

Evaluation of a Convective Diffusion Drug Dissolution Rate Model

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Abstract □ A recently introduced drug dissolution rate model based on convective diffusion was evaluated by experimentally determining dissolution rates. Alkyl *p*-aminobenzoates were used as the test compounds in a dissolution cell which promoted laminar flow of the liquid past the dissolving surface. The parameters evaluated were diffusivity, solubility, rate of shear, dissolving surface shape, and orientation of the surface relative to flow. The agreement between theory and experiment was quite satisfactory with respect to the functional dependence of the rate on these parameters as well as the actual magnitude of the rates.

Keyphrases □ Dissolution—evaluation of a convective diffusion drug dissolution rate model, evaluation of diffusivity, solubility, rate of shear, dissolving surface shape, and orientation of surface relative to flow □ Diffusion—evaluation of a convective diffusion drug dissolution rate model, alkyl *p*-aminobenzoates, discussion of various parameters □ Convective diffusion—drug dissolution rate model, experimental evaluation using dissolution rates of alkyl *p*-aminobenzoates

A convective diffusion model was introduced recently (1) to describe the phenomenon of drug dissolution rate. The equations given for the rate of dissolution, R , were:

$$R = 0.808D^{2/3}C_0\alpha^{1/3}bL^{2/3} \quad (\text{Eq. 1})$$

for a rectangular surface of width b and length L (in the direction of flow), and:

$$R = 2.157D^{2/3}C_0\alpha^{1/3}r^{5/3} \quad (\text{Eq. 2})$$

for a circular surface of radius r . In these equations, D is the diffusivity, C_0 is the solubility, and α is the rate of shear over the dissolving surface.

The experimental apparatus used to evaluate the applicability of the model, however, was not ideal with respect to one principle upon which the model was based. In particular, the tangential annular flow system did not facilitate the development of a well-behaved hydrodynamic boundary layer. The present report describes experimental studies on drug dissolution rates utilizing a flow system designed to produce a laminar layer over the dissolving solid. The data are evaluated in terms of the functional dependence of the experimental rate on the various parameters in Eqs. 1 and 2.

EXPERIMENTAL

A schematic diagram of the dissolution cell employed is shown in Fig. 1. It consists of two rectangular transparent plastic plates, which are fastened together by bolts and wing-nuts. The top plate has a liquid entry port on one end, which opens into a rectangular channel cut into the underside of the plate. The bottom plate is recessed to accommodate the die employed in the previous study (1). When installed, the surface of the die is coplanar with the surface of the bottom plate, and the die may be oriented with either the

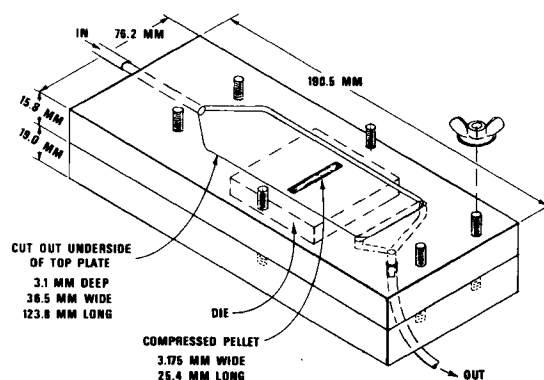


Figure 1—Schematic diagram of the dissolution cell.

long or short axis of the rectangular dissolving surface parallel to the direction of liquid flow. For exposing circular surfaces, the plastic die employed in the previous study was used. The bottom plate also has a vertical duct, which serves as an outlet for the flowing liquid.

As in the previous study (1), a compressed pellet of an alkyl ester of *p*-aminobenzoic acid was prepared in the metal or plastic die. The die was then placed in the recess of the lower plate, and the dissolution cell was assembled. Silicone grease was applied at the points of contact between the plates to ensure a watertight seal. The cell was positioned on a leveled, vibration-free platform and distilled water (25°C) was pumped through the cell at a set flow rate with an infusion syringe pump². The effluent liquid was assayed spectrophotometrically³ at 285 nm for the ester. The ester concentration, together with the flow rate, permitted calculation of the experimental dissolution rate.

The solubilities of the methyl through pentyl esters of *p*-aminobenzoic acid were determined by equilibrating an excess amount of each with distilled water for 2 days at 25°C. After filtration and appropriate dilution, the concentration was determined spectrophotometrically.

RESULTS AND DISCUSSION

The dissolution cell employed was designed with a relative long liquid flow channel to promote the development of laminar liquid flow in the region of the dissolving solid. To verify that was the case, the flow visualization technique used before (1), involving a water-soluble dye dispersed in polyethylene glycol 600 was employed. The dissolved dye displayed a wedge-shaped pattern, which flowed over the dissolving surface as desired. The liquid flow appeared to be uniform and homogeneous.

The dependence of the experimental dissolution rate on solubility was studied by determining the rates for the methyl through pentyl esters of *p*-aminobenzoic acid. The rates were determined with the long axis of the dissolving surface perpendicular to the direction of liquid flow and with a flow rate of 5.5 ml/min. The data are shown as a log-log plot of dissolution rate versus solubility, Fig. 2; this plot yields a least-squares slope of 0.978 and a correlation coefficient of 0.999. This slope corresponds satisfactorily with the slope of unity predicted by Eq. 1, assuming the diffusivities be essentially constant.

² Model 220, Sage Instruments, Cambridge, MA 02139

³ Zeiss recording spectrophotometer DMR 21, Oberkochen/Wuertt, W Germany.

* Plexiglas.

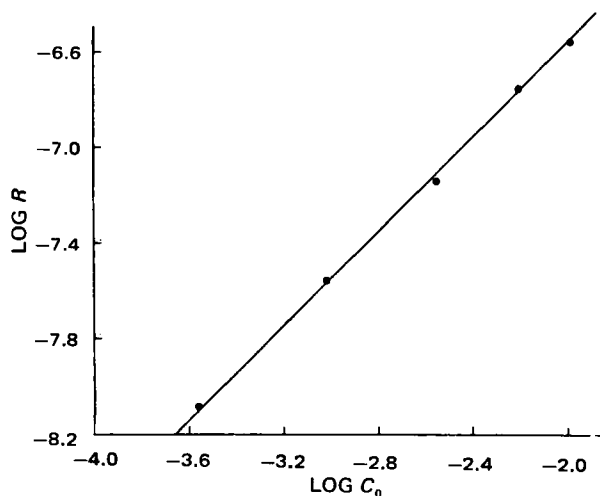


Figure 2—Log-log plot of dissolution rate as a function of solubility. $\log C_0$ for the methyl ester is -1.98 ; $\log C_0$ values decrease sequentially from the methyl to the pentyl ester.

The effect of the rate of shear can be demonstrated by measuring the dissolution rate at various rates of flow. If the edge and end effects are neglected, the velocity profile for flow in the dissolution cell, *i.e.*, flow between two parallel planes, is parabolic in nature (2). If the limiting slope of the velocity profile at either plane is taken to be the rate of shear, then it can be shown that (see Appendix):

$$\alpha = \frac{6Q}{H^2W} \quad (\text{Eq. 3})$$

where Q is the volumetric flow rate, and H and W are the height and width, respectively, of the channel in the dissolution cell. Inasmuch as α is directly proportional to Q in Eq. 3, a plot of $\log R$ versus $\log Q$ should give a straight line with a slope of ~ 0.33 according to Eq. 1. Such a plot is shown in Fig. 3 for ethyl *p*-aminobenzoate with the long axis of the dissolving surface perpendicular to (upper curve) and parallel with (lower curve) the direction of flow. The least-squares slope of the upper curve is 0.336 with a correlation coefficient of 0.999, and the corresponding values for the lower curve are 0.359 and 0.997. The agreement between theory and experiment with respect to the functional dependence of the dissolution rate on the rate of shear is quite satisfactory.

The convective diffusion equations are based on the fluid having a uniform density; *i.e.*, natural convection is not considered. To determine whether density gradients in the vicinity of the dissolving surface might be present and influence the experimental rates in the present studies, the experiments at different flow rates were repeated with the dissolution cell inverted. The data from these experiments are shown in Fig. 4. It can be seen that natural convection has an influence on the dissolution rate at relatively slow flow rates and when the long axis of the dissolving surface is parallel to the direction of flow (lower curve). The slopes and correlation coefficients of the upper and lower lines in Fig. 4 are 0.342 and 0.998 and 0.331 and 0.994, respectively, and are in good agreement with the theoretical slope of 0.333. The first four points from the lower set of data were omitted in the statistical calculations.

The relative position of the two lines in each set of data (Figs. 3 and 4) is due to the orientation of the rectangular dissolving surface with respect to the direction of flow. The die was designed with a length-to-width ratio of the dissolving surface of 8:1. As such, the convective diffusion theory (Eq. 1) would predict a two-fold increase in dissolution rate in going from an orientation having the long axis of the dissolving surface parallel to the direction of flow to that having the long axis perpendicular. The distance between the lines at about the midrange of the data (\log flow rate = 1.0) is 0.294 in Fig. 3 and 0.272 in Fig. 4. This correlation between theory and experiment is quite satisfactory inasmuch as Eq. 1 predicts the difference between the lines on these plots of 0.301 (*i.e.*, \log of 2). This effect emphasizes the importance of including convection along with diffusion when considering drug dissolution

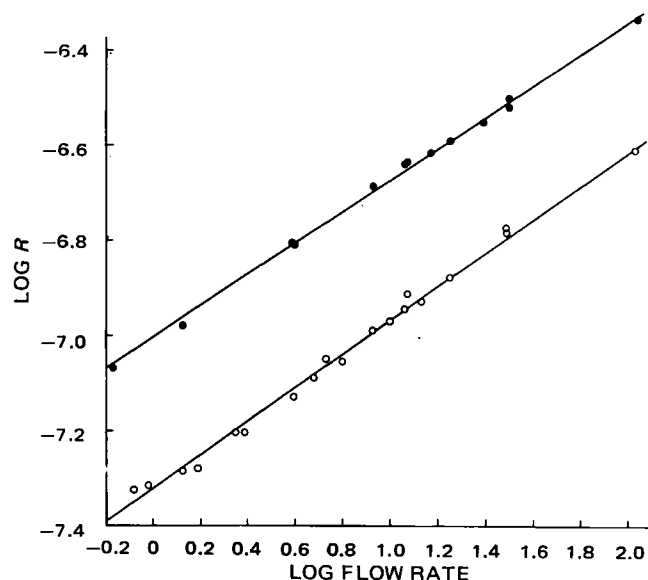


Figure 3—Log-log plot of dissolution rate as a function of fluid flow rate.

phenomena. To consider the dissolution rate simply as proportional to area is inadequate.

A further evaluation of the relationship between the geometry of the dissolving surface and the dissolution rate was accomplished by determining the dissolution rates from the surface of a series of circular disks of ethyl *p*-aminobenzoate. Equation 2 indicates that a log-log plot of dissolution rate versus radius would be linear with a slope of ~ 1.67 . Data from this series of experiments with a flow rate of 24 ml/min is shown in Fig. 5; the plot yields a least-squares slope of 1.619 and a correlation coefficient of 0.999. Additional data (not shown) having a flow rate of 14.7 ml/min gave a slope of 1.656 with a correlation coefficient of 0.998. The functional dependence of the dissolution rate on the radius as predicted by Eq. 2 is thus borne out by experiment.

The convective diffusion equations indicate that the dissolution rate is a function of the diffusivity to the two-thirds power. A convenient method of experimentally studying the dependence on the diffusion coefficient is to carry out experiments using a solubilized system (3). In this method, it is assumed that the free and solubilized solutes are in equilibrium in any small volume so that the sol-

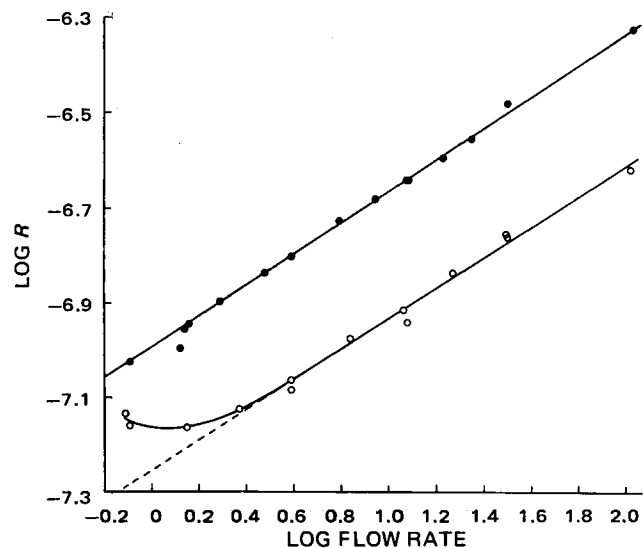


Figure 4—Log-log plot of dissolution rate as a function of fluid flow rate with the dissolution cell inverted.

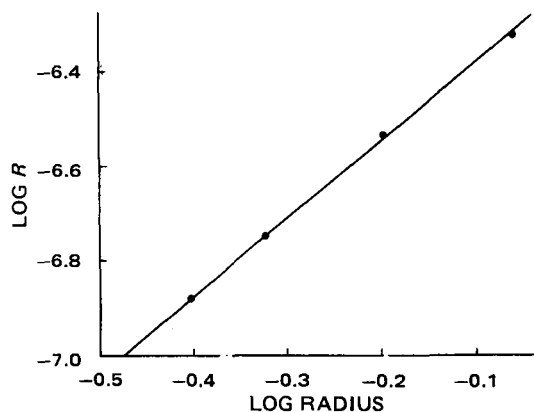


Figure 5—Log-log plot of dissolution rate as a function of tablet radius.

ubility and diffusivity measured on a macroscopic level may be employed as the effective parameters in a theoretical treatment.

Dissolution rate experiments were carried out with disks ($r = 0.476$ cm) of ethyl *p*-aminobenzoate at 37° and a flow rate of 14.9 ml/min. The liquid medium was water containing various concentrations (0–6%) of polysorbate 80, a system for which the effective solubility and effective diffusion coefficient of ethyl *p*-aminobenzoate have been determined (3). The data are shown in Fig. 6 as a plot of $\log R/C_0$ versus $\log D$, which yields a least-squares slope of 0.706 and a correlation coefficient of 0.990. These values are in satisfactory agreement with convective diffusion theory in that Eq. 2 indicates a slope of 0.667.

A dashed line of slope 1 is included in Fig. 6 to permit visual comparison of the experimental data with the expected relationship according to the commonly employed stagnant diffusion layer model (1). It is apparent that the convective diffusion model more accurately describes the role of diffusion in the process of dissolution into a moving liquid.

These considerations have focused primarily on the functional dependence of the dissolution rate on solubility, diffusivity, rate of shear, and geometry and orientation of the dissolving surface. To complete this evaluation, the actual value of a dissolution rate is calculated, based on independently determined parameters, and compared with the corresponding experimental dissolution rate. For this purpose, the rate corresponding to the first point (no polysorbate) on Fig. 6 is used. The diffusivity and solubility were reported (3) to be 9.86×10^{-6} cm²/sec and 7.27×10^{-6} mole/cm³, respectively. The rate of shear is calculated to be 4.25 sec^{-1} with Eq. 3 by substituting in the dimensions of the dissolution cell and the flow rate (14.9 cm³/min). These values, together with the dissolving surface radius of 0.476 cm, are substituted into Eq. 2 to give a theoretical dissolution rate of 2.03×10^{-7} mole/min. The experimentally determined dissolution rate for these conditions is 2.25×10^{-7} mole/min. The ability of the model to predict the dissolution rate to within 10% of the actual value inspires considerable confidence in the convective diffusion approach to describing drug dissolution rate.

The convective diffusion approach enables one to describe drug dissolution rates in terms of the fundamental processes of convection and diffusion. As discussed in Ref. 1, the model currently utilized to describe drug dissolution is the Noyes–Whitney equation, which includes the Nernst unstirred diffusion layer. This model is useful, but the general approach cannot account for such factors as agitation and the orientation of the surface relative to flow because convection is not included in the mathematical model.

The convective diffusion model considered in this report is also somewhat limited in that it describes dissolution under rather idealized conditions. Under these conditions, however, the model can quantitatively describe the effects of solubility, diffusivity, rate of shear (agitation), and geometry and orientation of the surface relative to flow. Any inability of the model to describe drug dissolution from tablets or other solid dosage forms will be primarily due to experimental conditions that differ from those assumed in the model, e.g., flow over a curved surface such that the boundary

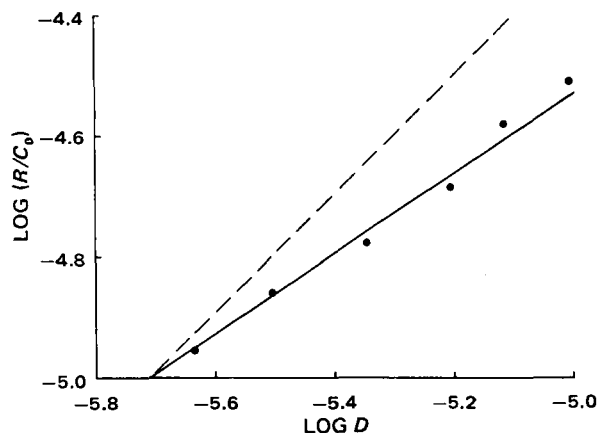


Figure 6—Log-log plot of (dissolution rate/solubility) as a function of diffusivity.

layer leaves the surface. The constant rate of shear was assumed in the model to retain a high degree of generality. It is recognized that the rate of shear over a surface can be more complex because of such conditions as end effects, distance downstream, curved surfaces, and natural convection.

APPENDIX

The flow pattern between two parallel planes a distance H apart (in the Z direction) is described by a parabolic function of Z . If the edge and end effects are ignored, the velocity function, v_x , for flow in a cell of width W and the length l is given by:

$$v_x = \frac{\Delta P H^2}{8 \mu l} \left[1 - \left(\frac{2Z - H}{H} \right)^2 \right] \quad (\text{Eq. A1})$$

where ΔP is the pressure difference over l , and μ is the viscosity (2). The volumetric flow rate, Q , is given by (2):

$$Q = \frac{\Delta P H^3 W}{12 \mu l} \quad (\text{Eq. A2})$$

Differentiating Eq. A1 with respect to Z yields:

$$\frac{dv_x}{dz} = \frac{\Delta P (H - 2Z)}{2 \mu l} \quad (\text{Eq. A3})$$

This differential is the rate of shear. In the vicinity of the dissolving surface, the rate of shear, α , may be considered to be constant and is thus obtained by substituting $Z = 0$ into Eq. A3. If this result is combined with Eq. A2, an equation relating α with the volumetric flow rate results:

$$\alpha = \frac{6Q}{H^2 W} \quad (\text{Eq. A4})$$

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