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Studies of dissolution behavior of highly soluble drugs using a rotating disk

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Summary

The dissolution behavior of highly soluble drugs having varying diffusion coefficients was investigated using the rotating disk methodology. The effect of solution viscosity as a result of high drug concentration causes the drug diffusion coefficient to be variable in the boundary layer. A modified Levich equation was obtained by an iterative numerical algorithm to solve the non-linear diffusion equation. The resulting equation predicts that a plot of dissolution rate vs the square root of the rotation speed of the disk is linear. Moreover, the slope is dependent upon the profile of diffusion coefficient vs drug concentration. To demonstrate the theory, the dissolution rates of the compressed disks of the model drugs, sodium ampicillin and sodium salicylate, were determined quantitatively at various rotation speeds, and compared with those predicted by the modified Levich equation. It shows that the modified Levich equation gives a close agreement with the experimental data. For comparison, the conventional Levich equation, which was derived for constant diffusion coefficients, was also employed to predict the dissolution rate of these drugs. The rates predicted by the Levich equation exhibit significant discrepancy from the experimental data.

Introduction

The rotating disk is frequently used for the intrinsic dissolution rate determination for drugs (Nogami et al., 1966, 1969; Prakongpan et al., 1976; Wu et al., 1976; Mooney et al., 1981; Grijseels et al., 1981). Its greatest advantages are that the boundary layer thickness is constant over the surface of the disk, and that it is not necessary to know the thickness of the diffusion boundary layer. Equations for the steady state mass transfer with constant diffusion coefficient at the surface of a rotating disk have been solved by Levich (1962) for both laminar and turbulent diffusion regimes. The boundary layer thickness and dissolution rate can be evaluated by simple equations by knowing the viscosity of the dissolution medium, the drug solubility, and the rotation speed of the disk. His theoretical derivations have been validated in a large number of drug dissolution studies with constant diffusion coefficient.

However, in dissolution studies of highly soluble or viscous drugs, the Levich equation often fails to give a close prediction of the dissolution rate, primarily due to the variable diffusion coefficient of the drug in the boundary layer. In evaluat-

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ing the dissolution rates of these drugs, the error due to improper values of drug diffusion coefficient could be enormous, because the dissolution rate is generally directly proportional to the drug diffusion coefficient.

The objectives of this paper are to develop a solution to predict the dissolution rates of drugs using the rotating disk system under the influence of variable drug diffusion coefficient in the boundary layer, and to demonstrate the theory experimentally.

Theory

The diffusion equation of rotating disk

The convective diffusion of a highly soluble drug dissolving on the surface of a rotating disk may be expressed by the following equation (Levich, 1962)

$$V(z)\frac{dC}{dz} = \frac{d}{dz}\left(D(C)\frac{dC}{dz}\right) \tag{1}$$

where C is the concentration of the drug in the diffusion region at distance z measured from the disk surface, $V(z)$ the fluid velocity on z-direction, and $D(C)$ the diffusion coefficient of the drug molecule (or ion) in the dissolution boundary layer.

Because of the high concentration of the drug and high viscosity of the solution, the diffusion coefficient $D(C)$ may not be constant in the entire boundary layer. Here we assume that the combined effect of concentration and viscosity on the diffusion coefficient can be incorporated into a function $D(C)$ to be determined by experiment.

The appropriate boundary conditions for solving Eqn. 1 are (Levich, 1962)

$$C = C_s,\ z = 0 \tag{2}$$

and

$$C = 0,\ z = \infty \tag{3}$$

where the concentration of the drug at the solid surface is assumed to be equal to the solubility C_s.

The fluid velocity $V(z)$ close to the disk surface for the case of constant viscosity in the diffusion boundary layer may be approximated by (Levich, 1962)

$$V(z) = -0.51\sqrt{\frac{\omega^3}{\nu_0}}\,z^2 \quad \text{for } z \ll \sqrt{\frac{\nu_0}{\omega}} \tag{4}$$

where ν_0 is the kinematic viscosity of the dissolution medium and ω is the rotation speed of the disk. Eqn. 4 was derived from the Navier-Stokes equation (Levich, 1962; Riddford, 1962) assuming that the density and viscosity of the solution in the boundary layer are constant. In order to derive the similar velocity profile as Eqn. 4 for the case of variable viscosity, it would be necessary to follow the similar procedure that results in Eqn. 4. Because of the complexity of the Navier–Stokes equation with variable viscosity, it may not be possible to obtain an analytical solution. Fortunately, it will be shown (Appendix A) that Eqn. 4 is a close approximation for the dissolution systems investigated in this work. Therefore, Eqn. 4 will be used as the expression for the velocity profiles in Eqn. 1 and subsequent derivations throughout the entire paper.

For the cases of constant drug diffusion coefficient in the entire boundary layer, an analytical solution to Eqn. 1 can be obtained by direct integration of Eqn. 1, giving the well known Levich equation (Levich, 1962), as

$$Q = 0.62AD^{2/3}\nu_0^{-1/6}\omega^{1/2}C_s \tag{5}$$

where Q is the rate of dissolution, A the surface area of the drug on the disk, D the diffusion coefficient of the drug, and ω the rotation speed of the disk.

Eqn. 5 indicates that the plot of the dissolution rate against $\omega^{1/2}$ gives a straight line passing through the origin with a slope equal to $0.62AD^{2/3}\nu_0^{-1/6}C_s$.

For the cases of variable diffusion coefficient, an analytical solution to Eqn. 1 may not be possible, and therefore the relationship between dissolution rate and rotation speed is difficult to establish. Suitable numerical methods for solving

a diffusion equation containing a variable diffusion coefficient have been extensively summarized by Crank (1975). The iterative numerical approach proposed by Crank and Henry (1949) was chosen in this work to solve Eqn. 1. The procedure is described below.

In order to solve Eqn. 1, it is convenient to introduce the following dimensionless variables:

$$X = \frac{z}{\delta} \tag{6}$$

$$Y = \frac{C}{C_s} \tag{7}$$

In Eqn. 6, δ is the diffusion boundary layer thickness for constant diffusion coefficient and constant viscosity defined by Levich (1962):

$$\delta = 0.51\left(\frac{D}{\nu_0}\right)^{1/3}\delta_0 \tag{8}$$

where δ_0 is the hydrodynamic boundary layer thickness for constant viscosity, approximated by (Levich, 1962):

$$\delta_0 = 3.6\left(\frac{\nu_0}{\omega}\right)^{1/2} \tag{9}$$

The introduction of Eqns. 6 and 7 conveniently confines the diffusion region X in the range of 0 to the vicinity of 1.0, corresponding to the values of Y from 0 to 1.0.

A new function $K(C)$ is defined as the ratio of the variable diffusion coefficient $D(C)$ to the diffusion coefficient in the bulk D_0, as

$$K(C) = \frac{D(C)}{D_0} \tag{10}$$

After combining Eqn. 4, and Eqns. 6–10 and substituting into Eqn. 1 yields,

$$\frac{f_1 X^2}{\nu_0^{1/2}}\frac{dY}{dX} = \frac{d}{dX}\left(K(C_s Y)\frac{dY}{dX}\right) \tag{11}$$

where

$$f_1 = \frac{-0.51\omega^{3/2}\delta^3}{D_0} \tag{12}$$

with the boundary conditions:

$$Y = 1,\ X = 0 \tag{13}$$

$$Y = 0,\ X = \infty \tag{14}$$

It is noted that the value of f_1 in Eqn. 12 is independent of ω since δ^3 is inversely proportional to $\omega^{3/2}$, as indicated by Eqns. 8 and 9.

According to Crank (1975), Eqn. 11 can be transformed to the following integral equation

$$Y = 1 - \frac{\int_0^X \frac{1}{K(C_s Y)}\exp\left(\int_0^t \frac{f_1\xi^2}{K(C_s Y)\nu_0^{1/2}}d\xi\right)dt}{\int_0^\infty \frac{1}{K(C_s Y)}\exp\left(\int_0^t \frac{f_1\xi^2}{K(C_s Y)\nu_0^{1/2}}d\xi\right)dt} \tag{15}$$

where t and ξ are dummy variables.

In Eqn. 15, since Y is an implicit unknown function of X, a direct integration of Eqn. 15 is not possible. A trial and error algorithm proposed by Crank and Henry (1949) is used here to obtain the numerical solution of the Y versus X profile. Since the function in the denominator of Eqn. 15 converges rapidly in integration, it is not necessary to integrate it to ∞. In practice, the upper limit of integration, ∞, can be replaced by a small value (e.g. δ) and adjusted according to the results of integration. The convergence of computation is attained when there is no further gain in the value of integration with increased value of the limit. The iterative computation procedure is described in Appendix B.

The rate of drug dissolution

The rate of drug dissolution, Q, can be evaluated at the surface of the disk by Fick's first law of diffusion, as

$$Q = -AD(C_s)\left.\frac{dC}{dz}\right|_{z=0} \tag{16}$$

The concentration gradient dC/dz in Eqn. 16 can

be replaced by $C_s\ dY/(\delta\ dX)$, resulting in the following equation for Q

$$Q = -\frac{AD(C_s)C_s}{\delta} dY/dX|_{X=0} \quad (17)$$

After replacing $D(C_s)$ by Eqn. 10, and $dY/dX|_{X=0}$ by S_0, Eqn. 17 can be rearranged as

$$Q = -\frac{AD_0K(C_s)S_0}{\delta} \quad (18)$$

where the initial slope in the Y–X profile, S_0, is obtained by taking the derivative of Eqn. 15 with respect to X and let $X = 0$, giving

$$S_0 = -\left\{K(C_sY)\int_0^\infty \frac{1}{K(C_sY)} \times \exp\left(\int_0^t \frac{f_1\xi^2}{K(C_sY)\nu_0^{1/2}} d\xi\right) dt\right\}^{-1} \quad (19)$$

It is noted that the value of S_0 in Eqn. 19 is independent of ω since f_1 is independent of ω as described earlier. The denominator of Eqn. 19 is obtained by the iterative computation procedure described earlier. Substituting δ_0 in Eqn. 9 into Eqn. 8, followed by inserting the resulting expression of δ into Eqn. 18 yields

$$Q = 0.556AD_0^{2/3}\nu_0^{-1/6}K(C_s)S_0C_s\omega^{1/2} \quad (20)$$

Eqn. 20 indicates that the plot of Q versus $\omega^{1/2}$ gives a straight line passing through the origin with a slope equal to $0.556AD_0^{2/3}\ \nu_0^{-1/6}\ K(C_s)S_0C_s$. This result is similar to the conventional Levich equation, Eqn. 5, except that the slope in Eqn. 20 is no longer independent of the profile of diffusion coefficient vs drug concentration. It depends on $K(C_s)$ and S_0 which need to be determined for each drug of interest.

For the case of constant viscosity in the boundary layer, $K(C_s)$ reduces to unity and the denominator of Eqn. 19 can be evaluated to give the value of 0.89 which is the same as the value obtained by Levich (1962, pp. 68). Thus Eqn. 20 reduces to Eqn. 5, indicating the validity of the derivations.

The diffusion coefficient of highly soluble drugs

Diffusion coefficients for solutes in liquid phase have been found to be strongly dependent on concentration and viscosity of the resulting solution. The direct measurement of a variable diffusion coefficient as a function of concentration is not a trivial matter, because of considerable experimental difficulties. In this paper, we will employ correlation equations reported in the literature to estimate its approximate values. Leffler and Cullinan (1970) derived a correlation equation for predicting the diffusion coefficient of non-electrolytes in terms of the concentration and viscosity of the mixture. For a concentrated electrolyte solution, such as sodium ampicillin and sodium salicylate, the equation derived by Gordon (1937) may be used:

$$D = D_0\frac{\mu_0}{\mu}\frac{1}{C_b'V_b}\left(1 + \frac{m\,\partial \ln \gamma_\pm}{\partial m}\right) \quad (21)$$

where

C_b' = molal density of solvent, g · mol/cm^3
V_b = partial molal volume of solvent, cm^3/g · mol
μ_0 = viscosity of solvent, cP
μ = viscosity of solution, cP
m = molality of solute, g · mol/1000 g solvent
$\gamma_\pm$ = mean ionic activity coefficient of solute

Note that Eqn. 21 as well as the equation derived by Leffler and Cullinan indicates that the diffusion coefficient of the compound is inversely proportional to the viscosity of the mixture. Thus the effect of viscosity on the diffusion coefficient of highly soluble drugs can dominate the effect of concentration at high solution viscosities.

The mean activity coefficient of the concentrated electrolyte in Eqn. 21 may be estimated by the following equation (Barrow, 1973):

$$\ln \gamma_\pm = -\frac{1.172Z_+Z_-m^{1/2}}{1 + m^{1/2}} \quad (22)$$

where

Z_+, Z_- = valences of cation and anion, respectively

m =the molal concentration of drug

In order to test the proposed theory, Eqns. 21 and 22 will be used for estimation of the variable diffusion coefficients of sodium ampicillin and sodium salicylate in Eqns. 1 and 10.

Materials and Methods

Materials

Anhydrous ampicillin (Sigma Chemical Co.), sodium ampicillin (Bristol Laboratories), sodium salicylate (Aldrich Chemical Co.), and sucrose (Sigma Chemical Co.) were used as received.

Viscosity-concentration profile determination

Unlike diffusion coefficient, the viscosity of a drug solution is difficult to be accurately predicted as a function of the concentration by a theoretical or empirical correlation equation. Fortunately, the instrument as well as experimental procedure for measuring the viscosity is relatively simple.

The Cannon-Fenske viscometers of sizes 50, 75, 150 and 200, purchased from Industrial Research Glassware Ltd., Union, NJ, were used to determine drug solution viscosity as a function of concentration. Prior to measuring the viscosities of the drug solutions, it is necessary to calibrate each viscometer by determining the viscometer constant, the kinematic viscosity of a given fluid divided by its efflux time in the viscometer. Distilled water was chosen as the standard fluid for obtaining the viscometer constant for size 50 viscometer, while sucrose solutions were chosen for sizes 75, 150 and 200 viscometer. The standard kinematic viscosities for distilled water and sucrose solutions at 25 °C were obtained from the literature (Perry, 1984; Dean, 1979). The efflux time of these standard fluids in the viscometer was then measured in a constant-temperature water bath maintained at 25 ± 0.2 °C. The obtained viscometer constants are then applicable for various drug concentrations at various temperatures.

To determine the viscosities of the drug solutions, a certain amount of drug was dissolved in a given volume of water, followed by measuring the efflux time of the prepared drug solution in the viscometer. The kinematic viscosities are simply equal to the product of the viscometer constant and the efflux time. The above drug solutions were also used to determine drug concentrations relative to standard solutions and to determine solution density. The concentrations of the drug solutions were measured by a conductance-resistance meter (YSI Model 32, YSI Scientific) utilizing an external standard curve. The density of the drug solution was determined by a pycnometer. The viscosities were then obtained by multiplying the kinematic viscosity by the density.

Solubility determination

To determine the solubility of anhydrous ampicillin, an excess of drug powder was added to a 25 ml glass vial, followed by adding 20 ml distilled water. The vial was rubber-stoppered, placed in a constant-temperature bath, maintained at 25 ± 0.2 °C, mechanically stirred. Samples were taken from the vial and filtered through 0.2 μm Millipore filters at certain time intervals; diluted with water to make final concentrations of about 1–2 mg/ml. The ampicillin concentrations of the diluted samples were assayed by a Spectronic 2000 (VWR) Spectrophotometer at wavelength 260 nm. The solubility of anhydrous ampicillin is obtained when there is no further variation of the concentration in the sample as a function of time.

Determination of the limiting equivalent ionic conductances

The limiting equivalent conductances of sodium ampicillin, sodium salicylate and sodium chloride to be used later in Eqn. 26 were determined in this section. A series of dilute solutions (0.000945–0.03191 gEq./liter), denoted as c, of sodium ampicillin, sodium salicylate and sodium chloride were prepared by dissolving a certain amount of these electrolytes into beakers with given amounts of distilled water. These beakers were then placed in a water bath to equilibrate to 25 °C. The conductances (L) of these solutions were measured by the same conductance probe. The measured conductances were then plotted against the corresponding concentrations. Straight lines were observed in these plots for all the 3 electrolytes within the range of concentration. The slopes (L/c) of the 3 straight lines were then determined

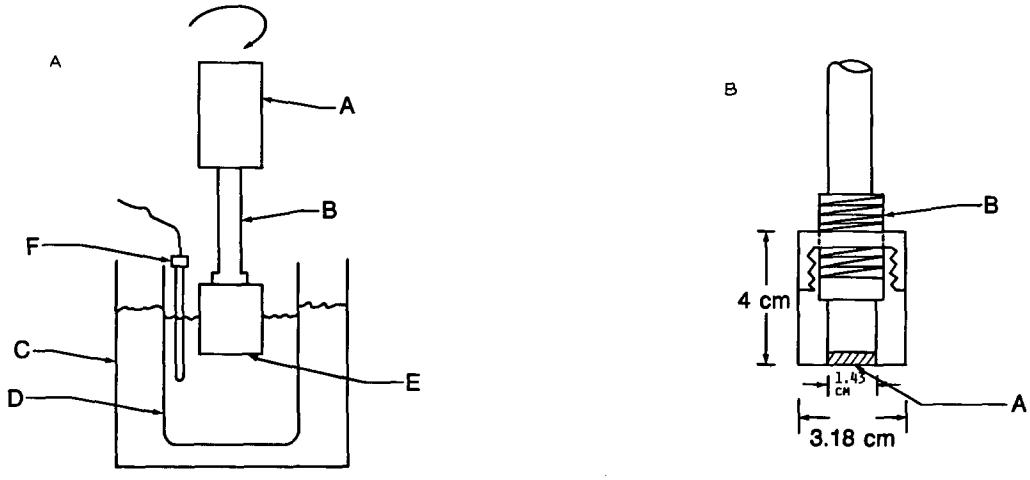

Fig. 1. A: Rotating disk apparatus for dissolution rate studies. A, constant speed motor; B, rotating shaft; C, water bath; D, reservoir; E, rotating disk; F, conductivity probe. B: The cross-section of rotating disk. A, drug disk; B, thread.

by linear regression. Since the limiting equivalent conductance of NaCl solution, Λ_{NaCl}, has been tabulated by Barrow (1973, p. 621), the cell constant of this probe can be calculated by the following equation (Barrow, 1973, p. 620)

$$\text{cell constant} = \frac{\Lambda_{NaCl}}{(L/c)_{NaCl}} \tag{23}$$

As soon as the cell constant is obtained by the sodium chloride data, the limiting equivalent conductances of sodium ampicillin, Λ_{NaAMP}, and sodium salicylate, $\Lambda_{NaSalicy}$, can be deduced from Eqn. 23 by replacing $(L/c)_{NaCl}$ with the corresponding values of these drugs. The resulting equivalent conductances can be expressed by (Barrow, 1973, p. 622)

$$\Lambda_{NaAMP} = \lambda_{+,Na} + \lambda_{-,AMP} \tag{24a}$$

and

$$\Lambda_{NaSalicy} = \lambda_{+,Na} + \lambda_{-,Salicy} \tag{24b}$$

where λ_+ in Eqns. 24a and 24b denotes the equivalent ionic conductance of sodium ion which can be found from the literature (Reid, 1987, p. 620). Thus the limiting equivalent ionic conductances of ampicillin, $\lambda_{-,AMP}$, and salicylate, $\lambda_{-,Salicy}$, can be readily obtained from Eqns. 24a and 24b.

Dissolution rate determination by rotating disk

The rotating disk dissolution apparatus is illustrated in Fig. 1. Fig. 1A shows that the reservoir was placed in a water bath maintained at $25 \pm 0.2°$ C. Fig. 1A illustrates the cutaway of the rotating disk. The drug disks with a cross-sectional area of 1.645 cm^2 ranging from 400 to 800 mg, were compressed directly into the die under a force of 3000 pounds by a Carver press (Fred S. Carver Inc., Menomonee Falls, WI).

For each dissolution run, 200 ml of distilled water was placed in the reservoir. The rotating disk containing the drug disk was then centered about 1.5 cm below the liquid level. For sodium ampicillin and sodium salicylate, a conductivity probe was inserted into the reservoir, half-way between the reservoir wall and the disk wall. The concentration–time profiles of the solution were determined by the conductance-resistance meter. For anhydrous ampicillin, an aliquot of the solution was withdrawn from the reservoir by a pipet at suitable time intervals for analysis in a Spectronic 2000 (VWR) spectrophotometer at wavelength 260 nm.

To ensure the laminar flow pattern at the surface of the rotating disk, the rotation speeds

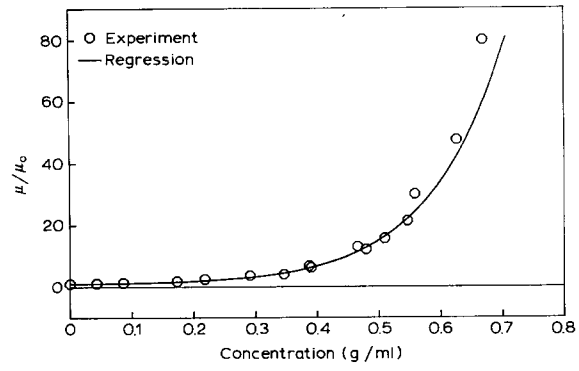

Fig. 2. The viscosity-concentration profiles of sodium ampicillin.

tested varied from 70 to 400 rpm corresponding to Reynolds numbers of 2080 to 11890.

Results and Discussion

Viscosity concentration profiles

The model drugs used for the study are sodium ampicillin, representing the case of extremely high viscosity, and sodium salicylate, the case of moderate viscosity. The viscosities of aqueous sodium ampicillin and sodium salicylate solution at 25 °C determined by Cannon-Fenske viscometer are plotted in Figs. 2 and 3. These data were fitted to Eqn. 25, by the non-linear least-squares method.

$$\frac{\mu}{\mu_0} = 1 + C^a \exp(bC) \qquad (25)$$

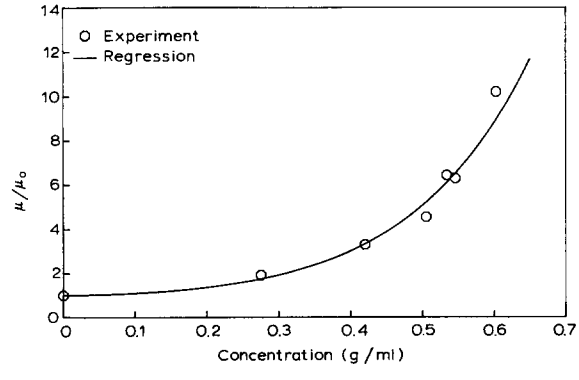

Fig. 3. The viscosity-concentration profiles of sodium salicylate.

TABLE 1

The constants and parameters used or obtained in this work

Sodium salicylate	*Sodium ampicillin*
$a = 1.159$	$a = 0.9562$
$a_0 = 1.0$	$a_0 = 1.0$
$a_1 = 0.3739$	$a_1 = 0.3189$
$b = 4.411$	$b = 6.759$
$b_0 = -0.1332$	$b_0 = -0.1374$
$C_s = 0.65$ g/ml	$C_s = 0.67$ g/ml
$D_0 = 10.0 \times 10^{-6}$ cm^2/s	$D_0 = 7.92 \times 10^{-6}$ cm^2/s
$d_1 = 0.995$	$d_1 = 0.9971$
$d_2 = 0.3719$	$d_2 = 0.3169$
$K(C_s) = 0.05947$	$K(C_s) = 0.01118$
$M_a = 160.1$	$M_a = 371.4$
$S_0 = 8.5363$	$S_0 = 33.106$
$\lambda_- = 33.71$ (cm^2/Ω/gEq.) ($^-$Salicy)	$\lambda_- = 21.16$ (cm^2/Ω/gEq.) ($^-$Amp)
$Z_+ = 1$	$Z_+ = 1$
$Z_- = 1$	$Z_- = 1$

Miscellaneous:
$A = 1.645$ cm^2
$C_s = 11.0$ mg/ml (anhydrous ampicillin)
$Fa = 96{,}500$ C/gEq.
$\nu_0 = 0.8930 \times 10^{-2}$ cm^2/s
$\lambda_+ = 50.1$ (cm^2/Ω/gEq.)

where a and b are constants, μ_0 the viscosity of the dissolution medium, and μ the viscosity of the drug solution. Since the absolute precision of measured viscosity is greater at low drug concentrations than at higher ones, it is necessary to weight the experimental data prior to least squares analysis. The appropriate weight chosen in this work is the reciprocal of the measured viscosity because the standard error of viscosity measured in this work was observed to be proportional to the magnitude of the measured viscosity.

The values of a and b in Eqn. 25 obtained for sodium ampicillin and sodium salicylate are listed in Table 1. The regression curves are plotted as the solid lines in Figs. 2 and 3, as seen, the regression models give an excellent fit of the data.

Diffusion coefficient D_0 for sodium ampicillin and sodium salicylate

When dissolved, molecules of sodium ampicillin and sodium salicylate dissociate into the cations Na^+ and the anions of ampicillin and salicy-

late. Despite differences between sizes of Na^+ and the anions both the positively and negatively charged ions diffuse at the same rate through the dissolution boundary layer. In this way, the electroneutrality is maintained.

The theory of diffusion of salts at low concentrations is well developed. For dilute solution of a single salt, the diffusion coefficient is given by the Nernst–Haskell equation (Reid et al., 1977)

$$D_0 = \frac{RT}{Fa^2} \frac{1/Z_+ + 1/Z_-}{1/\lambda_+ + 1/\lambda_-} \tag{26}$$

where

D_0 = diffusion coefficient at infinite dilution, cm^2/s

T = temperature, K

R = gas constant, equal to 8.314 $J \cdot mol^{-1} \cdot K$

λ_+, λ_- = limiting (zero-concentration) ionic conductances, ($cm^2/\Omega/gEq.$)

Fa = faraday, 96,500 C/gEq.

The value of λ_+ for sodium at 25 °C is 50.1 ($cm^2/\Omega/gEq.$) (Reid et al., 1987, p. 620), while the values of λ_- for ampicillin and salicylate were determined by Eqn. 24, to be 21.16 and 33.71 ($cm^2/\Omega/gEq.$), respectively. With these data, the value of D_0 for sodium ampicillin evaluated by Eqn. 25 is 7.92×10^{-6} cm^2/s, and 10.7×10^{-6} cm^2/s for sodium salicylate, which is in excellent agreement with the the value of 10.0×10^{-6} cm^2/s obtained by Desai et al. (1966).

Evaluation of $C_b'V_b'$

The values of $C_b'V_b'$ for aqueous sodium ampicillin and sodium salicylate were determined from the concentration–density data. The partial molar volumes, V_b', of water were determined by the graphical method of tangent intercepts, as described by Lewis and Randall (1923). The values of V_b' for sodium ampicillin and sodium salicylate solutions were observed to be constant in the entire range of concentrations, being 17.9 and 17.8, respectively. The values of $C_b'V_b'$ form straight lines for both solutions. The resulting expressions are listed below.

$$C_b'V_b' = d_1 + d_2C \tag{27}$$

The values of d_1 for sodium ampicillin and sodium salicylate are 0.9971 and 0.995, respectively, while the values of d_2 are equal to 0.3169 and 0.3719, respectively.

Evaluation of $1 + m\ \partial \ln\gamma_\pm/\partial m$

The experimental density–concentration data of sodium ampicillin and sodium salicylate indicate a straight line relationship given by

$$d = a_0 + a_1C \tag{28}$$

where d is the density in g/ml, C the concentration in g/ml. The values of a_0 and a_1 are: 1.0 and 0.3189 for sodium ampicillin; 1.0 and 0.3739 for sodium salicylate.

Thus the molal concentration m in Eqn. 22 can be converted to the concentration C, g/ml, by the following equation:

$$m = \frac{1000\ C}{(a_0 + a_1C - C)M_a} \tag{29}$$

where M_a is the molecular weight of the drug.

The first derivative of Eqn. 22 can be expressed by

$$\frac{m\ \partial \ln \gamma_\pm}{\partial m} = 0.5862 m Z_+ Z_- \left(\frac{1}{(1+\sqrt{m})^2} - \frac{1}{m+\sqrt{m}} \right) \tag{30}$$

Experiment shows that the values of the left hand side of Eqn. 30 are nearly constant. Thus we obtain

$$1 + \frac{m\ \partial \ln \gamma_\pm}{\partial m} = 1 + b_0 \tag{31}$$

In Eqn. 31, the values of b_0 are equal to -0.1374 ± 0.009 for sodium ampicillin and -0.1332 ± 0.01 for sodium salicylate. These values imply that for viscous drug solutions, the effect of viscosity on drug diffusion coefficient is much stronger than the effect of drug concentration.

The final expression for diffusion coefficients

After incorporating Eqns. 25, 27 and 31 into Eqn. 21, the final expression for the diffusion coefficient of highly soluble drugs is

$$D(C) = \frac{D_0(1 + b_0)}{(d_1 + d_2C)(1 + C^a \exp(bC))} \qquad (32)$$

Eqn. 32 is the desirable expression for the variable diffusion coefficient, since it is only a function of drug concentration. For iterative computation of Eqn. 15, the value of $K(C_sY)$ in Eqn. 15 is obtained by introducing Eqn. 32 into Eqn. 10.

Results of iterative computations

The numerical integration of Eqn. 15 was conducted by a FORTRAN program developed based on the trapezoidal rule. Prior to using the computer program to solve the variable diffusion coefficient problem, it was first tested by solving the simpler case of constant diffusion problem, by replacing $K(C_sY)$ in Eqn. 15 by a constant. The resulting concentration profile $1 - Y$ is plotted as curve A in Fig. 4, which is identical to the analytical solution obtained by Levich (1962) and Riddiford (1966). The validated procedure was then used to solve the dimensionless concentration profiles of sodium ampicillin and sodium salicylate by Eqn. 15. The results are plotted as curves B and C in Fig. 4. The thickness of the diffusion boundary layer, defined as the boundary at which the drug

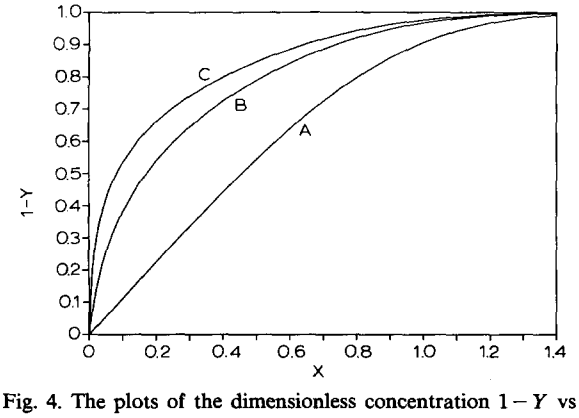

Fig. 4. The plots of the dimensionless concentration $1 - Y$ vs the dimensionless distance X. A, constant diffusion coefficient; B, sodium salicylate; C, sodium ampicillin.

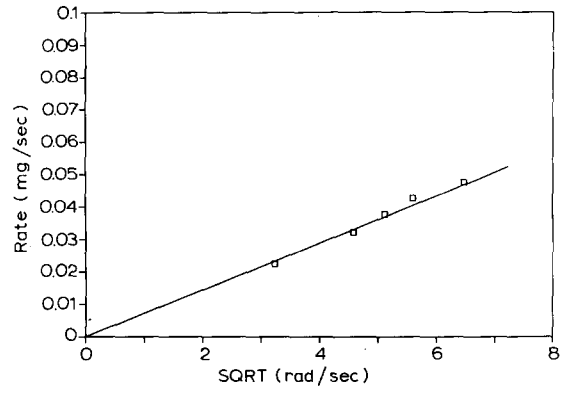

Fig. 5. The dissolution rates of anhydrous ampicillin on the rotating disk; □, experiment; ———, conventional Levich equation.

concentration drops to 1% of C_s, estimated from Fig. 4, are 1.15δ for sodium ampicillin, 1.2δ for sodium salicylate, and 1.4δ for the case of constant diffusion coefficient. The results imply that the thickness of the viscous boundary layer is significantly thinner than the one with dilute concentration. The values of $K(C_s)$ and S_0 computed by Eqns. 10 and 19 are: 0.01118 and 33.106 for sodium ampicillin, and 0.05947 and 8.5363 for sodium salicylate.

Dissolution rate of anhydrous ampicillin

The solubility of anhydrous ampicillin determined is 11.0 mg/ml which reasonably falls between the solubility at 21°C, 10.098 mg/ml (Marsh and Weiss, 1967), and at 37°C, 13.9 mg/ml (Tsuji et al., 1978).

Since the aqueous solubility of anhydrous ampicillin is relatively low, the effect of boundary layer viscosity on its diffusion coefficient is negligible. The accumulated mass of release vs time profiles indicates linearity for all the tested rotation speeds. The rate of dissolution at each speed was obtained from the slope of the straight lines. The resulting rates are then plotted against $\omega^{1/2}$ as shown in Fig. 5. The squares in Fig. 5 indicate the experimental data while the solid line is plotted by Eqn. 5 using the diffusion coefficient of 4.58×10^{-6} cm^2/s (Padfield et al., 1975) and the solubility of 11.0 mg/ml, determined in this work. As indicated in Fig. 5, the dissolution rates computed

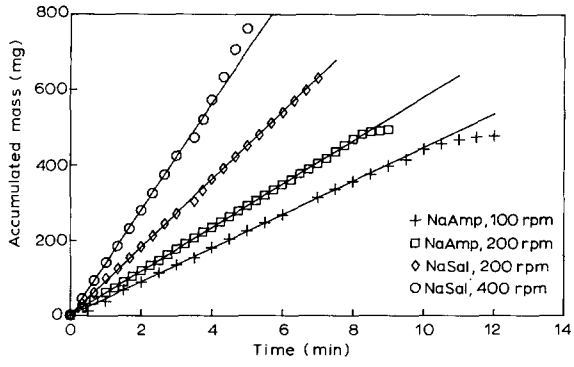

Fig. 6. The typical plots of the accumulated mass vs time profiles of the dissolved sodium ampicillin and sodium salicylate from the rotating disk; ———, regression.

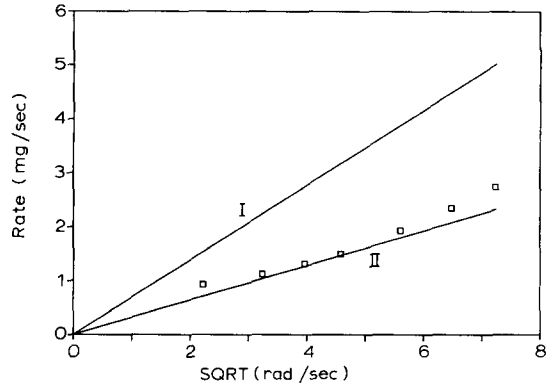

Fig. 8. The dissolution rates of sodium salicylate on the rotating disk; □, experiment; I, conventional Levich equation; II, modified Levich equation.

by the Levich equation closely agree with the observed rate of dissolution. This fact indicates that because of the low solubility of anhydrous ampicillin, the diffusion coefficient of ampicillin in the boundary layer is a constant and equal to that in the bulk.

Dissolution rates of sodium salicylate and sodium ampicillin

The accumulated mass vs time profiles of sodium salicylate and sodium ampicillin at various rotation speeds form straight lines for most part of the dissolution, as indicated by the typical examples of Fig. 6. The rates of dissolution, obtained from the slopes of the straight line portion of these curves are plotted against the square root of the rotation speeds, as shown by the squares in Figs. 7 and 8. The dissolution rates predicted by the conventional Levich equation, using D_0 as the drug diffusion coefficient, are plotted as curve I in Figs. 7 and 8. The dissolution rates predicted by the modified Levich equation, Eqn. 20, are then plotted as curve II in Figs. 7 and 8, using the previously computed values of $K(C_s)$ and S_0 as well as the following data: $A = 1.645$ cm^2, and $\nu_0 = 0.8930 \times 10^{-2}$ cm^2/s. Note that in Figs. 7 and 8, the dissolution rate predicted by the Levich equation without correction of diffusion coefficient shows significant discrepancy from the experimental data. The slope of curve I in Fig. 7 gives 176% error while that in Fig. 8 shows 99% error. After correction, the error of the slopes of Curve II in Fig. 7 was reduced to 6%, and reduced to 8% in Fig. 8. The close agreement between the experimental values and the corrected dissolution rates indicates that the proposed theory has been suitably applied to the rotating disk dissolution.

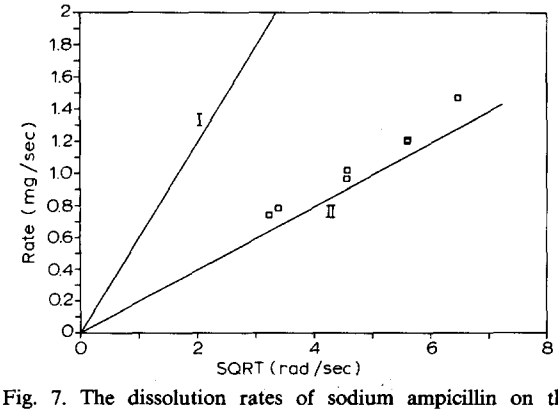

Fig. 7. The dissolution rates of sodium ampicillin on the rotating disk; □, experiment; I, conventional Levich equation; II, modified Levich equation.

Conclusions

This paper indicates the inherent weakness of using of conventional Levich equation to predict the dissolution rates of highly soluble drugs using a rotating disk. The modified Levich equation (Eqn. 20) has been derived and shown to give excellent agreement with the experimentally mea-

sured dissolution rates. It is shown that in order to predict the dissolution rates of these drugs, the effects of viscosity and concentration on the diffusion coefficient of the drug in the boundary layer are important considerations for solving the diffusion equation. The derivation and computation procedures developed in this paper may be extended to predict the dissolution rate of these drugs in other dissolution systems.

Appendix A

The purpose of this section is to investigate the validity of using Eqn. 4 to express the velocity profile of the viscous boundary layer. For the drugs having variable viscosity in the boundary layer, the following equation may be used to study the sensitivity of the velocity, $V'(z)$, to the variable viscosity

$$V'(z) = -0.51\sqrt{\frac{\omega^3}{\nu(z)}}\, z^2 \text{ for } z \ll \sqrt{\frac{\nu_0}{\omega}} \qquad \text{(A-1)}$$

where $\nu(z)$ denotes the viscosity–distance profile of the velocity boundary layer. By examining Eqns. 4 and A-1, it can be conceived that the values of $V(z)$ and $V'(z)$ and their first derivatives satisfy the following boundary conditions:

$$V(z) = V'(z) = 0, \text{ at } z = 0 \qquad \text{(A-2)}$$

and

$$\frac{\partial V(z)}{\partial z} = \frac{\partial V'(z)}{\partial z} = 0, \text{ at } z = 0 \qquad \text{(A-3)}$$

The viscosity profile $\nu(z)$ for each drug in Eqn. A-1 can be expressed by

$$\nu(z) = \nu(C) = \nu_0\left[1 + (C_s Y)^a \exp(bC_s Y)\right] \qquad \text{(A-4)}$$

Eqn. A-4 was deduced from Eqn. 25 by assigning $\nu = \mu/\rho$ and $\nu_0 = \mu_0/\rho$, where ρ is the density of the fluid in the boundary layer which is fairly constant and can be assumed to be equal to the density of the bulk solution.

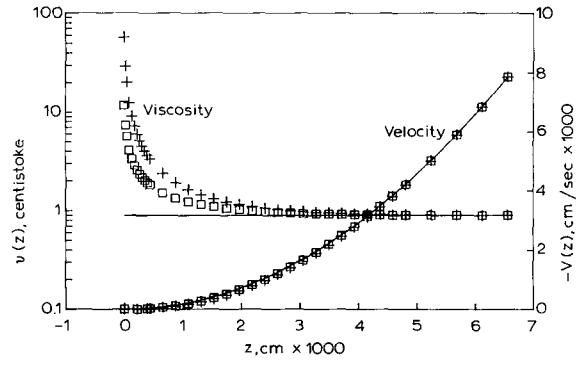

Fig. A-1. The plots of viscosity and velocity profiles vs distance in the boundary layer at 100 rpm. ———, Constant viscosity, using $\nu_0 = 0.893$ centistoke for the kinematic viscosity and Eqn. 4 for the velocity. +, Sodium ampicillin, using Eqns. A-1 and A-4. □, Sodium salicylate, using Eqns. A-1 and A-4.

To compare the velocity profiles in this region, the values of $V(z)$ for constant viscosity were computed by Eqn. 4, and those of $V'(z)$ for sodium ampicillin and sodium salicylate were computed by Eqn. A-1, Eqn. A-4 and Fig. 4. The resulting velocities, for the typical case $\omega = 100$ rpm, were plotted in Fig. A-1 along with the corresponding viscosity profiles computed by Eqn. A-4 and Fig. 4. As shown, in the region adjacent to the dissolving surface, $z \Rightarrow 0$, the velocities of the 3 cases are equal to zero despite the significant difference of their viscosity profiles. This is apparently due to the effect of the boundary condition, Eqn. A-2. When the position moves away from the dissolving surface, the viscosities of sodium ampicillin and sodium salicylate sharply decline and eventually approach the viscosity of the bulk solution. Thus at the location far away from the dissolving surface, at $z > \delta$, the plots of the 3 velocity profiles essentially coincide due to the same viscosity. In the transition region, $0 < z < \delta$, it can be seen that the difference in velocity among the 3 plots is slightly higher than the above two extreme cases. However, the difference is insignificant, probably due to the second boundary condition, Eqn. A-3. The plots of the velocity profiles for other values of rotation speeds, ω, can be obtained by the same procedure resulting in the same conclusions.

To further verify the validity of using Eqn. 4 in this work, both Eqns. 4 and A-1 were used to

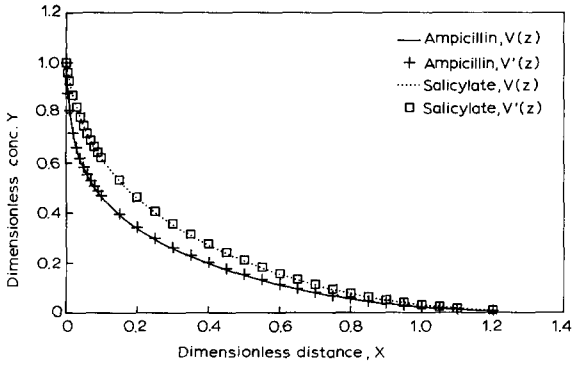

Fig. A-2. The plots of the dimensionless concentration profiles vs the dimensionless distance in the diffusion boundary layer. ———, ·····, Using Eqn. 15; +, □, using Eqns. 15 and A-4.

compute the concentration profiles of sodium ampicillin and sodium salicylate. The concentration profiles using Eqn. 4 are directly computed by Eqn. 15. The results have been obtained earlier and illustrated in Fig. 4, in the form of $1 - Y$ vs X. The concentration profiles using Eqn. A-1 can also be obtained by the same procedure by replacing ν_0 in Eqn. 15 by Eqn. A-4, followed by numerical integration. This new Y–X profile was computed and plotted in Fig. A-2 along with the old Y–X profile that is replotted from Fig. 4. As indicated in Fig. A-2, the difference between the old and new profiles for both drugs is negligible.

The results of Figs. A-1 and A-2 strongly imply that Eqn. 4 is a close approximation for the velocity equation used in this work.

Appendix B

The iterative computation procedure for solving Eqn. 15 includes the following steps:

(1) Select an appropriate value of the upper integration limit.
(2) Select appropriate values of Y at the selected intervals of X.
(3) Evaluate $K(C_s Y)$ from Eqn. 9.
(4) Compute the new values of Y for all selected values of X by Eqn. 15.
(5) Repeat the steps (2) and (3) starting from the new values of Y.
(6) Convergence is attained when two successive approximations yield the same values of Y everywhere to the order of accuracy required.
(7) Verify that the value of Y reaches zero at the selected upper limit of integration. If not the range of integration limit is adjusted until convergence attained.

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