide at 238 nm.

Equation 4 is theoretically correct for systems that are considered to be semiinfinite in length. The semiinfinite nature of the dissolution column employed in this study may be determined by rearrangement of the Einstein formula (21) to give:

$$t = \frac{x^2}{(2D)^{1/2}} \quad (\text{Eq. 7})$$

The 42-cm. column would no longer be considered semiinfinite after approximately 1750×10^6 sec. (5.5 years). The maximum time period employed in this study was 30 hr.

RESULTS AND DISCUSSION

Dissolution in Ascending Model—The ascending model orients the solid surface, and hence the solid-liquid interface, beneath the column of liquid into which dissolution is occurring. A comparison between the experimental amount dissolved and that predicted theoretically by Eq. 4, assuming a saturated solution exists at the solid-liquid interface, is shown in Table I and the relationship between an experimental and theoretical concentration profile is shown in Fig. 4. The excellent agreement between the experimental concentration and the concentrations predicted theoretically by Fick's second law leaves little doubt that, under the conditions of the ascending model, the dissolution process is controlled by diffusion of the solute from a saturated layer adjacent to the solid surface. In this case, the mass transfer step, diffusion, is slow compared to the interfacial solvation at the solid surface.

Diffusion is defined as the random movement of molecules from a region of high concentration to a region of lower concentration in a direction upward through the gravitational field. The restricted geometry of the ascending dissolution column, in which precision temperature control eliminates convection currents, permits only random molecular movement upward through the gravitational field, thereby assuring that diffusion is the only mass transfer process operable. Since solute diffusion is a very slow mass transfer

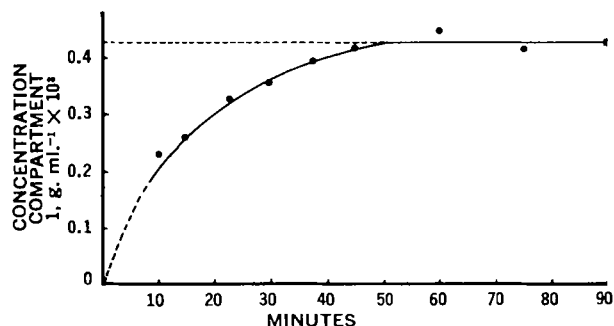


Figure 6—Change in concentration in Compartment 1 of the diffusion column with time.

Table II—Comparison of Calculated and Experimental Values Based on the Effective Interfacial Concentration at $t = 0$

Minutes	Calculated Amount Dissolved ^a , g. $\times 10^3$	Experimental Amount Dissolved, g. $\times 10^3$	Percent Deviation ^b
10.0	1.1475	1.1927	-3.07
15.0	1.4898	1.4502	+2.66
22.5	2.5676	2.6697	-3.98
30.0	3.2182	3.2262	-0.25
37.5	4.3527	4.4168	-1.47
45.0	4.4570	4.5373	-1.80
60.0	6.2032	6.5338	-5.33
75.0	6.6305	6.9467	-4.77
90.0	7.1948	7.4670	-3.78

^a Obtained by numerical integration, Fig. 7, using the effective interfacial concentration of 0.425×10^3 g. ml.⁻¹. ^b Deviation of experimental from calculated values.

process, the experimental observation that the solvation of the solid was faster than molecular diffusion in the ascending column was not unexpected. However, most dissolution processes do not occur under the restricted condition of solute movement inherent in the ascending model; this model must be considered a specific case of a more general phenomenon in which the mass transfer of solute following dissolution is not restricted to molecular movement by diffusion.

Dissolution in Descending Model—While predictions based on Fick's law of diffusion accurately describe solute concentrations developed in an ascending dissolution column, any deviation in the model system produces effects which cannot be attributed to molecular diffusion alone. In the descending model, the solid surface and solid-liquid interface are at the top of the liquid column and the solute moves in a downward direction following dissolution. From a comparison of the amount dissolved as a function of time (Fig. 5), it easily can be seen that the dissolution rate of *m*-acetotoluide was much faster in the descending model than in the ascending model. Obviously, in the descending model, molecular diffusion cannot be contributing substantially to the mass transfer of the solute and other dynamic factors must be considered.

Because the mass transfer rate has become quite fast, as evidenced by Fig. 5, it is again important to consider the relative magnitudes of the mass transfer and interfacial rates in the dissolution process. Evidence for assuming that the solvation rate of the solid, or the interfacial rate, is slower than the mass transfer rate when dissolution from the solid surface occurs in the descending direction is presented in Fig. 6. Figure 6 is a plot of the solute concentration in the first compartment adjacent to the solid surface as a function of time. A concentration is obtained which is apparently in equilibrium with the concentration at the solid surface. This concentration, 4.25×10^{-4} g. ml.⁻¹, was interpreted as being the effective concentration existing at the solid-liquid interface. Using this value of the effective interfacial concentration to calculate the amount dissolved from the area under the curve produced excellent agreement with the experimentally determined amount dissolved (Table II).

An examination of the concentration gradients developed in the descending column (Fig. 7) reveals the presence of a solute front traveling through the column, as evidenced by an abrupt drop in

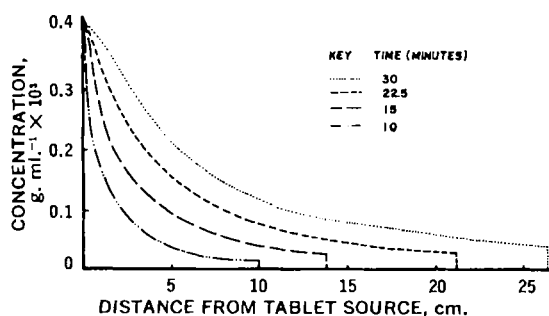


Figure 7—Solute concentration gradients developed in the descending dissolution column as a function of time.

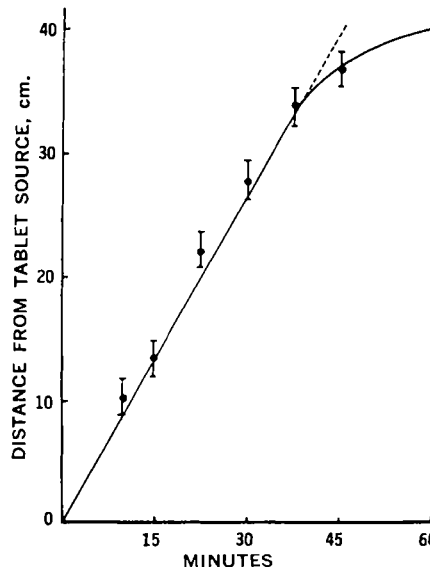


Figure 8—Relationship between distance of solute front from tablet source and time for dissolution in the descending column.

solute concentration at some time-dependent distance from the solid surface. The velocity at which the solute front moves can be determined from a plot of the distance at which the concentration drop occurs as a function of time (Fig. 8). The velocity of the solute front moving through the column, calculated as the slope of Fig. 8, was found to be 1.267×10^{-2} cm. sec.⁻¹. The presence of this finite solute front requires that consideration be given to a mass transfer model which does not involve the asymptotical approach to zero concentration implicit in the solution to the diffusion equation (Eq. 4).

Scheidegger (22) developed a theoretical treatment of fluid flow through porous media based on a random-walk model with autocorrelation. Autocorrelation assumes that there is a correlation between molecular movement in subsequent time steps but that correlation does not exist between nonadjoining movements. This is in contrast to molecular diffusion in which no correlations exist and the molecular movement is completely random. The latter concept, random-walk without autocorrelation, gives rise to the common diffusivity equation:

$$\frac{\partial c}{\partial t} = D' \frac{\partial^2 c}{\partial x^2} \quad (\text{Eq. 8})$$

in which D' is a dispersion coefficient rather than a molecular diffusion coefficient and is dependent on fluid viscosity and fluid velocity (22). The dispersion coefficient, D' , reduces to the molecular diffusion coefficient at low fluid velocities but increases with increasing velocity of fluid flow because of increased mixing caused by the connecting flow channels in the porous medium (23). Solutions of Eq. 8 predict the asymptotic solute front characteristic of diffusion equations rather than the finite solute front observed experimentally. The inclusion of autocorrelation in the random-walk model, however, gives rise to the telegraph equation:

$$A \frac{\partial^2 C}{\partial t^2} + \frac{\partial C}{\partial t} = D' \frac{\partial^2 C}{\partial x^2} \quad (\text{Eq. 9})$$

instead of the diffusivity equation. In this telegraph equation, D' is

Table III—Values of Coefficient, A , and Dispersion Coefficient, D' , Calculated from Experimental Data

Minutes	A , sec. $\times 10^{-2}$	D' , cm. ² /sec. $\times 10^3$
10.0	1.36	2.2
15.0	1.70	2.7
22.5	2.50	4.0
30.0	2.50	4.0
Average	2.01	3.3

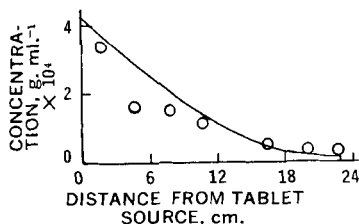


Figure 9—Comparison of theoretical (—) and experimental (O) concentration gradients for descending dissolution at the end of 30 min. The theoretical concentration is that predicted by Eq. 12 with $A = 200$ sec. and $v = 1.267 \times 10^{-2}$ cm./sec.

again the dispersion coefficient, and the coefficient A is related to the gradient of pressure in the column (22) and can best be determined experimentally as described below. The solution to Eq. 9 for the boundary and initial conditions of the descending column:

boundary conditions
 $C = C_i = 4.25 \times 10^{-4}$ g. ml. $^{-1}$ $x = 0, t > 0$ (Eq. 10)

initial conditions
 $C = 0$ $x > 0, t = 0$ (Eq. 11)

was given by Goldstein (24) as:

$$C = C_i \left\{ 1 - \frac{e^{-t/2A}}{2Av} \int_0^x \left[I_0(Y) + \frac{t}{2A} \frac{I_1(Y)}{Y} \right] dx \right\} \quad (\text{Eq. 12})$$

where I_0 and I_1 are the "Bessel functions of imaginary argument:"

$$I_0(Y) = \sum_{m=0}^{\infty} \frac{(1/2 Y)^{2m}}{(m!)^2} \quad I_1(Y) = \sum_{m=0}^{\infty} \frac{(1/2 Y)^{2m+1}}{m!(m+1)!} \quad (\text{Eq. 13})$$

and:

$$Y = \frac{(v^2 t^2 - x^2)^{1/2}}{2Av} \quad (\text{Eq. 14})$$

The velocity term, v , in Eqs. 12–14 is the velocity of the solute front and is related to the dispersion coefficient, D' , by the equation (25):

$$D' = Av^2 \quad (\text{Eq. 15})$$

Equation 12 has a discontinuity at $x = vt$ with a jump of $C_i \exp(-t/2A)$, representing the concentration of the advancing solute front. Therefore, the values of the coefficient A can be determined experimentally from the relationship:

$$C_{\text{solute front}} = C_i e^{-t/2A} \quad (\text{Eq. 16})$$

and are given in Table III. From these values, the magnitude of the dispersion coefficient can easily be calculated (Table III). The average dispersion coefficient calculated for the solute *m*-acetotoluide, 3.3×10^{-2} cm. 2 /sec., was much greater than the molecular diffusion coefficient for this solute, 1.1×10^{-5} cm. 2 /sec. However, it differs by only one power of 10 from that calculated by Aronofsky and Heller (26), 3×10^{-3} cm. 2 /sec., for a similar flow velocity of a liquid in a porous medium.

The telegraph equation, Eq. 9, has been suggested to describe fluid flow through porous media. To make comparisons, such as that involving the dispersion coefficients, between a system consisting of liquid flow through porous media and a solute flowing through a stationary liquid, the application of Eq. 9 and the relationship of liquid flow through porous media to the experimental design of the dissolution column must be considered. The present dissolution system, in which the hydrated solute molecules flow through a stationary liquid solvent, may be considered analogous to the flow of a liquid through a porous bed. The fluid elements and holes which comprise the liquid state can act in the same manner in channeling the movement of the solvated solute molecules as does the solid porous material in channeling the flow of a pure liquid. Figure 9 shows the correlation between the theoretical concentration predicted by Eq. 12 and the experimentally determined concentrations. It is evident from Fig. 9 that the mathematical treatment of solute flow through a stationary liquid as a random-walk model with autocorrelation adequately describes the concentration gradient developed during dissolution in the descending model. The solvent then appears to act as a stationary porous barrier to the flow of solute, providing perhaps an even greater physical barrier than

porous media itself as evidenced by the experimental points below the theoretical curve.

More important from the standpoint of understanding the mechanism of dissolution, however, is the fact that the theoretical concentration curve arising from the autocorrelation model in Fig. 8 was developed using the effective interfacial concentration, 4.25×10^{-4} g. ml. $^{-1}$, which illustrates the validity of the interfacial concentration determined experimentally in the dissolution column model. Since *m*-acetotoluide is probably representative of a great many organic compounds, it is tempting to conclude that the presence of an interfacial concentration, less than saturation, is a general phenomenon in those cases in which dynamic forces, other than molecular diffusion alone, are responsible for solute mass transfer. Such would be the case in most real situations in which a solid is dissolving, as indicated by the specific requirements for pure molecular diffusional transport. Additional studies are required to justify the hypothesis of interfacial control of solid dissolution as a general phenomenon; however, in consideration of these present results and their implications, further assumptions that a particular dissolution process is diffusion controlled should be carefully examined and justified experimentally.

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