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The dissolution of salicylic acid in micellar solutions of polysorbate 20

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Dissolution rates of salicylic acid in micellar solutions of polysorbate 20 have been determined at pH 1·0 to 4·0 using a pH-stat to maintain the pH. At any one pH, as the concentration of polysorbate 20 was increased up to 12% w/v, the dissolution rate increased, but a further increase up to 20% w/v polysorbate 20 only slightly increased the dissolution rate. At any one concentration of polysorbate 20 the dissolution rate increased linearly as the pH was increased. The dependence of dissolution rate on such parameters as viscosity of the dissolution medium, diffusion layer thickness and diffusion cofficient has been examined.

The use of surfactants as a means of increasing solubility and dissolution rate of drugs with low water solubility is well established (Gibaldi & Feldman, 1970). The influence of such agents on heterogeneous reactions has been investigated at the physico-chemical level and it is known, for example, that increased viscosity resulting from the addition of surfactants can bring about a decrease in the rate of a diffusion controlled process. Factors controlling dissolution in pharmaceutical systems are less clearly documented. Within the context of *in vitro* dissolution testing most workers have used non ionizing drugs or weakly ionizing drugs at one pH in the presence of surfactants as their test system (Parrott & Sharma, 1967; Elworthy & Lipscomb, 1968). In general, they found that dissolution rate increased with increasing surfactant concentration until a maximum rate was obtained followed by a decreasing rate with further increases in surfactant concentration. The most common explanation to account for these observations was that the surfactant increased the viscosity of the dissolution media thereby decreasing drug diffusion. More information concerning pH effects is required for a clearer understanding of the influence of surfactants on the dissolution of drugs, such as weak acids, which are exposed to changing pH environment in the gastrointestinal tract.

In a previous communication we investigated the dissolution of a weak acid at different pH. We have now extended the work to take account of the influence of micellar concentrations of surfactant on dissolution at different pH.

MATERIAL AND METHODS

Materials

The preparation of non disintegrating discs of salicylic acid (BDH) has been previously described. Polysorbate 20 (Koch light) was characterized according to the method of Crooks, Collett & Withington (1974) and used as obtained. NaOH AR (Fisons) as 0·01M and 0·1M solutions in distilled water was used as the titrant.

Methods

Solubility. The solubility of salicylic acid was determined at 37 ° in a series of

aqueous solutions containing various concentrations of polysorbate 20 at pH 1·0 to 4·0 and in a series of aqueous solutions of methyl cellulose at pH 1·0.

Viscosity. Viscosities of filtered saturated solutions of salicylic acid in various concentrations of polysorbate 20 at pH 1·0 to 4·0 were determined at 37 ° in a Rheometer R.M.15 (Contraves, Zurich). The viscosities of filtered saturated solutions of salicylic acid in methyl cellulose solutions were measured at pH 1·0.

Density. Densities of filtered saturated solutions of salicylic acid in various concentrations of polysorbate 20 at pH 1·0 to 4·0 were measured in 50 cm^3 bottles.

Dissolution studies. Dissolution rates at 37 ° were obtained using the method reported previously (Collett, Rees & Dickinson, 1972). A series of aqueous solutions containing various concentrations of polysorbate 20 or methyl cellulose at the required pH were used as the dissolution media. pH control was effected by using a Radiometer pH-stat assembly (Copenhagen, Denmark). The stirrer speed was 80 rev min^{-1}.

Assay procedure. Samples were diluted appropriately with 0·1M hydrochloric acid and assayed spectrophotometrically for salicylic acid at 298 nm. At this wavelength, polysorbate 20 showed some ultraviolet absorbance and this was taken into account when calculating the amount of salicylic acid in a solution.

RESULTS AND DISCUSSION

Table 1 shows the saturation solubilities of salicylic acid in micellar solutions of polysorbate 20. There is a linear relation between solubility and concentration of polysorbate 20 at pH 1·0 to 4·0. This effect is attributed to the solubilization of salicylic acid by the micelles of the surfactant (Gibaldi, Feldman & Weiner, 1970). Also, as the pH is increased so the saturation solubility of salicylic acid is increased.

Table 1. *Saturation solubilities (kg m^{-3}) of salicylic acid in aqueous polysorbate 20 solutions at pH 1·0 to 4·0.*

% w/v Polysorbate 20	pH 1·0	2·0	3·0	4·0
0	2·64	3·6	6·58	25·89
1	3·25	4·2	7·13	26·53
2	3·53	4·77	7·83	33·56
4	5·62	6·98	10·16	36·13
5	6·98	7·54	12·76	38·78
8	8·20	8·43	15·45	43·80
12	11·3	11·76	19·18	52·10
16	14·7	16·86	26·62	68·40
20	17·3	18·00	34·72	78·04

The saturation solubilities of salicylic acid in methyl cellulose solutions at pH 1·0 are presented in Table. 2 These solubilities show a small increase as the concentration of methyl cellulose is increased. It is possible that adsorption of salicylic acid by methyl cellulose produces this increased solubility.

Dissolution experiments were performed using 0 to 20% w/v aqueous polysorbate 20 solutions at pH 1·0 to 4·0 as dissolution media. Plots of amount of salicylic acid dissolved as a function of time were found to be linear. Dissolution rate constants were obtained from the slopes of these lines. Fig. 1 is a plot of dissolution rate constants against polysorbate 20 concentration. Inspection of these curves indicates that the dissolution rate constants are influenced by both pH and polysorbate 20

Table 2. *Viscosities (mN m^{-2} s) of aqueous methyl cellulose and polysorbate 20 solutions, and the dissolution rate constants and saturation solubilities of salicylic acid in methyl cellulose solution, all at pH 1·0.*

% w/v methyl cellulose	% w/v polysorbate 20	Viscosity mN m^{-2} s	Dissolution rate constant kg s^{-1} × 10^{8}	Solubility of salicylic acid kg m^{-3}
1	20	2·63	1·44	3·9
0·75	16	1·90	1·67	3·9
0·50	12	1·37	1·68	3·5
0·375	8	1·15	1·68	3·37
0·25	5	0·98	1·78	3·21
0·125	3	0·82	1·74	3·33

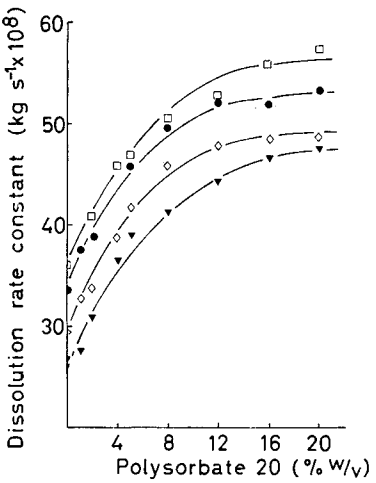

FIG. 1. Plot of dissolution rate constants (kg s^{-1} × 10^{8}) against concentration of polysorbate 20 at several pH values ▼ pH 10·, ◇ pH 2·0, ● pH 3·0, □ pH 4·0.

concentration. At any one concentration of polysorbate 20, the dissolution rate constant increases as the pH is increased. At any one pH, as the concentration of polysorbate 20 is increased up to 12% w/v, the dissolution rate constant is also increased. However, when the concentration of polysorbate 20 is increased from 12 to 20% w/v, the dissolution rate constant only increases very slightly.

According to Noyes-Whitney (1897), the simplest theory describing dissolution, an increase in total solubility should lead to an increase in dissolution rate. We did not observe a linear increase in dissolution rate with increasing surfactant concentration. More specific theories indicate that parameters, such as viscosity of the dissolution medium, drug diffusion coefficient and diffusion layer thickness are involved in the control of dissolution rate. It follows that a better understanding of the effects of micellar concentrations of surfactant on dissolution rate at controlled pH will be obtained if estimates of these parameters are known.

Diffusion layer thicknesses, shown in Table 3, have been calculated from an equation by Nelson (1957) utilizing density and viscosity values presented in Table 4.

$$\delta = \sqrt{\frac{\eta}{d} \times \frac{1}{\text{r.p.s.}}} \qquad .. \quad .. \quad .. \quad (2)$$

where r.p.s. = revolutions per second of the stirrer in the dissolution cell, d is the

density and η is the viscosity, in poise, of a saturated solution of solute. The diffusion layer thicknesses at each concentration of polysorbate 20 remain relatively constant as the pH is increased from 1·0 to 4·0. At each pH level, the diffusion layer thickness increases as the concentration of polysorbate 20 is increased. A two-way analysis of variance was performed on the values of diffusion layer thickness. The variance ratios at $P = 0{\cdot}01$ indicate that the concentration of polysorbate 20 has a significant effect on the diffusion layer thickness. Thus, at pH 1·0 to 4·0 the diffusion layer thickness is controlled by the amount of polysorbate 20 present in the dissolution medium and not by the pH of the dissolution medium.

Table 3. *(a) Diffusion layer thicknesses ($m \times 10^2$) and (b) diffusion coefficients ($m^2\ s^{-1} \times 10^{10}$) as a function of pH and concentration of aqueous polysorbate 20 solutions.*

% w/v Polysorbate 20	pH 1·0		2·0		3·0		4·0	
	a	b	a	b	a	b	a	b
0	0·0751	17·7	0·0748	14·0	0·0745	7·0	0·0765	2·45
1	0·0737	14·9	0·0732	13·7	0·0739	9·4	0·0765	2·69
2	0·0749	15·9	0·0756	12·5	0·0759	8·7	0·0791	2·13
4	0·0779	11·4	0·0777	9·7	0·0793	7·5	0·0835	2·21
5	0·0789	9·8	0·0807	9·7	0·0816	6·2	0·0855	2·06
8	0·0831	8·8	0·0855	9·5	0·0888	5·7	0·0924	1·98
12	0·0897	6·9	0·1004	7·2	0·1008	4·8	0·1127	1·78
16	0·1127	5·6	0·1141	5·0	0·1115	3·4	0·1256	1·44
20	0·1245	4·8	0·1415	4·7	0·1295	2·7	0·1533	1·29

Table 4. *(a) Viscosities ($mN\ m^{-2}\ s$) and (b) densities ($kg\ m^{-3} \times 10^3$) of filtered saturated solutions of salicylic acid in aqueous polysorbate 20 solutions at pH 1·0 to 4·0.*

%w/v Polysorbate 20	pH 1·0		2·0		3·0		4·0	
	a	b	a	b	a	b	a	b
0	0·7473	0·999	0·7392	0·994	0·7351	0·995	0·7700	1·181
1	0·7211	0·996	0·7136	0·993	0·7286	0·999	0·7845	1·123
2	0·7433	0·998	0·7499	0·985	0·7659	0·998	0·8439	1·117
4	0·8091	0·999	0·8062	1·000	0·8395	1·002	0·9418	1·128
5	0·8297	1·001	0·8681	0·998	0·8902	1·003	0·9881	1·178
8	0·9153	1·006	0·9797	1·005	1·0584	1·006	1·1609	1·144
12	1·0839	1·010	1·3620	1·012	1·3700	1·010	1·7409	1·142
16	1·7245	1·019	1·7729	1·021	1·6847	1·015	2·1750	1·193
20	2·1140	1·023	1·7629	1·035	2·2860	1·025	3·2671	1·195

Diffusion coefficients have been calculated according to a modified Nernst-Brünner equation which relates the diffusion coefficient, D, to the dissolution rate, dC/dt, from a constant surface area, S, the diffusion layer thickness, δ, and the corresponding saturation solubility, Cs,

$$D = \frac{(dC/dt)\ /S}{Cs}\ \delta \quad .. \quad .. \quad .. \quad .. \quad (3)$$

The values for diffusion coefficients, presented in Table 3, decrease with increasing pH. Other workers, Edwards (1951), reported the diffusion coefficients for salicylic acid (0·0005M) at pH 1·0 and pH 4·5 as $11{\cdot}7 \times 10^{-10}\ m^2\ s^{-1}$. Thus in very dilute solution the diffusion coefficients are independent of pH and the diffusion coefficients of ionized and unionized forms of salicylic acid are similar. However, Edwards did

report that diffusion coefficients were not independent of concentrations. Similarly Deshmukh & Fleming (1969) reported a decrease in diffusion coefficient of sodium salicylate from $1{\cdot}0 \times 10^{-9}$ to $0{\cdot}76 \times 10^{-9}$ m^2 s^{-1} with a thirtyfold increase in solute concentration. In the present work as the pH was increased from 1·0 to 4·0 the saturation solubility of salicylic acid increased from 0·019 to 0·18M with a corresponding decrease in the diffusion coefficient. It seems likely that large increases in salicylic acid concentration are responsible for the decrease in diffusion coefficients.

In the presence of polysorbate 20 the diffusion coefficients decrease rapidly as the concentration of polysorbate 20 is increased up to 8% w/v and then only slowly as the polysorbate 20 concentration is increased up to 20% w/v. The concentration of salicylic acid in solution increases linearly with the concentration of polysorbate 20 at pH 1·0 to 4·0. The viscosity of the salicylic acid: polysorbate 20 solution also increases with polysorbate 20 concentration. Plots of diffusion coefficient and viscosity against polysorbate 20 concentration are mirror images indicating an inverse relation between diffusion coefficient and viscosity of solution. Dissolution rate increases rapidly up to 8% w/v polysorbate 20 and then only slowly up to 20% w/v.

Braun & Parrott (1972) have shown a similar relation between dissolution rate and diffusion coefficient using benzoic acid and polysorbate 80. However, above 8% w/v polysorbate 80 they reported a decrease in dissolution rate. This decrease in dissolution rate was attributed to the increased viscosity of the dissolution medium. An alternative explanation is that the absence of pH control in Braun and Parrott's work caused the dissolution rate to decrease due to a change in pH with increasing amount of solute dissolved.

In our work, the dissolution rate did not decrease in high concentrations of polysorbate 20, although these solutions exhibited a high viscosity. Nevertheless, it was thought worthwhile to study the effects of the viscosity of the dissolution medium on the dissolution rate. Aqueous solutions of methyl cellulose were prepared at such concentrations that their viscosities were equivalent to known viscosities of aqueous polysorbate 20 solutions. Dissolution rate constants were determined at pH 1·0 and are presented in Table 2. In contrast to the dissolution rates in polysorbate 20, the dissolution rate constants of salicylic acid in methyl cellulose solution decrease slightly as the methyl cellulose concentration is increased with a corresponding increase in the viscosity. But the choice of methyl cellulose may not be justified since methyl cellulose owes its viscosity to a gel-like structure, whilst polysorbate 20 is a micellar structure. However, it would appear from the dissolution rate constants obtained that the effects due to solubilization by polysorbate 20 are more pronounced than the effects due to the viscosity of the dissolution medium.

REFERENCES

BRAUN, J. R. & PARROTT, E. L. (1972). *J. pharm. Sci.*, **61**, 175–178.

COLLETT, J. H., REES, J. A. & DICKINSON, N. A. (1972). *J. Pharm. Pharmac.*, **24**, 724–728.

CROOKS, P., COLLETT, J. H. & WITHINGTON, R. (1974). *Pharm. Acta. Helv.*, in the press.

DESHMUKH, A. & FLEMING, R. (1969). *J. Pharm. Pharmac.*, **21**, 915–975.

EDWARDS, L. J. (1951). *Trans. Farad. Soc.*, **47**, 1191–1210.

ELWORTHY, P. H. & LIPSCOMB, J. L., (1968). *J. Pharm. Pharmac.*, **20**, 923–933.

GIBALDI, M. & FELDMAN, S. (1970). *J. pharm. Sci.*, **59**, 579–589.

GIBALDI, M., FELDMAN, S. & WEINER, N. D. (1970). *Chem. Pharm. Bull.*, **18(4)**, 715–723.

NELSON, E. (1957). *J. pharm. Sci.*, **46**, 607–614.

NOYES, A. A. & WHITNEY, W. R. (1897). *J. Am. chem. Soc.*, **19**, 930.

PARROTT, E. L. & SHARMA, V. K. (1967). *J. pharm. Sci.*, **56**, 1341–1343.