J. Pharm. Pharmac., 1972, **24**, 724–728 *Received March* 14, 1972

Some parameters describing the dissolution rate of salicylic acid at controlled pH

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Rates of dissolution of salicylic acid have been determined at constant pH in the absence of buffer salts by use of a pH-stat. The dissolution rate increased with increasing pH up to a maximum of pH 4·0. An increase in stirring speed brought about an increase in dissolution rates at each pH. Diffusion layer thickness and diffusion coefficients have been determined utilizing viscosity and density measurements.

Higher blood levels in man have been reported following the administration of salts of weak acids rather than the weak acids themselves (Furez, 1958; Nelson, Knoechel & others, 1962). *In vitro* investigations of relative dissolution rates of weak acids and their salts in solvents at a range of pH levels including those of gastrointestinal fluids have also been made (see for example Nelson, 1957; Gibaldi, 1970).

There have been difficulties in the analysis and interpretation of *in vitro* findings that could be the result of the addition of buffering agents to the system, the arbitrary selection of agitation intensity and the use of an insufficient number of pH levels. Although the difficulties of relating agitation intensities used in dissolution systems *in vitro* to *in vivo* systems have been acknowledged (Gibaldi, Feldman & others, 1968), the selection of agitation intensities for *in vitro* tests remains empirical. Also, the effect of pH on dissolution rate at various agitation intensities has not been extensively investigated. We have examined the relation between these two parameters for the *in vitro* dissolution of a weak acid. The influence of pH has been divided into effects on diffusion coefficient and diffusion layer thickness.

MATERIALS AND METHODS

Materials. Salicylic acid A.R. (BDH) was used as the dissolving solid. Non-disintegrating discs, diameter 19·05 mm, were prepared by compression of 1·0 g of acid in an Apex type A14 hydraulic press at 300 MNm^{-2}. NaOH A.R. (Fisons) as 0·1 and 0·01M solutions in distilled water was used as titrant.

Solubility determinations. An excess of salicylic acid was added to 30 ml of distilled water in 50 cm^3 Quickfit Erlenmeyer flasks and the pH adjusted to the required value. The flasks were shaken (2 strokes/s) over a stroke length of 3 cm in a water bath (37 $\pm$ 0·1°) for a minimum of five days and the pH was finally adjusted to the required value.

Viscosity determinations. Viscosities of filtered saturated solutions were determined at 37 $\pm$ 0·1° in a Rheometer R.M.15 (Contraves, Zurich). The shear rates ranging from 225·9 to 766·3 s^{-1} were increased and then decreased for all viscosity measurements. An interval of 30 s was allowed between readings.

Density and weight/cm^3 determinations. The densities of saturated solutions at pH 1·0 to 4·0 were determined in 50 cm^3 density bottles. The high viscosities of solutions at pH 5·0 to 7·0 made the use of density bottles impracticable, therefore the densities of these solutions were obtained by placing solutions in 25 cm^3 volumetric

flasks and weighing. In all cases glassware was calibrated with distilled water at 37 ± 0·1°.

Dissolution rate determinations: (a) *Apparatus.* The dissolution cell was similar to that of Rahman (1971). It consisted of a 500 cm³ Perspex cylinder 9·5 cm diameter. A titanium disc holder, machined to the exact dimensions of the disc, fitted into a central cavity of the Perspex base so that the single face of the disc exposed to dissolution medium formed part of the smooth cell base. Stirring was effected by a Perspex paddle driven by synchronous motors (Crouzet Ltd.) and the distance between the paddle and disc was maintained constant. A pH stat (Radiometer, Copenhagen) comprising pH meter 26, titrator 11 and autoburette ABU 11, enabled the pH of the dissolution medium to be monitored and maintained at any required pH by the automatic addition of titrant. The Radiometer electrodes (glass type G202C and calomel reference type K401) and the tip of the titrant delivery tube were situated in the dissolution cell.

(b) *Procedure.* Salicylic acid discs were mounted in the titanium holder in the dissolution cell, 200 cm³ of distilled water at 37 ± 0·1° and the required pH were added to the cell and the stirrer motor started. At suitable intervals 2 cm³ samples were removed.

Assay procedure. Before assay, samples of salicylic acid solution from the dissolution cell were passed through a Millipore filter (0·45 nm pore size) where necessary, and saturated salicylic acid solutions were passed through a sintered glass filter, pore size 4. Appropriate dilutions were made in 0·1M HCl before spectrophotometric determinations of salicylic acid at 298 nm.

RESULTS AND DISCUSSION

The Noyes-Whitney equation relates the rate of dissolution of a solute to the difference in concentration between the saturation solubility, C_s, and the concentration, C, of the dissolved solute in the bulk solution.

$$\frac{dC}{dt} = KS(C_s - C) \qquad (1)$$

S is the area of solid surface exposed to the solvent and K is the dissolution rate constant. The experimental design in the present work was such that $C_s \gg C$ with S remaining constant and in these circumstances equation (1) can be reduced to the following form

$$\frac{dC}{dt} = K'C_s \qquad (2)$$

K′ is the reduced dissolution rate constant.

Fig. 1 shows the typical plots of the amount of salicylic acid dissolved versus time. In all cases these plots have been found to be linear, indicating that equation (2) satisfactorily provides a kinetic description of the dissolution process. The values of dissolution rate constant obtained following dissolution in solvent at constant pH and different stirring rate, are shown in Table 1. At any one stirring speed the dissolution rate constant increases linearly with pH up to and including pH 4·0. Beyond this pH the rate constant is invariant; a phenomenon similar to that reported for tolazamide acid in buffer solutions (Higuchi, Mir & others, 1965).

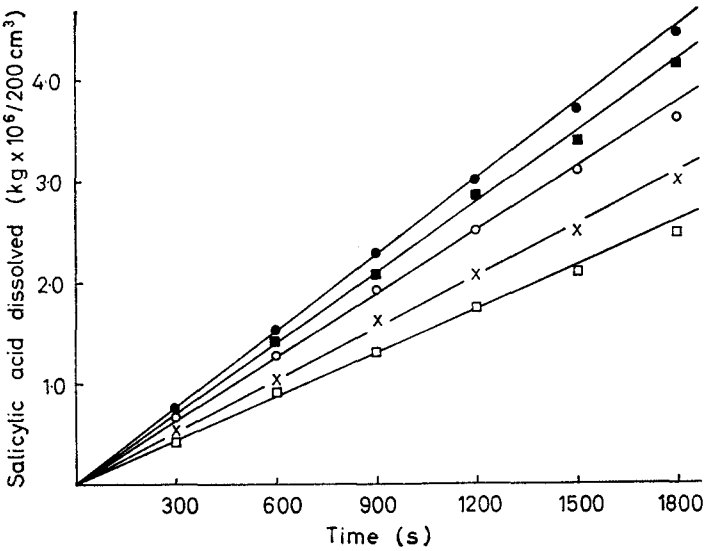

FIG. 1. Plot of amount of salicylic acid dissolved at pH 1·0 as a function of stirring speed □ 40, × 60, ○ 80, ■ 100, ● 120 rev/min.

Table 1. *Dissolution rate constant* (K g/s × 10^{10}) *at various pH values and stirring rates.*

	Stirring rate rev/min				
pH	120	100	80	60	40
1·0	2·477	2·272	2·027	1·684	1·385
2·0	2·848	2·699	2·229	1·988	—
3·0	3·356	3·262	2·776	2·601	1·997
4·0	3·598	3·307	3·025	2·600	1·974
5·0	3·629	3·363	2·908	2·608	2·019
6·0	3·719	3·353	2·970	2·690	1·942
7·0	3·639	3·349	3·029	2·644	2·007

The relation between dissolution rate constant and stirring speed for cells similar in principle to that used in this work is given by:

$$K'C_s = a(\text{rev/min})^b \quad .. \quad .. \quad .. \quad (3)$$

where a and b are constants. The value of b is 0·5 for a diffusion controlled process (Cooper & Kingery, 1962; Bircumshaw & Riddiford, 1952). Values of b at each pH have been estimated from plots of log $K'C_s$ versus log (rev/min) and are:

pH	1·0	2·0	3·0	4·0	5·0	6·0	7·0
Slope	0·5399	0·5514	0·4951	0·5413	0·5299	0·5689	0·4344

In all cases the values are close to the theoretical value for a diffusion controlled process having a mean of 0·537 and standard deviation of 0·023, and are similar to the value of b=0·49 reported by Levy (1963) for salicylic acid at pH 1.0.

According to Jost (1960) the diffusion layer thickness (δ) in the case of a solvent flowing linearly over a dissolving solid may be calculated from

$$\delta = \sqrt{\frac{\eta\xi}{dv}} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where η is the viscosity of the medium in poise, ξ is the linear dimension of the surface of the solid in cm across which a dissolution medium flows, v is the velocity

of flow in cm/s, d is the density of the medium. Nelson (1957) modified the equation such that

$$\delta = \sqrt{\frac{\eta}{d} \times \frac{1}{\text{rev/s}}} \quad .. \quad .. \quad .. \quad .. \quad (5)$$

where rev/s = the revolutions per second of the stirrer in a dissolution cell, similar in principle to the one used in this work. Values of diffusion layer thickness calculated from data in Table 3, by use of equation (5) are shown in Table 2. At all

Table 2. *Diffusion layer thickness* δ *m* $\times$ 10^2 *calculated from equation* (5) *and diffusion coefficients D* m^2 $\times$ 10^{10} *calculated from equation* (6) *as a function of pH and stirring rate.*

	Stirring rate rev/min									
	120		100		80		60		40	
	δ	D	δ	D	δ	D	δ	D	δ	D
1·0	0·06126	16·5	0·06724	15·1	0·07512	13·5	0·08663	11·2	0·1066	0·2
2·0	0·06096	13·9	0·06692	13·1	0·07475	10·8	0·08622	9·7	—	—
3·0	0·06076	7·0	0·06669	6·8	0·07450	5·8	0·08592	5·4	0·1057	4·2
4·0	0·06237	2·44	0·06845	2·24	0·07647	2·05	0·08820	1·76	0·1086	1·34
5·0	0·1486	0·13	0·1631	0·12	0·1822	0·10	0·2102	0·09	0·2587	0·07
6·0	0·1941	0·10	0·2131	0·10	0·2381	0·08	0·2746	0·074	0·3379	0·05
7·0	0·1941	0·10	0·2131	0·10	0·2380	0·08	0·2745	0·070	0·3379	—

Table 3. *Density, equilibrium solubility and viscosity at* 37° *of salicylic acid solutions as a function of pH.*

pH	Density K g m^{-3}	C_s K g m^{-3} $\times$ 10^3	Viscosity* mNm^{-2} s
1·0	995·66	2·64	0·7473
2·0	994·47	3·61	0·7392
3·0	995·68	8·40	0·7351
4·0	1010·29	25·89	0·7700
5·0	1180·94	502·6	5·2171
6·0	1245·50	639·9	9·3885
7·0	1244·80	663·8	9·3805

* pH 1·0–4·0 MS–0 system below shear rate of 766·3 s^{-1}
pH 5·0 A cup below shear rate of 399·0 s^{-1}
pH 6·0 & 7·0 A cup below shear rate of 225·9 s^{-1}

stirring speeds other than 40 rev/min, δ increases with pH; over the pH range investigated there is a 300% increase in thickness. The value of 610 μm obtained at pH 1·0 compares with that of 700 μm reported by Levy (1963). The effect of stirring speed on δ is less pronounced than the effect of pH, 50% being the maximum increased in thickness as the stirring rate is reduced from 2 to 0·66 rev/s. These observations indicate that in the case of an acidic drug, pH has a greater control over the dissolution rate over the range of pH values and stirring rates tested, than does stirring rate.

On the assumption that the dissolution under the experimental conditions used is a diffusion controlled process, then the data may be examined in terms of the model of Nernst & Brunner (1904). They presented a model which includes a diffusion controlled process in the solution phase and dissolution rate is given by

$$\frac{dC}{dt} = \frac{D.S}{h}(C_s - C) \quad .. \quad .. \quad .. \quad .. \quad (6)$$

where K (the dissolution rate constant) has been partitioned into D, the solute

molecule diffusion coefficient, and h is the effective diffusion layer thickness. The other terms are as defined in equation (1). When C = 0 then equation (6) may be re-arranged to give:

$$D = \frac{\left(\frac{dC}{dt}/S\right)h}{C_s} \quad .. \quad .. \quad .. \quad .. \quad (7)$$

Thus the diffusion coefficients may be calculated from the slope of a plot of dissolution rate per unit area at different pH versus equilibrium solubility at the corresponding pH and the corresponding diffusion layer thickness. Furthermore, in cases of non-linearity of the plots of dissolution rate/unit area versus equilibrium solubility an estimate of the value of $(dc/dt)/C_sS$ may be obtained from the gradient at any one point. Higuchi, Parrott & others (1958) have treated the Nernst-Brunner equation in a similar manner and applied it to the dissolution of a weak acid in solutions of buffers at basic pH values.

Table 2 shows diffusion coefficients as a function of pH and stirring rate. The value for the diffusion coefficient at 120 rev/min and pH 1·0 is $16{\cdot}5 \times 10^{-10}m^2s$ which is of the same order as that of $11{\cdot}7 \times 10^{-10}m^2s$ at pH 1·0 reported by Edwards (1951). Diffusion coefficients at any one stirring speed decrease approximately one hundred-fold as pH is increased from pH 1·0 to pH 7·0 (salicylic acid concentration increases from 0·022 to 4·8M). According to the data of Edwards (1951) the diffusion coefficient of salicylic acid in 0·005M solutions at pH 1·5 is the same as that in a bulk solution at pH 4·5 at an equivalent molarity. It can therefore be assumed that in a very dilute solution the diffusion coefficient of the protonated and non-protonated forms of salicylic acid are equivalent. Similarly, Edwards reports that the diffusion coefficient of salicylic acid at pH 1·5 decreases by about 10% as the concentration of salicylic acid increases from 0·0005 to 0·005M. It is probable that the reduction in the value of diffusion coefficient reported here and the increased viscosity of saturated solution observed at the higher pH values are a result of a large decrease in the volume fraction of free water.

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