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On the determination of true dissolution rate parameters from rotating disc experiments

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Summary

A vertical rotating disc method has been used to further investigate the dissolution process. By varying the initial drug concentration in the receptor solution, the dissolution rate could be resolved into both the dissolution step and the re-entry step. Sulfamethizole, alaproclate-HCl and FLA 731 with very different aqueous solubilities served as model substances. Dissolution rates at infinite rotating speed were obtained at each initial concentration by using a previously described extrapolation procedure. Results are in good agreement with equilibrium solubility data and previously determined 'intrinsic' rates of dissolution.

Introduction

The dissolution from a solid surface has been described as a process which is mainly diffusion controlled, and various rate models taking into account the influence of experimental conditions have been reported (Higuchi et al., 1958; Nelson, 1958; Nelson and Shah, 1975; Shah and Nelson, 1975; Grijseels et al., 1981). In electrochemistry, rotating discs have been applied to study the ion transport in an electrochemical field (Levich, 1962; Riddiford, 1964). From these investigations, basic theories of fluid flow in the vicinity of centrically mounted rotating discs have been developed. In a previous paper (Nicklasson et al., 1981), a principle was indicated for a direct experimental determination of the rate of dissolution. The essential feature is that the rate of dissolution obtained by performing an extrapolation to infinite rotation speed and/or infinite distance from the

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center of rotation (Nicklasson et al. 1982b) reflects a condition where, at infinite dilution, the process next to the disc surface is almost entirely governed by the rate of mass transfer from solid to aqueous phase.

The aim of the present paper is to supply experimental evidence that conforms with this dissolution model. In particular the dissolution rate is studied as a function of the initial drug concentration in the receptor phase.

Materials and Methods

Chemicals

The drug substances sulfamethizole (Mv = 270) [1], alaproclate (Mv = 310) [2] and FLA 731 (Mv = 426) [3] were used as obtained.

Dissolution rates

Discs were prepared with an available surface area of 0.50 cm^2 in accordance with a method previously described for the determination of intrinsic rates of dissolution (Nicklasson et al., 1981). The discs were mounted vertically on a round rotating support by using a water-insoluble glue. Dissolution rates were determined spectrophotometrically (Pye Unicam SP8-100) in 50.0 ml of distilled water at 37°C. The dissolution medium was continuously recirculated through a flow cuvette using a peristaltic pump.

The release was also studied at various initial drug concentrations in the bulk solution (sulfamethizole 0.005–0.020 mg/ml; alaproclate 1.0–10.0 mg/ml; and FLA 731 2.5–15.0 mg/ml). The rotating speed of the discs was varied between 100 and 500 rpm. By using an extrapolation procedure, dissolution rates at infinite rotating speed were obtained.

The pH-values of the different aqueous drug solutions were determined (Orion 601A pH meter) to 4.8–5.0 for sulfamethizole, 4.3–4.5 for alaproclate, and 6.3–6.5 for FLA 731.

Diffusion coefficients

The diffusion coefficients for alaproclate and sulfamethizole were determined in water at 37°C to be 8.0×10^{-6} cm^2/s and 6.1×10^{-6} cm^2/s, respectively. 10 ml of a 5 mg/ml drug solution was placed in the upper compartment of a diffusion cell with a Spectrapor 1 membrane (Spectrum Medical Industries, U.S.A.). The drug was allowed to diffuse through the membrane into 86 ml of sink which was stirred with a magnet at 60 rpm. The sink was analyzed in the same way as in the dissolution experiments.

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[1] Syntetic, Grinsted Verket A/S, Denmark.

[2] Alanine 2-(4-chlorophenyl)-1,1-dimethyl ethyl ester hydrochloride monohydrate, Astra Läkemedel AB, Sweden.

[3] S(−)-3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)-methyl]-2,6-dimethoxybenzamide hydrochloride, Astra Läkemedel, Sweden.

Solubilities

The saturation concentrations in water at 37°C were determined for the drug substances as previously described (Nicklasson et al., 1981).

Theoretical aspects

Mass transfer from solid to aqueous phase is governed by: (a) the intrinsic tendency of the compound to dissolve; (b) the tendency of dissolved substance to re-enter the disc; and (c) the diffusion or convective flow in directions away from the disc. When the solution in the immediate vicinity of the solid/liquid phase boundary is in equilibrium with the solid surface, the rate of dissolution will be zero. Due to the principle of microscopic balance, however, the equilibrium is maintained by opposing directions but equal magnitude of processes (a) and (b). The overall rate of these processes taken separately is governed by a frequency factor (probability of transfer per molecule) as well as by a population number for the state in question. Assuming the solid to be a pure substance with surface properties independent of the solution state leads to the conclusion that the rate of mass transfer from the solid to the liquid phase (process (a)) is constant for given temperature and pressure. Furthermore, taking the solution to be sufficiently dilute to allow activity to be substituted by concentration one may write for the overall rate of dissolution, G.

$$G = k_1 - k_2 c \tag{1}$$

which at equilibrium reduces to

$$G_{eq} = 0 = k_1 - k_2 c_{eq} \tag{2}$$

Here k_1 is the 'microscopic' rate of transfer from the solid to the liquid phase as opposed by the 'microscopic' rate of the reverse process, $k_2 c$. Both k_1 and k_2 contain the frequency factors mentioned above and c_{eq} is the saturation concentration of the solid in the solution. It is clear that k_1 ought to be a characteristic parameter of the solid (in contact with the solvent in question) and it is sometimes called the 'intrinsic rate of dissolution'.

It could be concluded that the validity of Eqn. 1 for non-equilibrium concentrations is an example of linear response to a disturbance of equilibrium.

Although k_1 is a fundamental dissolution parameter for the solid/liquid interface, the value of the rate constant k_2 is also of interest since it governs the re-entry process. According to the dissolution model given by Eqn. 1, the constant k_2 could be evaluated from ordinary dissolution experiments if the substance concentration in the recipient solution is varied.

Consider a disc, mounted at a distance, R, well removed from the center of the rotating support. During one revolution of the disc surface, each volume element of the liquid adjacent to the disc is exposed to dissolution for only a very short moment. This time of exposure, τ, corresponds to a small fraction of one complete

revolution. If the diameter of the disc is a, the fraction of one revolution during which each liquid element is exposed to the disc will be proportional to $a/(2\pi R)$. This number becomes small when the ratio a/R is made small. The angular velocity of the disc is $\omega = 2\pi\nu$ where ν is the number of revolutions per second. The time for one complete revolution becomes $1/\nu = 2\ \pi/\omega$. Multiplication of the fraction of exposure with the time for one revolution leads to the time of exposure, τ, according to

$$\tau = \frac{a}{R\omega} \tag{3}$$

Let δ_m be the amount of solute dissolved from the disc into an adjacent volume element per revolution. δ_m will be proportional to $G\tau$, i.e.

$$\delta_m \propto G\tau \propto \frac{Ga}{R\omega} \tag{4}$$

When the support is in rotation, the average solute concentration in the vicinity of the disc surface will depend on the hydrodynamic situation and the types of transport processes that are in operation. With the disc arrangement used (see above) the liquid flow over the solid surface will be turbulent, thus probably averaging out the solute concentration over some small distance perpendicular to the surface. Outside this layer, diffusion and convection may set up a steady-state transport directed away from the disc. According to this model it will be expected that the average concentration, $\bar{c}$, in the liquid layer adjacent to the disc will be proportional to δ_m if the liquid initially consists of only solvent. If initially the concentration is c_0 the average concentration in the layer will be

$$\bar{c} = c_0 + k'\delta_m \tag{5}$$

where k' is a proportionality factor. Combining Eqns. 1, 4 and 5 gives

$$G = k_1 - k_2\left(c_0 + k_3\frac{Ga}{R\omega}\right) \tag{6}$$

where k_3 is another proportionality factor. In Eqn. 6 the observed dissolution rate G can be separated out, giving

$$\frac{1}{G} = \frac{1}{k_1 - k_2c_0} + \frac{k'_3}{\omega} \tag{7}$$

where

$$k'_3 = \frac{k_3ak_2}{R(k_1 - k_2c_0)} \tag{8}$$

Plotting $1/G$ (G is the observed dissolution rate) as a function of $1/\omega$ according to

Eqn. 7 gives straight lines with intercepts equal to $1/(k_1 - k_2c_0)$. Both the 'intrinsic rate of dissolution' from solid to aqueous phase, i.e. k_1, as well as the rate constant for re-entry from aqueous to solid phase, i.e. k_2, can then be calculated by plotting the inverse of the intercepts (i.e. $k_1 - k_2c_0$) obtained at each initial recipient phase concentration as a function of c_0.

Results and Discussion

The 3 drug substances were selected due to their difference in dissolution and solubility properties (Nicklasson et al., 1981). The solubilities in water at 37°C are shown in Table 1.

Fig. 1a–c show the principle of the extrapolation procedure for the drug compounds both in pure water and at different initial concentrations in the receptor phase. As can be expected from Eqn. 7, the intercepts attained at $c_0 > 0$ seem to be higher than those attained in pure water. However, the intercepts are not statistically different on the 5% level. The dissolution rates determined at finite speeds of revolution, on the other hand, are significantly different. The 95% confidence intervals of the dissolution rates for alaproclate at 200 rpm were found to be 0.37–0.38 and 0.26–0.30 mg/(cm^2 · s) at $c_0 = 0$ and $c_t = 7.5$ mg/ml, respectively. At 500 rpm, the corresponding confidence intervals were calculated to be 0.77–0.79 and 0.50–0.52 mg/(cm^2 · s). Similar results were obtained also for sulfamethizole and FLA 731. This may therefore indicate that the mass transport from solid to aqueous phase is slower at higher initial concentrations in the bulk solution.

The intercepts obtained at various initial concentrations of the drug compounds have been plotted as a function of c_0 in Fig. 2a–c. The values of k_1 and k_2 for each drug compound can be calculated from the intercepts and the slopes according to Eqn. 1. The k_1 values can also be calculated from Eqn. 2 using the k_2 values obtained from the slopes. In order not to affect the surface of the discs, our experimental technique is based on continuous registration of the amount dissolved

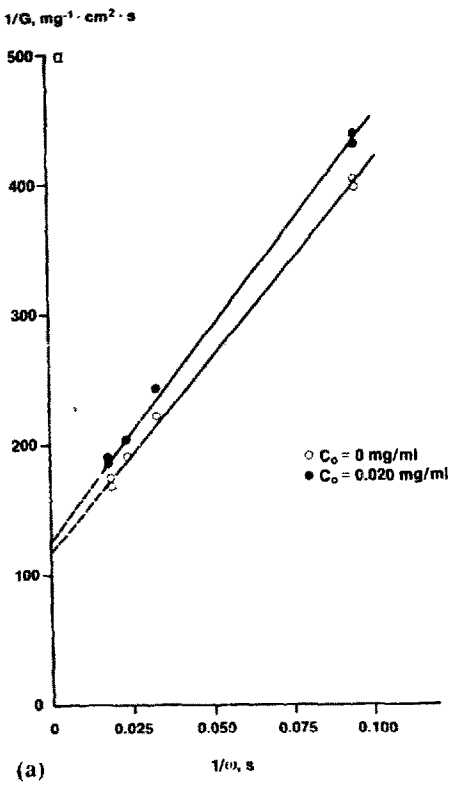
TABLE 1

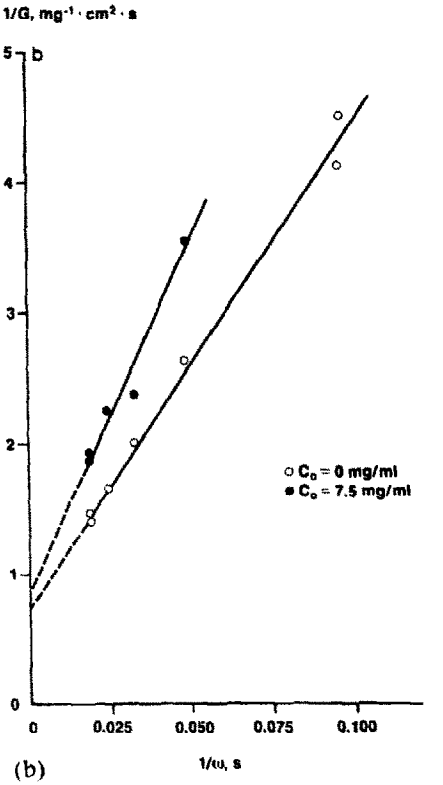
SOLUBILITIES AND INITIAL DISSOLUTION RATES IN PURE WATER AT 37°C

Substance	S (mg/ml)	k_1 (mg/(cm^2 · s))		
		a	b	c
Sulfamethizole	0.8	0.0081	0.0083	0.0096
Alaproclate	130	1.39	1.32	1.34
FLA 731	375	4.19	4.03	4.70

The solubilities have been determined from equilibrium experiments. The rate constants in columns b and c have been obtained by the procedure described in this paper.

a = in pure water; b = extrapolation to zero initial concentration according to Eqn. 1; c = according to Eqn. 2.





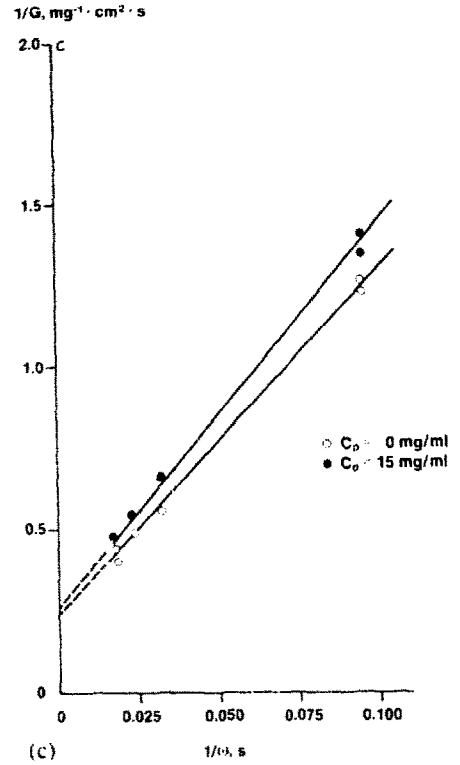


Fig. 1. $1/G$ versus $1/\omega$ for discs mounted vertically on the rotating support. (a) sulfamethizole (b) alaproclate (c) FLA 731

during a short period of time (1–2 min). During this time, a very small amount of the disc is dissolved. To avoid a loss of analytical sensitivity, it was therefore not possible to use any higher bulk concentrations. At high concentrations, alaproclate even formed slightly opaque solutions. For all the compounds, difficulties in reading the absorbance values continuously were still present when c_0-reference solutions were used. Thus, the slopes in Fig. 2a–c are very small due to the narrow

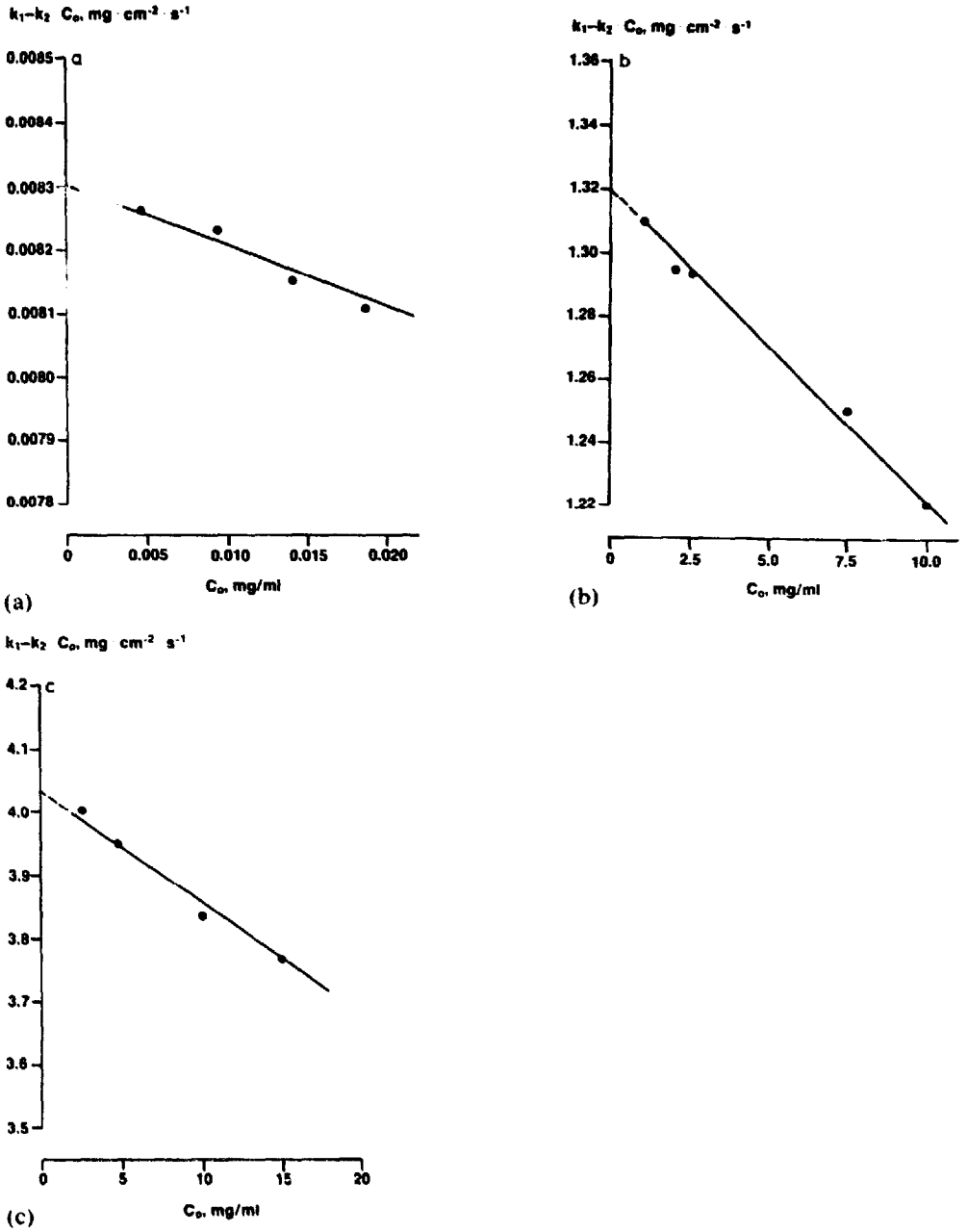


Fig. 2. Dissolution rates ($k_1 - k_2c_0$) at infinite rotation speed as a function of initial receptor phase concentration (c_0). (a) sulfamethizole (b) alaproclate (c) FLA 731

concentration range that could be investigated. However, in essence they reflect an extrapolated difference between the lines in Fig. 1a–c, which clearly indicates that the trend is real and of good confidence. Recently, a way to determine the dynamic solubility of cholesterol by plotting dissolution rates versus bulk concentrations and extrapolating to zero dissolution rate was published (Feld and Higuchi, 1981). The same extrapolation procedure can be performed in Fig. 2a–c. At zero dissolution rate, dynamic solubility values of 0.69, 129 and 351 mg/ml were calculated for sulfamethizol, alaproclate and FLA 731, respectively. In spite of long extrapolations, these values are in agreement with the experimental ones shown in Table 1. This indicates that the relationships between dissolution rates and bulk concentrations shown in Fig. 2a–c are applicable.

Table 1 shows the values of k_1 determined by the different approaches. The similar initial dissolution rates obtained indicate that the stated convective dissolution model for our rotating disc technique is valid. The relatively more divergent results obtained by using Eqn. 2 are mainly explained by a larger error in the evaluation of k_2, cf. the small slopes in Fig. 2a–c.

An interesting observation is that the value of k_2 seems to be relatively independent of the dissolution and solubility properties of the substance. This is consistent with previously reported experiments from which a mean k_2-value of 0.0115 cm/s can be calculated (Nicklasson et al., 1982a). In this study, k_2 was calculated to be 0.0122, 0.0103 and 0.0125 cm/s for sulfamethizole, alaproclate and FLA 731, respectively. The relative substance independence might be due to the character of k_2. Since it measures the re-entry process, k_2 will depend on the type of transport taking place in the aqueous phase. If this transport is diffusion controlled, the rather constant k_2-values will follow from the similar diffusion coefficients of the substances, i.e. 6.1×10^{-6} cm/s for sulfamethizole and 8.0×10^{-6} cm/s for alaproclate in water at 37°C. The molecular weight for FLA 731 is similar to the ones for alaproclate and sulfamethizole. A substantial difference in diffusion coefficient is therefore not expected for FLA 731. No matter what the time mechanism of transport that governs k_2 is, its substance independence would in the case of a strongly hydrodynamic process indicate highly reproducible experimental conditions.

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