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## Studies of some characteristics of molecular dissolution kinetics from rotating discs

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### Summary

The maximum mass transfer from solid to liquid phase, i.e. the intrinsic rate of dissolution, has been shown to be experimentally accessible with good precision using a generalized rotating disc method in combination with extrapolation to infinite speed of revolution and/or infinite distance from the disc to the center of rotation. The method has with very good result been applied to the determination of dissolution rates from non-disintegrating discs of sulfamethizole and alaproclate hydrochloride in water. In the present paper, assumptions for the theory of such experiments are reviewed and compared with numerical values for a number of characteristic kinetic parameters applying simple mathematical models. This comparison supports the assumptions made. The modified rotating disc method described in this paper could therefore be recommended as part of a preformulation program for new solid drug compounds.

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### Introduction

Several theories have been put forward in an attempt to model the details of the dissolution process. Invariably they build on a combination of diffusive and hydro-

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dynamic effects. Sometimes the resistance to mass transfer away from the surface of the dissolving substance has been regarded as a function of the ratio between the diffusion coefficient and a postulated diffusion layer thickness (Nernst and Brunner, 1904; Higuchi, 1967; Levich, 1962; Mauger et al., 1979). To some degree the numerical ambiguity of experimentally determined dissolution rates is circumvented by treating them as relative numbers. Ultimately certain substances could be used as references to normalize the rate values for any technique. However, it seems preferable to devise procedures for the determination of dissolution rates that allow a controlled variation of experimental parameters. The advantage is 2-fold. In the first place conditions can be brought close to those of an 'ideal' dissolution experiment if data are properly extrapolated. Secondly, the variation of observed dissolution rate with experimental parameters furnish better insight as to the processes involved.

On the molecular level and in the vicinity of the phase boundary between the substance to be dissolved and the medium into which it dissolves, the rate of dissolution is a balance between molecules leaving and re-entering the solid. The process of re-entering is sensitive to the experimental arrangements, since it is proportional to the concentration of the solute in the immediate vicinity of the dissolving surface (Nicklasson et al., 1983). This concentration is governed by diffusive and convective transport in the dissolution region and depends upon the geometry of the experimental set up, the stirring rate (flow rate over the surface), pattern of hydrodynamic bulk flow, etc. Recently an experimental procedure was suggested (Nicklasson et al., 1982b) making possible the determination of a limiting (maximum) rate of mass transfer which can be defined as the intrinsic rate of dissolution. By varying the hydrodynamic flow conditions in a controlled way an extrapolation could be performed to conditions approaching those for which the concept of intrinsic rate of dissolution would apply. This means a theoretical condition corresponding to the transfer of substance from the solid surface in contact with fresh solvent without any rate-determining diffusion step inside the liquid phase next to the solid. Thus, the intrinsic rate of dissolution is the most direct parameter to describe the dissolution properties. For energetic reasons, it can be expected that the intrinsic rate of dissolution is closely related to the solubility (Hamlin et al., 1965; Levich, 1962; Nicklasson et al., 1981; Noyes and Whitney, 1897; Shah and Nelson, 1975).

It is clearly realized that the hydrodynamic problems involved in a complete treatment of the dissolution rate are very complex. This complexity becomes particularly obvious when one tries to evaluate the form and values of the various proportionality factors involved. However, as far as proportionalities go the problem is much simpler and the present paper deals only with such questions, i.e. essentially scaling in certain experimental parameters. It is the aim to demonstrate and discuss the orders of magnitude of certain dimensions and rates regarding drug dissolution from rotating disc experiments by applying a molecular approach. Numerical figures for 'boundary layer thicknesses', 'residence times' and 'average concentration gradients' are calculated at conditions where both diffusion controlled dissolution and intrinsic rate of dissolution would apply.

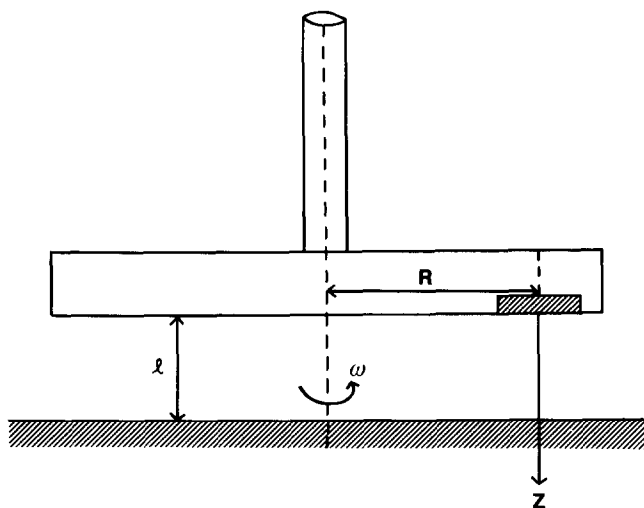


Fig. 1. Schematic presentation of an eccentrically mounted disc on a horizontal rotating support.

## Experimental

### Chemicals

The drug substances alaproclate hydrochloride <sup>1</sup> ( $M_v = 310.2$ ) and sulfamethizole <sup>2</sup> ( $M_v = 270.3$ ) were used as model compounds.

### Dissolution rates

Discs were compressed in a single-punch tabletting machine using flat-faced punches. The discs were prepared in accordance with a previously described method (Nicklasson et al., 1981). The discs were mounted eccentrically on a round horizontal rotating support as demonstrated in Fig. 1. The distance ( $R$ ) from the center of the support to the disc was 1.6 cm. Dissolution rates were determined spectrophotometrically <sup>3</sup> in 50.0 ml of distilled water at 37°C. The water was continuously recirculated through a flow cuvette using a peristaltic pump. The rotating speed of the discs was varied between 200 and 500 rpm.

### Solubilities

Substance in excess of solution saturation was added to distilled water at 37°C. The resulting suspensions were equilibrated for 18–20 h using a magnetic stirrer. Samples of 5 ml were filtered through 0.1  $\mu$ m polycarbonate filters <sup>4</sup> and diluted to

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<sup>3</sup> Pye Unicam SP8-100, U.K.

<sup>4</sup> Nuclepore, U.S.A.

suitable concentrations for spectrophotometry. The solubilities were determined to be 130 mg/ml for alaproclate and 0.8 mg/ml for sulfamethizole.

#### *Diffusion coefficients*

The diffusion coefficients for alaproclate and sulfamethizole in distilled water at 37°C were determined by using a diffusion cell with a Spectrapor 1 membrane<sup>5</sup>. 10 ml of drug solution was placed in the upper compartment of the cell. The drug was allowed to diffuse through the membrane into 86 ml of distilled water which was stirred with a magnet at 60 rpm. The sink was analyzed in the same way as in the dissolution experiments. The diffusion coefficients were calculated to be  $8.0$  ( $7.9$ ,  $8.1$ )  $\times 10^{-6}$  cm<sup>2</sup>/s for alaproclate and to  $6.1$  ( $5.9$ ,  $6.3$ )  $\times 10^{-6}$  cm<sup>2</sup>/s for sulfamethizole applying the theory described by (Higuchi, 1962).

### **Results and Discussion**

As already pointed out in the Introduction it is quite clear that the hydrodynamic situation in any rotating disc system is complex (Dworak and Wendt, 1977; Gregory and Riddiford, 1956; Grijseels et al., 1981; Levich, 1962; Millsaps and Pohlhausen, 1952; Riddiford, 1966). On the other hand a great deal of complexity is avoided if one only aims at finding scaling conditions that can be utilized as a guide for extrapolation to dissolution regimes where neither diffusion nor convection is the rate-limiting step. In this sense the discussion presented below does not pretend to be complete nor exact. Furthermore, in real dissolution experiments there is always a regime in the vicinity of the solid surface which from hydrodynamic flow considerations has certain average dimensions and coupled to this, through a diffusion process, also a certain average solute concentration and concentration gradient. To get some idea about the order of magnitude of these numbers even a fairly crude model might be helpful. The presentation below will be given under these premises.

#### *Dissolution rate models*

The rate of dissolution,  $G$ , can be considered as governed by two processes, the true dissolution rate,  $k_1$ , and the 'rate of re-entry',  $k_2\bar{c}$ . Here  $\bar{c}$  is the time average concentration of solute in the immediate vicinity of the disc. It is the value of  $\bar{c}$  which is sensitive to the hydrodynamic field of flow as well as to the convection and diffusion processes in the medium. Thus,  $G$  is given by:

$$G = k_1 - k_2\bar{c} \quad (1)$$

In experiments of the rotating disc type, the effective diffusion layer thickness is of central importance to our understanding of the dissolution process. In the vicinity of the solid surface, a region with a high concentration gradient exists in which molecular diffusion is present due to reduced liquid bulk motion. Levich (1962) has

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derived an expression for the effective diffusion layer thickness in a laminar flow system of a centrally mounted rotating disc

$$\delta = 1.612 \cdot D^{1/3} \cdot \nu^{1/6} \cdot \omega^{-1/2} \quad (2)$$

The form of this expression can be assumed to be applicable within certain dimensional limits also for the present experimental conditions since the available drug surface can be regarded as part of a larger centrally rotating disc, i.e. the drug disc is sunk into the surface of the large rotating support, cf. Fig. 1.

In a paper by Millsaps and Pohlhausen (1952) the hydrodynamics of a large rotating disc system is treated in some detail. It is shown theoretically how both the velocity and the direction of flow vary with radial distance and angular velocity. From the velocity profile also an average hydrodynamic thickness of the liquid layer in the vicinity of a rotating disc has been calculated. Combining that theory with an argumentation similar to the one published earlier (Nicklasson et al., 1982b; Nicklasson et al., 1983), an expression for  $G$  at laminar flow is obtained, namely:

$$G = k_1 - k_3 \frac{1}{R\sqrt{\omega}} \quad (3)$$

Obviously, this leads to  $\bar{c}$  being inversely proportional to  $R\sqrt{\omega}$ . For large values of  $R$  and/or  $\omega$ ,  $G$  will approach the intrinsic rate of dissolution  $k_1$ . Experimentally,  $k_1$  is obtained by measuring  $G$  as a function of  $R$  and  $\omega$  and extrapolating to  $(R\sqrt{\omega})^{-1} = 0$

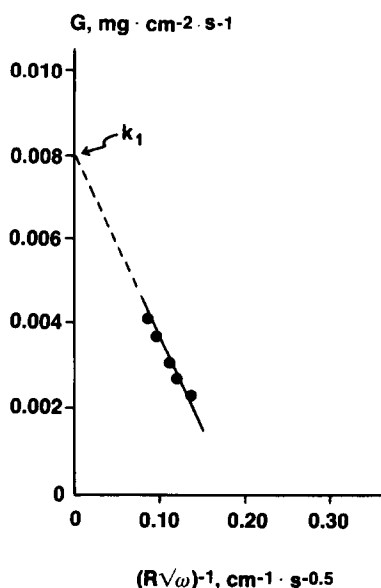


Fig. 2. Plot of  $G$  versus  $1/R\sqrt{\omega}$  for sulfamethizole in water at 37°C. The discs are mounted eccentrically,  $R = 1.6$  cm.

in a diagram  $G$  versus  $(R\sqrt{\omega})^{-1}$ . This means, essentially, that if  $R\sqrt{\omega}$  is sufficiently large, the concentration gradient governing the diffusion flow becomes so large that the Fickian flow no longer is the rate-determining step (Nicklasson et al., 1982a and b). The procedure is illustrated for sulfamethizole in Fig. 2. Some data for the dissolution rates of alaproclate hydrochloride and sulfamethizole are presented in Table 1.

#### *Diffusion boundary layers*

Utilizing the extrapolated values of the dissolution rate  $G$ , i.e.  $k_1$ , and visualizing a zone of transient concentration in the vicinity of the dissolving surface, it is possible to discuss in an approximate way, certain numerical aspects of the experimental dissolution process described. In the first place, one can estimate the apparent thickness of the diffusive zone in the vicinity of the disc through which the diffusion flow is identical to  $k_1$  (at  $(R\sqrt{\omega})^{-1} = 0$ ). The flux from the disc into a perfect sink can according to Fick's law be written as

$$|J| = D \left| \frac{dv}{dx} \right| = \frac{DC_s N_A}{hM_v} \quad (4)$$

In principle it is not necessary to assume the existence of a stagnant diffusive layer (Nernst and Brunner, 1904) for this expression to be valid. All depends upon how the relation between  $C_s$  and  $h$  is defined. One may for instance consider  $h$  to be the effective average distance (also taking a non-stagnant hydrodynamic flow into consideration) over which the concentration falls from  $C_s$  to zero. However, the model does not explicitly consider the influence of liquid velocity on the dissolution rate. In a more direct way an effective diffusion boundary layer thickness,  $\delta$ , could be calculated from Eqn. 2. The concepts 'stagnant diffusion layer' ( $h$ ) and 'effective diffusion layer' ( $\delta$ ) are discussed by Grijseels et al. (1981). In Fig. 3, values of the diffusion layer thickness  $h$  calculated from Eqn. 4 by inserting  $G = |J|$  are shown for

TABLE 1

DISSOLUTION RATES  $\pm$  S.E.,  $n = 6$  AND  $\delta/h$ -RATIOS FOR ALAPROCLATE AND SULFAMETHIZOLE AT VARIOUS ROTATING SPEEDS.  $R = 1.6$  cm

Rotating speed (rpm)	Alaproclate		Sulfamethizole	
	mg/(cm <sup>2</sup> ·s)	$\delta/h$	mg/(cm <sup>2</sup> ·s)	$\delta/h$
200	0.30 $\pm$ 0.002	0.60	0.0024 $\pm$ 0.00005	0.68
250	0.41 $\pm$ 0.004	0.57	0.0027 $\pm$ 0.00001	0.68
300	0.52 $\pm$ 0.004	0.57	0.0032 $\pm$ 0.00006	0.68
400	0.57 $\pm$ 0.002	0.54	0.0036 $\pm$ 0.00005	0.67
500	0.65 $\pm$ 0.005	0.55	0.0041 $\pm$ 0.00007	0.67
$\infty$	1.39 $\pm$ 0.098 *	0.57 **	0.0081 $\pm$ 0.0001 *	0.68 **

\* Calculated from Eqn. 3 by extrapolation to  $(R\sqrt{\omega})^{-1} = 0$ ,  $n = 5$ .

\*\* Estimated mean value,  $n = 5$ .

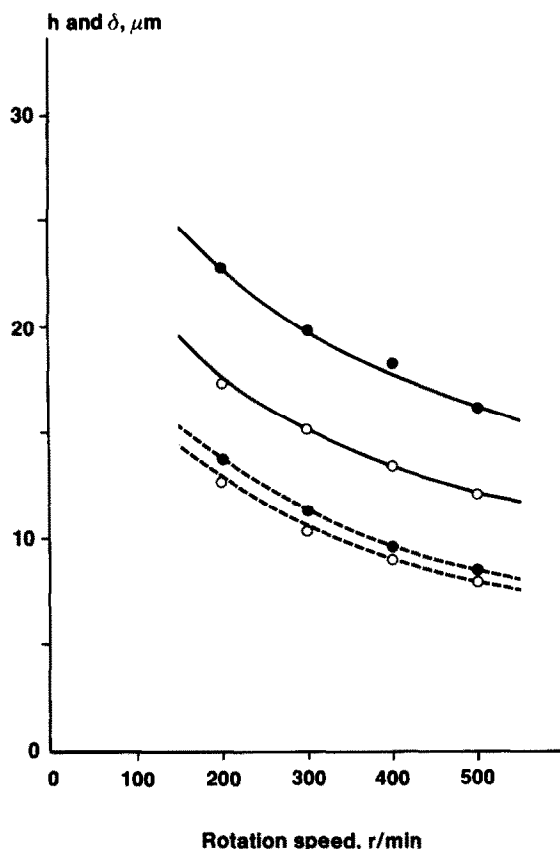


Fig. 3. Diffusion layer thickness as a function of rotation speed of the disc ( $R = 1.6$  cm). Solid lines denote the Nernst stagnant diffusion layer thickness,  $h$ , and dotted lines denote the effective diffusion layer thickness,  $\delta$ . ●, alaproclate-HCl; ○, sulfamethizole.

alaproclate and sulfamethizole at various rotating speeds. The 'effective diffusion layer thickness',  $\delta$ , calculated from Eqn. 2 are also shown in Fig. 3. The experimentally observed diffusion coefficients were used at both calculations. Obviously, the  $\delta$ -values cannot be calculated at infinite speed of rotation, cf. Eqn. 2. However, the stagnant diffusion layer thickness ( $h$ ) at  $R\sqrt{\omega} \rightarrow \infty$  can be calculated by inserting the  $k_1$ -value obtained from Eqn. 3 into Eqn. 4. By assuming that the  $\delta/h$ -ratio is independent of rotation speed,  $\delta$  can then be estimated. As can be seen in Table 1, the  $\delta/h$ -ratios do not vary with  $\omega$  and differ only little between the substances in spite of the large difference in  $G$ . The  $\delta/h$ -ratio at infinite speed of rotation was calculated as the mean value from the ratios obtained at finite speeds of rotation. For alaproclate  $h = 7.4 \mu\text{m}$  at  $R\sqrt{\omega} \rightarrow \infty$  which corresponds to a  $\delta$ -value of  $4.2 \mu\text{m}$ . The corresponding values of  $h$  and  $\delta$  for sulfamethizole are  $6.0$  and  $4.0 \mu\text{m}$ , respectively. The agreement is much better than to the order of magnitude which gives good confidence as to the significance of the calculated layer thickness.

### Time scales

Having access to the necessary concentration gradient to provide a diffusional flow equal to  $k_1$ , one can estimate the time scale for the formation of such a gradient from an initial state of pure solvent in contact with the solute disc. The physical situation is analogous to that of a free diffusion experiment and hence one can write:

$$\left| \frac{dv}{dx} \right|_{\max} \approx \frac{\Delta v}{\sqrt{4\pi Dt}} \approx \frac{C_s N_A}{M_v \sqrt{4\pi Dt}} \quad (5)$$

At the disc surface the concentration gradient is, cf. Eqn. 5,

$$\left| \frac{dv}{dx} \right|_{\text{disc surface}} \approx \frac{C_s N_A}{h M_v} \quad (6)$$

and since  $(dv/dx)_{\max} \approx (dv/dx)_{\text{disc surface}}$  one finds from Eqns. 5 and 6:

$$t_c \approx \frac{h^2}{4\pi D} \quad (7)$$

where  $t_c$  is the characteristic time associated with the formation of the stagnant diffusion layer. The release from rotating discs is not only governed by a free diffusion process but also by convection. Thus, the stagnant diffusion layer model presented by Nernst and Brunner (1904) cannot be assumed. A more accurate value for the diffusion layer thickness in such a system is the effective diffusion boundary layer,  $\delta$ , according to Eqn. 2 and by substituting  $h$  for  $\delta$  in Eqn. 7 will give the corresponding value of  $t_c$  pertinent to the hydrodynamic conditions. Fig. 4 shows  $t_c$  as a function of the effective diffusion layer thickness for alaproclate. As mentioned earlier, the estimated  $\delta$ -value at  $(R\sqrt{\omega})^{-1} = 0$  is  $4.2 \mu\text{m}$  for alaproclate. The value of  $t_c$  corresponding to this  $\delta$ -value is only  $1.8 \times 10^{-3}$  s, see Fig. 4. The  $t_c$ -value for sulfamethizole is  $2.1 \times 10^{-3}$  s. These values are very small compared to residence times reported at diffusion layers of about  $10$ – $15 \mu\text{m}$ . At a Nernst diffusion layer thickness of about  $12 \mu\text{m}$ , a residence time of  $0.1$  s for phenylbutazone at  $\text{pH} = 6.5$  has been stated (Mooney et al., 1981). The shortest distance to travel in order for the disc to come in contact with fresh solvent is assumed to be the diameter of the disc ( $a_d$ ). The corresponding time for this process is  $a_d/(R\omega)$ , (Nicklasson et al., 1982b). For a disc diameter corresponding to a  $1 \text{ cm}^2$  surface area and for a rotating speed of  $500 \text{ rpm}$  this latter time becomes equal to  $t_c$  at  $R = 12.0 \text{ cm}$  for alaproclate and  $10.3 \text{ cm}$  for sulfamethizole. With the present experimental set up,  $R = 1.6 \text{ cm}$ , a rotating speed of about  $3760 \text{ rpm}$  is needed to obtain a condition for alaproclate where  $t_c$  is equal to the time it takes to travel the distance  $a_d/(R\omega)$ . The corresponding value for sulfamethizole is about  $3230 \text{ rpm}$ , yielding an  $(R\sqrt{\omega})^{-1}$ -value of  $0.034 \text{ cm}^{-1} \cdot \text{s}^{-0.5}$ . This is close to the  $y$ -axis where the extrapolated  $k_1$  value is obtained as demonstrated in Fig. 2. However, problems with the laminar flow pattern are likely to arise at these rotating speeds making this experimental condition practically impossible to achieve. Using a lower agitation where the hydrodynamics of the

$t_c, s \times 10^3$

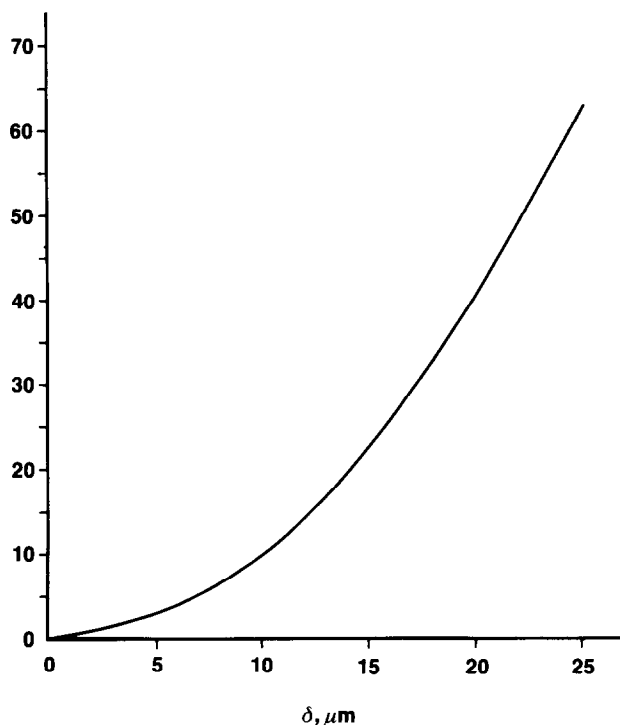


Fig. 4. Plot of the time to set up a concentration gradient ( $t_c$ ) as a function of the effective diffusion boundary layer ( $\delta$ ) for alaproclate-HCl in water at 37°C.

experimental system is under control and then extrapolating to  $(R\sqrt{\omega})^{-1} = 0$  therefore seems preferable.

#### *Molecular aspects of dissolution rate*

The number of molecules dissolving per second from an area on the crystal surface of the size of one molecule,  $A$ , disregarding diffusion and convection effects, can be expressed as:

$$\left| \frac{dN_+}{dt} \right|_A = \frac{k_1}{M_v} \cdot N_A \cdot A \quad (8)$$

For  $R\sqrt{\omega} \rightarrow \infty$ , 5400 alaproclate molecules per second and only 36 sulfamethizole molecules per second are dissolved according to Eqn. 8. The number of molecules dissolving within the time of formation of the concentration gradient, ( $t_c$ ), is about 10 for alaproclate and less than one molecule for sulfamethizole. For alaproclate, a

concentration of  $1.2 \times 10^{19}$  molecules per ml is obtained within the effective diffusion boundary layer (volume:  $4.2 \mu\text{m} \times 1.0 \text{ cm}^2$ ). The concentration of a saturated alaproclate solution is  $2.5 \times 10^{20}$  molecules per ml corresponding to 130 mg/ml. Thus, the average concentration within  $\delta$  is only about 5% of that of a saturated solution. This is also the case for sulfamethizole which implies that the concentration gradient is within the  $\delta$  layer instead of outside a saturated layer as defined by the Nernst and Brunner theory (1904).

In a convective system such as that of a rotating disc, a velocity gradient is developed in the liquid perpendicular to the disc surface (Z-direction Fig. 1). This velocity gradient is given by

$$\frac{dv}{dz} = \frac{\omega R}{l} \quad (9)$$

The relative speed at distance  $\delta$  (along the z-axis) from the disc surface can then be expressed as

$$\delta \cdot \frac{dv}{dz} = \delta \cdot \frac{\omega R}{l} \quad (10)$$

The time necessary to renew the crystal surface each time one molecule has dissolved,  $\tau$ , is equal to

$$\tau = \left| \frac{dN}{dt} \right|_A^{-1} \quad (11)$$

For alaproclate,  $\tau = 1.85 \times 10^{-4}$  s and for sulfamethizole  $2.77 \times 10^{-2}$  s as calculated from Eqns. 8 and 11. The time ( $t_c$ ) it takes to form the diffusion layer thickness ( $\delta$ ) is similar for the two compounds. However, the  $\tau$  values differ about 150 times. The time necessary to renew the crystal surface is thus shorter for the much more soluble alaproclate compared to sulfamethizole. The corresponding speeds of revolution,  $\omega_r$ , can then be expressed as

$$\omega_r = \frac{a_m l}{\delta R \tau} \quad (12)$$

If the disc is mounted 1.6 cm (R) from the rotating support,  $l = 0.5$  cm and  $\delta = 4.2 \mu\text{m}$ , a  $\omega$ -value of  $0.20 \text{ s}^{-1}$  is obtained for alaproclate. This angular velocity corresponds to a rotating speed of 1.92 rpm. The rotating speed for sulfamethizole at the same R and l conditions, but where  $\delta = 4.0 \mu\text{m}$ , is, however, only 0.013 rpm. If R is limited as in our case, the calculations show that the surface area should be as small as possible (ideally the area of one molecule) in order to obtain the initial mass transfer from solid to liquid phase at a finite rotating speed. The small disc surfaces needed will, however, be very difficult to prepare. For most practical purposes these experimental difficulties can be overcome by extrapolation to  $(R\sqrt{\omega})^{-1} = 0$  using a larger disc surface ( $0.5\text{--}1.0 \text{ cm}^2$ ).

In a previous paper (Nicklasson et al., 1982b), it was shown that closely similar values of  $k_1$  were obtained by extrapolations at various hydrodynamic conditions, i.e. laminar and turbulent flow. It was concluded that a value of  $k_1$  so obtained was a good measure of the intrinsic rate of dissolution. It is obvious from the numerical figures given above that the extrapolation procedure suggested earlier (Nicklasson et al., 1982b; Nicklasson et al., 1983) operates in intervals in which the experimental parameters  $R$  and  $\omega$  are clearly compatible with the theoretical assumptions. Thus, for most practical purposes, the dissolution rate model for rotating discs according to Eqn. 3 seems to be a good approach to obtain the maximum rate of transfer from solid to liquid phase. If a diffusion process is still present in the system, it can be considered as infinitesimal compared to the total mass transport at infinite rotation speed and/or infinite distance from the center of the rotating support. By applying this experimental approach for obtaining an absolute dissolution rate it is possible to compare data for different compounds on an equal basis, since there are no rate-limiting steps present, i.e. diffusion or convection. This might therefore be an adjunct for the determination and characterisation of in vitro dissolution kinetics and it is recommended in preformulation programs for new solid drug compounds together with other rotating disc methods which are more suitable for relative determinations.

#### List of symbols

$\delta$	= effective diffusion boundary layer
$\nu$	= kinematic viscosity
$\omega$	= angular velocity
$\tau$	= time for one molecule to dissolve
$l$	= perpendicular distance from the (rotating) disc surface to the (stationary) bottom of the container
$a_m$	= diameter of a molecule, $\sim 5 \times 10^{-8}$ cm
$a_d$	= diameter of the disc (8.0 mm in the present experiments)
$A$	= area of a molecule, $\sim 2 \times 10^{-15}$ cm <sup>2</sup>
$C_s$	= aqueous solubility, mg/cm <sup>3</sup>
$D$	= diffusion coefficient
$G$	= observed dissolution rate, mg/(cm <sup>2</sup> · s)
$h$	= Nernst stagnant diffusion layer thickness
$k_1$	= initial mass transfer from solid to aqueous phase i.e. intrinsic rate of dissolution, mg/(cm <sup>2</sup> · s)
$k_2$	= rate constant for reentry from solution
$k_3$	= proportionality constant
$M_v$	= molecular weight
$N_A$	= Avogadro's number
$R$	= distance from the rotating support to the disc, cf. Fig. 1
$t$	= time
$\frac{dv}{dx}$	= flux of molecules per volume unit and distance

$$\frac{dv}{dz} = \text{velocity gradient perpendicular to the disc surface}$$

$$\left| \frac{dN}{dt} \right|_A = \text{number of molecules dissolving from an area of the crystal surface corresponding to the size of a molecular diameter}$$

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