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# Influence of Fluid Motion in Dissolution-Rate Determinations

## S. BISAILLON* and R. TAWASHI

**Abstract** □ A method is presented for dissolution-rate studies based on three-dimensional movement of the dissolution cell around its axis. By using this agitating system, the solute flux from benzoic acid and iodine disks was studied at different flow velocities. The results obtained were compared with the rotating-disk method. The dependence of dissolution rate on the power of flow velocity and on the activation energy was determined experimentally. The Reynolds and Peclet numbers were calculated from the parameters of the experiments, and the values obtained were compared with theory for laminar and turbulent flow.

**Keyphrases** □ Dissolution rates—effect of fluid motion and activation energy, Turbula shaker mixer and rotating-disk methods compared □ Fluid motion—effect on dissolution rates □ Rotating-disk method—compared with Turbula shaker mixer method, influence of flow velocity and activation energy on dissolution rates □ Turbula shaker mixer—dissolution-rate determinations, compared to rotating-disk method

Dissolution is the rate-determining step of numerous mass-transfer processes such as catalysis, adsorption, extraction, and drug absorption. Modern hydrodynamic concepts such as theories of turbulent or laminar flow and boundary layer (1–4) are now being used in the solving of problems involved with systems of hydromechanical equations. Information on the effect of agitating intensity in dissolution test procedures is scarce and insufficient (5–8) for developing a routine control procedure. An unexpected variable (vibration effect) in the latest USP and NF rotating-basket dissolution tests was reported by Beyer and Smith (9).

The present publication deals with the effect of speed of agitation on the rate of solute transfer in geometrically similar systems. The dissolution behavior in a new

**Table I—Equations for Evaluation of the Dimensionless Reynolds and Peclet Numbers**

| | |
|---|---|
| Reynolds' number = | $\dfrac{\text{momentum transfer by turbulent flow}}{\text{momentum transfer by molecular transport}}$ |
| Peclet's number = | $\dfrac{\text{mass transfer by convective diffusion}}{\text{mass transfer by molecular diffusion}}$ |

$$N_{RE} = \frac{UL^2}{\nu} = \frac{UL^2\rho}{\eta} \quad : \quad N_{PE} = \frac{UL^2}{D}$$

agitating system based on a three-dimensional movement of the dissolution cell around its axis was tested experimentally and compared with data obtained from the rotating disk. The data obtained could be used to predict the quantitative performance of the agitating system and to find a better design for a dissolution test procedure. The choice of the agitating system described in this study is based on previous experience in solid mixing and in solubility determinations. Solid–solid mixing was improved remarkably by using this agitating system (10), and in solubility studies of poorly soluble drugs, the equilibrium was reached after a shorter period of time than with other conventional methods (11).

## THEORETICAL CONCEPTS

The analysis of the behavior of flows by similarity theory is now widely applied. Even if geometrical similarity, identity of boundary conditions, and Reynolds' number are sufficient conditions for the similarity of two flows, only a few systems have been satisfactorily solved from their cylindrical convective diffusion equation.

Taking into consideration the streamlines at the surface of a rotating disk serving as the reaction site, Cochran (12) developed the cylindrical convective diffusion equation for the rotating disk, from which Levich (1, 13) came to the following expression:

$$R = kD^{2/3}\nu^{-1/6}\omega^{1/2}c_s \qquad \text{(Eq. 1)}$$

It can be rearranged to give:

$$K_T = kD^{2/3}\nu^{-1/6}\omega^{1/2} \qquad \text{(Eq. 2)}$$

The significance of each term in these equations is listed in the *Appendix* at the end of this article.

These equations refer to the laminar flow regime, which can be defined as the steady advance of the fluid in a separate layer. When one passes to the turbulent regime, not necessarily by increasing

**Table II—The Reynolds ($N_{RE}$) and Peclet ($N_{PE}$) Numbers as Calculated for the Turbula Shaker Mixer and for the Rotating Disk**

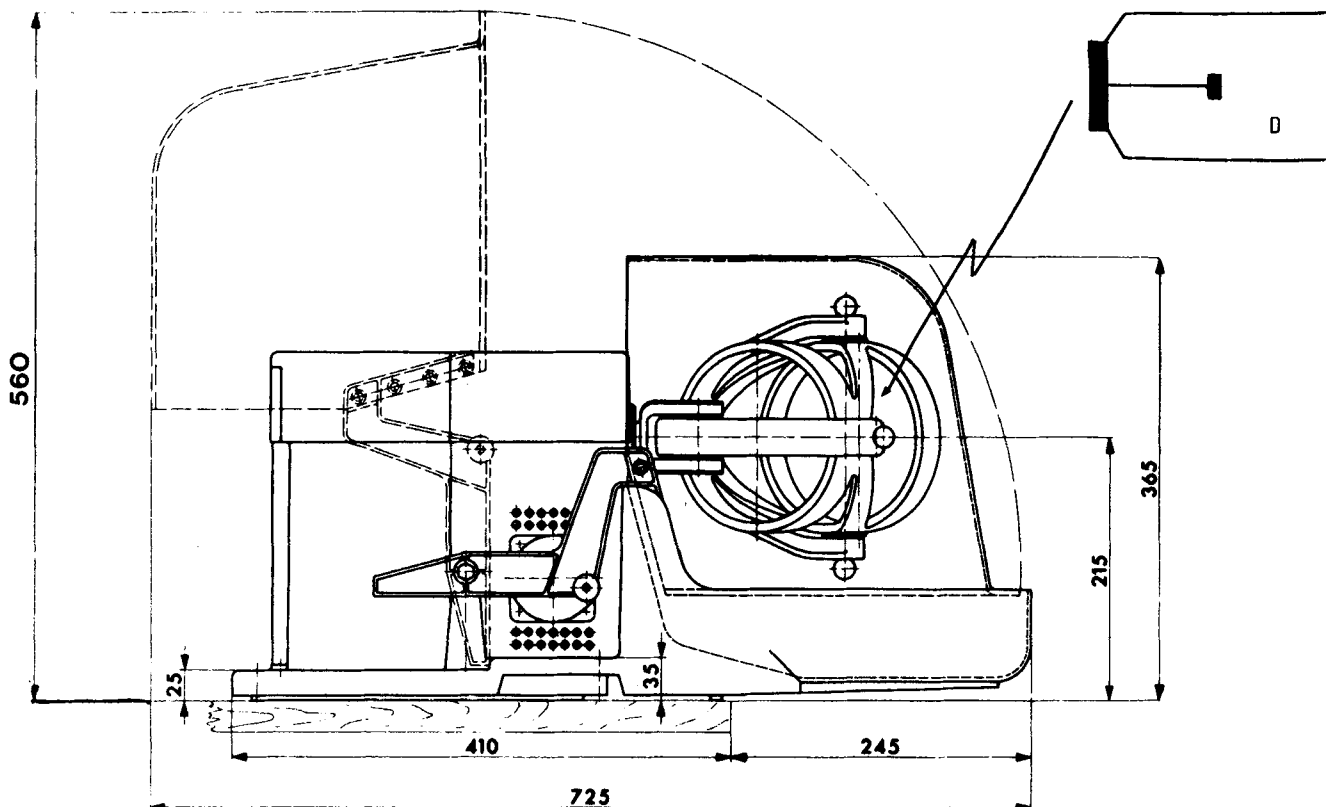| | $N_{RE}$ | | $N_{PE}$ | |
|---|---|---|---|---|
| Temperature | Rotating Disk | Turbula | Rotating Disk | Turbula |
| 25° | 200 | 27,000 | $0.20 \times 10^5$ | $27.7 \times 10^6$ |
| 37° | 250 | 34,300 | $0.15 \times 10^5$ | $20.7 \times 10^6$ |

**Figure 1**—*Turbula shaker mixer (dimensions in millimeters). D is the dissolution cell.*

the speed of rotation, one is in the presence of unsteady chaotic motion in which the flow velocity fluctuates about some average value. Levich (1, 13) found that when the flow was laminar, the exponent attributed to the speed of rotation was 0.5; when one passes into turbulent regime, the exponent passes to unity.

Similarity theory, along with the analysis of variables in well-defined equations, often refers to dimensionless analysis. From the cylindrical convective diffusion equations, two dimensionless groups could be used in this respect. The Reynolds number represents the momentum transfer of the fluid by turbulence divided by molecular transport, and the Peclet number represents the ratio between mass transfer in the fluid by convective diffusion and molecular diffusion (Table I). In this table, $U$ = speed of rotation in centimeters per second, $L$ = diameter in centimeters, $v$ = kinematic viscosity where $v = \rho/\eta$ and $\rho$ = density in grams per milliliters and $\eta$ = viscosity in poises, and $D$ = diffusion coefficient in square centimeters per second. Values of the Reynolds number, which indicate the passage from laminar to turbulent flow, are in the region of $10^4$–$10^5$. No exact value can be given. Geometrical conditions, especially in the critical region, can contribute markedly to produce turbulence. The Peclet number for liquids, in which $D$ is in the order

of $10^{-5}$–$10^{-6}$, is generally in the order of $10^5$–$10^5$. Higher value show an improvement in mass transfer in the solution.

The activation energy of the transport process can also confirm the presence of laminar or turbulent flow in a system. The dependence of the dissolution-rate constant on the temperature is related to the activation energy of the process by:

$$K_T = Ae^{-Ea/T} \qquad \text{(Eq. 3)}$$

and:

$$\log K_T = \log A - E_a/T \qquad \text{(Eq. 4)}$$

A plot of $\log K_T$ versus $1/T$ gives a linear curve in which the slope represents the activation energy of the process. Nogami *et al.* (3)
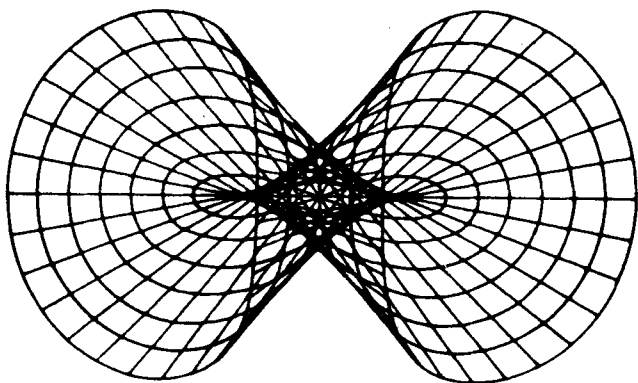


**Figure 2**—*Path of the motion traveled by equidistant points on the container axis (plane projection vertical to transmission shafts).*
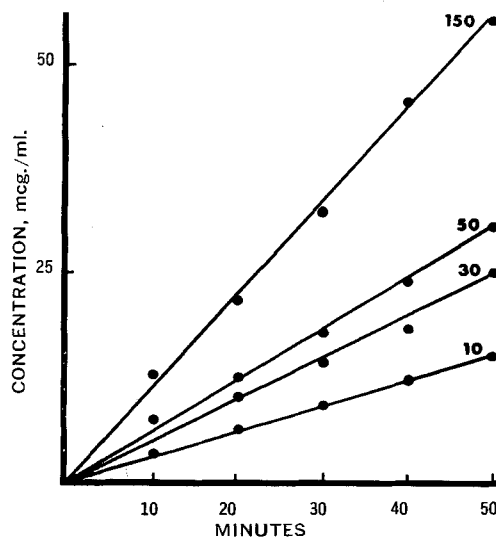


**Figure 3**—*Dissolution of benzoic acid by the rotating-disk method as a function of time at 37° and at different speeds of rotation.*

| Temperature | Diffusion Coefficient, cm.²/sec. | Solubility $(C_s)$, g./l. | Dissolution Rate $(R)$, g./cm.²/sec. Rotating Disk | Dissolution Rate $(R)$, g./cm.²/sec. Turbula | $K_T(R/C_s)$, cm./sec. Rotating Disk | $K_T(R/C_s)$, cm./sec. Turbula |
|---|---|---|---|---|---|---|
| 20° | $7.573 \times 10^{-6}$ | 2.75 | — | $6.20 \times 10^{-6}$ | — | $2.214 \times 10^{-3}$ |
| 30° | $9.830 \times 10^{-6}$ | 3.74 | $3.38 \times 10^{-6}$ | — | $0.904 \times 10^{-3}$ | — |
| 37° | $11.591 \times 10^{-6}$ | 4.43 | $4.52 \times 10^{-6}$ | $14.32 \times 10^{-6}$ | $1.020 \times 10^{-3}$ | $3.233 \times 10^{-3}$ |
| 45° | $13.794 \times 10^{-6}$ | 5.62 | $6.50 \times 10^{-6}$ | $21.40 \times 10^{-6}$ | $1.157 \times 10^{-3}$ | $3.808 \times 10^{-3}$ |

reported values of 3.3–3.5 kcal./mole for the energy of activation in rotating-disk experiments in the laminar region, with a rotating velocity of 60–120 r.p.m. When the flow was in the turbulent region, values of 4.4–4.6 kcal./mole were reported by Levich (1). These considerations are increasingly important in examining the effect of fluid motion on dissolution rates and the effect of agitating intensity on other mass-transfer processes.

## MATERIALS AND METHODS

**Apparatus**—The essential features of the agitating system used in this study are the flow pattern and agitating intensity provided by the shaker mixer (Turbula shaker mixer[1]). The model used in this work is presented in Fig. 1. The fluid flow produced by this shaker is based on the principle of "inversion kinematics" developed by Schatz (14). The mixing vessel, a 2-l. cylindrical container, is subjected to a rhythmically pulsating three-dimensional movement. This movement is an alternative acceleration and retardation in which the potential energy resulting from the braking phase passes directly into the generation of the subsequent acceleration. Figure 2 demonstrates the path of motion traveled by equidistant points on the axis of the mixing chamber.

**Dissolution-Rate Studies**—The materials investigated were benzoic acid and iodine. Both pure substances were compressed into a disk, 1.88 cm. in diameter, with a pressure of 50,000 p.s.i. The compressed disk was placed in a die at the center of the dissolution cell, and one of the flat surfaces was exposed to the dissolution medium.

When a given speed of rotation is imparted to the whole container, the drug disk rotates the same number of revolutions as the dissolution cell. The temperature of the dissolution medium was kept

constant during the dissolution-rate studies by a specially designed, thermostatically controlled cabinet around the shaking system. The dissolution medium was 1500 ml. of 0.1 $N$ HCl to assure sink conditions in the study of dissolution behavior of the test substances. The 2-l. dissolution cell, with the same amount of 0.1 $N$ HCl, was used to study the dissolution of the test substances using the rotating-disk technique. In these experiments, temperature was regulated by a thermostatically controlled water bath, and the drug disk was rotated by a synchronized motor[2] at different speeds of rotation. The height of the centered drug disk from the bottom of the cell was the same in both the Turbula and in these experiments. Samples were withdrawn at different intervals of time, filtered, and analyzed spectrophotometrically[3].

## RESULTS AND DISCUSSION

A study of the effect of speed of rotation on the dissolution behavior of a benzoic acid compressed disk showed a marked difference in the rates between the two methods (Figs. 3 and 4). This difference became more evident when the log dissolution rate was plotted against the speed of rotation for the two processes (Fig. 5). Experimental values, computed from the work of Emanuel and Olander (15) on the dissolution of benzoic acid by the rotating disk, showed good agreement with the present findings. The two curves were parallel but they did not superimpose because of the different temperature used in the two studies. The slopes of these curves were calculated, and the values obtained corresponded to the exponents of the angular velocity in the Levich equation, the revolutions per minute being directly proportional to the distance (in centimeters per second) traveled by the disk. A value of 0.5 was calculated for both rotating-disk curves, while for the Turbula a value of approximately 1 was obtained (1.035). The value obtained indicates the passage of the flow from laminar to turbulent This change in the exponent of the speed of rotation was verified with iodine (Fig. 6) and the same relation was obtained: the exponent of the flow velocity was close to unity (0.908).

The dimensionless Reynolds and Peclet numbers were determined for the two methods. In calculating both these numbers, the
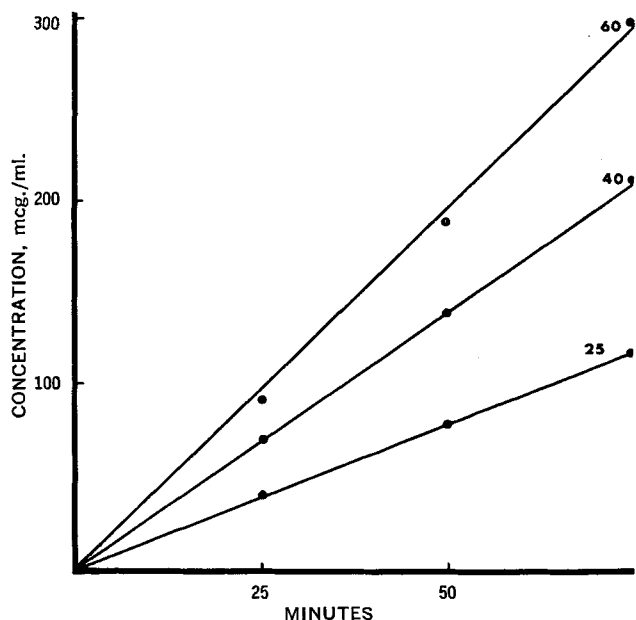
**Figure 4**—Dissolution of benzoic acid in the Turbula shaker mixer as a function of time at 37° and at different speeds of rotation.
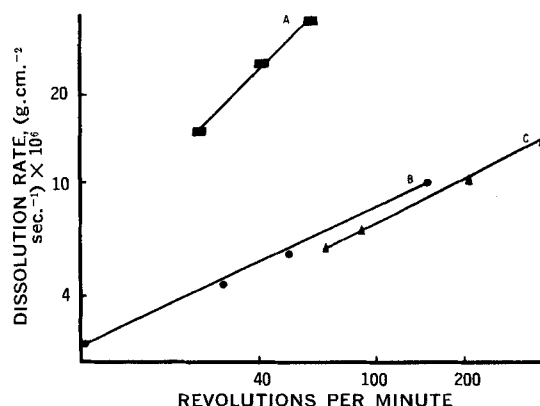
**Figure 5**—Comparison of the rate of dissolution of benzoic acid as a function of speed of rotation. A is the dissolution rate in the Turbula; B is the dissolution rate from the rotating-disk method; C is the dissolution rate computed from Reference 2.
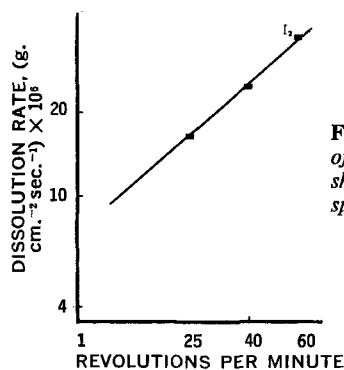
**Figure 6**—*Rate of dissolution of iodine at 37° in the Turbula shaker mixer as a function of speed.*

**Table IV**—Energy of Activation Computed from the Arrhenius Plot (Fig. 7) and Compared with Literature[a]

| Laminar Flow | | Turbulent Flow | |
|---|---|---|---|
| $E_A{}^1$ | $E_A{}^N$ | $E_A{}^2$ | $E_A{}^L$ |
| cal./mole | | cal./mole | |
| 3475 | 3500 | 4419 | 4600 |

[a] $E_A{}^N$ is the reported value by Nogami *et al.* (3); $E_A{}^L$ is the reported value by Levich (1); $E_A{}^1$ is the value obtained for the rotating-disk method; $E_A{}^2$ is the value obtained in the Turbula shaker mixer.

*L* (signification already mentioned) used was 1.88 cm. for the rotating disk and 22 cm., the diagonal of the moving dissolution cell, for the Turbula shaker mixer. It is apparent from Table II that at two different temperatures, a remarkable difference exists in the two processes. The Peclet and Reynolds numbers were 135 times greater for the Turbula apparatus than in the rotating-disk system. For the Turbula shaker, the Reynolds number obtained was in the critical region of the passage from laminar to turbulent regime, although the speed of rotation was only 30 r.p.m. As mentioned previously, the geometrical conditions favored the creation of chaotic motions; they reinforced each other instead of damping the turbulent eddies.

The effect of temperature on the dissolution-rate constant was further studied for the two processes. The diffusion coefficients at various temperatures were calculated from molar volumes (16); the solubilities, dissolution rates, and dissolution-rate constants were determined experimentally as a function of temperature (Table III). From these parameters and from an Arrhenius plot (Fig. 7), the activation energy for the dissolution processes was determined. The values obtained were compared with values reported in the literature for the laminar and turbulent regimes (Table IV). For the rotating disk, there is a good agreement between the value obtained and that reported by Nogami *et al.* (3). In the Turbula shaker mixer, comparison demonstrates that even at low revolutions per minute, the dissolution mass transfer has an activation energy consistent with the turbulent flow regime as mentioned by Levich (1).

In summary, the computation of the solute flux rate from the surface of a disk in the Turbula shaker mixer was found to be proportional to a higher power of flow velocity (close to unity), which is consistent with turbulent flow This finding was supported
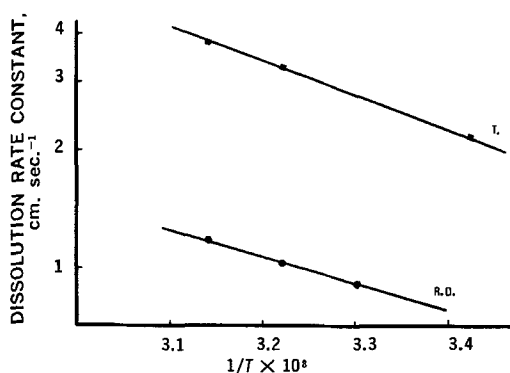
by the determination of the energy of activation and by the calculation of the Reynolds and Peclet numbers.

With the improvement of the mixing conditions by energetic movement and random agitation of the fluid, the transfer of solute by random turbulent eddies remarkably increased the rate of dissolution. Hence, if the agitating system described is capable of providing a higher dissolution at low revolutions per minute, it may offer a convenient and practical way to increase the rate of other heterogeneous processes such as catalysis, extraction, adsorption, and crystallization.

### APPENDIX

| | | |
|---|---|---|
| $R$ | = | dissolution rate in g./cm.$^2$/sec. |
| $k$ | = | constant |
| $D$ | = | diffusion coefficient in cm.$^2$/sec. |
| $\nu$ | = | kinematic viscosity in stokes |
| $\omega$ | = | angular velocity in rad./sec. |
| $c_s$ | = | solubility in g./l. |
| $K_T$ | = | dissolution-rate constant in cm./sec. |

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**Figure 7**—*Temperature dependence of the dissolution-rate constant of benzoic acid for the rotating disk (R.D.) and the Turbula shaker mixer (T).*