

Some relations between dissolution rates and physical parameters of a drug in aqueous micellar solutions of a non-ionic surfactant

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Dissolution rates of salicylic acid from a constant surface area into a series of aqueous micellar polysorbate 20 solutions at pH 1.0 to 4.0 have been measured using two different methods; a stirred beaker and a rotating disc technique. The micellar molecular weight of polysorbate 20 has been obtained from light scattering and differential refractometry data and used with other independently determined physical data to calculate diffusion coefficients of the diffusing species. Linear multiple regression analysis was used to assess the dependence of drug dissolution rate on the diffusion coefficient and the viscosity of the dissolution medium.

Several theories have been proposed to describe the dissolution mechanisms of solids into aqueous media. Mechanisms which are diffusion controlled differ from each other primarily in the dependence of dissolution rate on the diffusion coefficient of the diffusing species. This dependence has led Higuchi (1967) to suggest that the effects of additives such as colloidal solubilizers could be used to differentiate dissolution mechanisms. Micelle solubilized drug has a lower diffusion coefficient than free drug, so that changes in dissolution rate due to additive will be related to the magnitude of dependence of dissolution rate on diffusion coefficients of the diffusing species.

Several workers have investigated relations between drug dissolution rate and diffusion coefficient (Gibaldi, Feldman & others, 1968; Gibaldi, Feldman & Weiner, 1970). With ionizing solutes the work has been limited to dissolution at one pH. In some cases physical data used for the calculation of diffusion coefficients were not specific to the drug dissolution system.

In this work, dissolution has been measured by two methods at different pH values, since the mechanism of dissolution may be related to the hydrodynamics of the system. Physical data for the calculation of diffusion coefficients have been obtained independently. Relations have been investigated between experimentally determined dissolution rates, calculated diffusion coefficients of the diffusing species and viscosity of the dissolution medium.

MATERIALS AND METHODS

Salicylic acid (BDH) and polysorbate 20 (Koch-light) have been described previously together with the preparation of non-disintegrating discs of salicylic acid (Collett, Rees & Dickinson, 1972; Rees & Collett, 1974).

Light scattering measurements were made on a Fica 42000 photogoniometer (A.R.L. Ltd.). The scatter at angles between 45° and 135° was measured at a wavelength of 546 nm for several dilute aqueous solutions of polysorbate 20.

The solutions were filtered at least twice through a 0.1 μm pore size Millipore filter into a glass cuvette before measurement of the scatter.

Differential refractometry. The change in refractive index with concentration of several dilute aqueous polysorbate 20 solutions (dn/dC) was determined at 0° and 180° using a differential refractometer (Polymer Consultants Limited).

Dissolution studies. Two methods have been used to determine dissolution rates: (a) A modified beaker method has been described previously (Collett & others, 1972). (b) A rotating disc method in which the salicylic acid, mounted in a titanium disc holder, was placed in the end of a stirrer so that the exposed face of the disc (2.84 cm²) formed a continuous surface with the end of the stirrer. The distance between the surface of the disc and the base of the dissolution cell was 1.5 cm. This assembly resulted in the disc surface facing downwards and being rotated on the end of the stirrer shaft in 200 cm³ of dissolution medium.

The dissolution cell was common to both methods. pH control was accomplished by a pH stat assembly (Radiometer, Copenhagen). The procedures for the determination of viscosity, density and solubility have been reported previously along with the assay procedure for salicylic acid (Collett & others, 1972).

RESULTS

Dissolution studies

Plots of amount of salicylic acid dissolved as a function of time were linear for both the stirred beaker and rotating disc methods. Apparent zero order dissolution rate constants, which are presented in Table 1, were obtained for dissolution into a series

Table 1. *Dissolution rate constants (kg s⁻¹ × 10⁸) for salicylic acid into aqueous solutions of polysorbate 20 at different pH levels (a - stirred beaker method, b - rotating disc method).*

Polysorbate 20 % w/v	pH							
	1.0		2.0		3.0		4.0	
	a	b	a	b	a	b	a	b
0	2.69	1.85	2.94	2.14	3.23	2.40	3.56	2.45
1	2.75	2.05	3.27	2.35	3.82	2.68	4.06	2.75
2	3.21	2.14	3.39	2.48	3.88	2.80	4.08	3.04
4	3.64	2.48	3.87	2.92	4.37	2.97	4.55	3.35
5	3.91	2.72	4.19	3.02	4.49	3.15	4.56	3.67
8	4.13	3.22	4.59	3.37	4.99	3.63	4.96	3.96
12	4.44	3.57	4.79	3.72	5.27	4.07	5.27	4.45
16	4.66	3.69	4.84	3.86	5.16	4.18	5.63	4.49
20	4.75	4.01	4.80	4.08	5.32	4.44	5.76	4.65

of aqueous polysorbate 20 solutions (1 to 20% w/v) at pH 1.0 to 4.0. The dissolution rate constants obtained by both methods increased rapidly at all pH values as the concentration of polysorbate 20 was increased up to about 12% w/v. Thereafter, any further increase in polysorbate 20 concentration up to 20% w/v only slightly increased the dissolution rate constant. At any one concentration of polysorbate 20 the dissolution rate constant increased as the pH was increased.

Calculation of micellar molecular weight of polysorbate 20

(a) Anhydrous micellar molecular weight (m) is related to the change in refractive index with concentration (dn/dC) and the light scattered at 90° (S_{90}) by equation (1) which is a modification of Rayleigh's equation (Strutt, 1871).

$$\frac{1}{m} = K^1 \left[\left(\frac{dn}{dC} \right)^2 \times \frac{C}{S_{90}} \right] \dots \dots \dots (1)$$

Where K^1 is a constant for the light scattering instrument. Equation (1) may only be used for systems in which dimensions of the solute do not exceed $\lambda/20$ where λ is the wavelength of the light. A linear relation was found between S_{90} and the concentration of polysorbate 20; the reciprocal of the slope being 0.002855. A mean value of 0.123 was calculated for dn/dC ; refractive indices are:

For aqueous polysorbate 20 solutions (% w/v)				
Angle	0.0	0.5	1.0	1.5
0°	5.942	5.492	5.021	4.580
180°	5.288	5.729	6.193	6.663

Substituting the values for dn/dC and S_{90} into equation (1) gave an anhydrous micellar molecular weight of 40 816. This value does not include associated water molecules that may be trapped in the core of the micelle and between oxyethylene chains.

(b) Hydrated micellar molecular weight. The hydration of the micelles can be calculated using equation (2) within the restrictions imposed by the Einstein equation and under the assumption that the micelles are spherical.

$$[\eta] = 2.5 (\bar{v} + \delta^1 v_1^\circ) \dots \dots \dots (2)$$

Where $[\eta]$ is the intrinsic viscosity, \bar{v} is the partial specific volume of the solute, v_1° is the density of the solvent, and δ^1 is the grams of solvent associated with each gram of solute. Intrinsic viscosity was obtained from the intercept of a plot of η_{sp}/C against C , where C is the concentration in grams of polysorbate 20 per 100 cm^3 of solution and η_{sp} is the specific viscosity:

Aqueous polysorbate 20 solutions (% w/v):								
	1	2	4	5	8	12	16	20
η_{sp}	0.0105	0.0769	0.2062	0.3481	0.5527	1.0423	1.7134	2.7228

The partial specific volume of polysorbate 20 was derived from a plot of density against concentration of the solution according to the equation:

$$\rho = \rho_o + (1 - \bar{v} \rho_o)C \dots \dots \dots (3)$$

Where ρ and ρ_o are respectively density of solution and solvent, C is the concentration of solute and \bar{v} is the required partial specific volume.

Substitution of the calculated values in equation (2) gave a value of 0.51 for δ^1 and thus a total micellar molecular weight of 61 629.

Calculation of diffusion coefficients

Diffusion coefficients of benzoic acid and of salicylic acid in micellar solution have been calculated by means of the Stokes Einstein equation (Gibaldi & others, 1970).

$$D = \frac{RT}{6\pi\eta N} \sqrt[3]{\frac{4\pi N}{3M\bar{v}}} \dots \dots \dots (4)$$

Where D is diffusion coefficient, R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent in poise, \bar{v} is the partial specific volume of the micelles, M is the micellar molecular weight and N is Avogadro's number.

Partial specific volumes for a multicomponent micelle system were obtained utilizing an equation reported by Kraemer (1940).

$$\bar{v} = \bar{v}_1 + \sum_{i=1}^n t_i \bar{v}_i / (1 + \sum_{i=1}^n t_i) \quad \dots \quad (5)$$

where \bar{v} , \bar{v}_1 and \bar{v}_i are respectively, partial specific volumes for the multicomponent micelle system, solute and surfactant, t_i is the number of g of the i^{th} component with partial specific volume \bar{v}_i combining with 1 g of surfactant.

Diffusion coefficients of salicylic acid in micellar polysorbate 20 solutions have been calculated by substituting the values for partial specific volume and micellar molecular weight into the Stokes Einstein equation.

Effective diffusion coefficients have been used in the analysis of data in which there is more than one diffusing species (Higuchi, 1967). The effective diffusion coefficient, D_{eff} is given by:

$$D_{\text{eff}} = \frac{D_s C_s + D_m C_m}{C_s + C_m} \quad \dots \quad (6)$$

Where D is diffusion coefficient and C is saturation solubility of the solute, subscripts s and m refer to aqueous and micellar phases respectively.

DISCUSSION

Gibaldi & others (1970) have used a generalized form of the dissolution rate equation to investigate the relation between dissolution rate, dr , and diffusion coefficient.

$$dr = (D_{\text{eff}})^{1/n} C_t K^* \quad \dots \quad (7)$$

Where $1/n$ is the diffusion coefficient exponent, $C_t = C_s + C_m$ and K^* accounts for all other parameters such as viscosity, stirring speed, etc.

A plot of $\log(dr/C_t)$ against $\log D_{\text{eff}}$ should theoretically give a straight line with the slope of the line being equal to the exponent ($1/n$) of the diffusion coefficient.

Plots of $\log(dr/C_t)$ against $\log D_{\text{eff}}$ at pH 1.0 to 4.0 have been made for dissolution data obtained from the stirred beaker type apparatus. A linear relation was found and the slopes of these plots are shown in Table 2. The values for these slopes are

Table 2. Slopes of plots of $\log(dr/C_t)$ against $\log D_{\text{eff}}$ for the stirred beaker and rotating disc methods.

		pH			
		1.0	2.0	3.0	4.0
Stirred beaker	0.77 (± 0.02)	0.80 (± 0.05)	0.90 (± 0.03)	0.73 (± 0.09)
Rotating disc	0.65 (± 0.03)	0.68 (± 0.03)	0.73 (± 0.03)	0.57 (± 0.09)

Figures in brackets are standard errors of regression coefficients.

similar and indicate that the mechanism of dissolution operating is the same at all pH levels. The diffusion layer theory of dissolution predicts a slope of 1.0 for a plot of

$\log (dr/C_t)$ against $\log D_{\text{eff}}$. Singh, Desai & others (1968) have reported that the slopes of plots of $\log(dr/C_t)$ against $\log D$ for the dissolution of benzocaine into polysorbate 80 solutions in a beaker type system were 0.83 and 0.811 for stirrer speeds of 50 and 150 rev min^{-1} , respectively. They concluded that these slopes indicated that the mechanism proposed by the diffusion layer theory was operative. Our data for a weakly ionizing compound indicates a similar relation between $\log (dr/C_t)$ and $\log D_{\text{eff}}$ to that reported for benzocaine and indicates that the mechanism proposed by the diffusion layer theory may well be operative.

Plots of $\log (dr/C_t)$ against $\log D_{\text{eff}}$ have been made using the data obtained with the rotating disc apparatus at pH 1.0 to 4.0. The plots obtained were linear and the slopes of the lines are presented in Table 2. According to the Levich theory of dissolution (1962) which describes the dissolution of a solid from a rotating disc, the exponent of the effective diffusion coefficient should be equal to 0.666. It can be seen from Table 2 that the slopes obtained suggest that the mechanism controlling dissolution using the rotating disc apparatus is adequately described by the Levich theory, at all pH levels.

Singh & others (1968) have reported that plots of $\log (dr/C_t)$ against $\log D_{\text{eff}}$ deviated from linearity above 4% w/v polysorbate 80 for both the stirred beaker and rotating disc methods. These authors concluded that the viscosities of polysorbate 80 solutions were responsible for this effect. In our work linearity was observed up to 12% w/v polysorbate 20.

In order to accommodate a viscosity effect in a mechanism describing dissolution, it was decided to factorize the K^* of equation (7). The equation used was:—

$$\log (dr/C_t) = \frac{1}{n} \log D_{\text{eff}} + a \log \eta + K'' \quad \dots \quad (8)$$

Where η is the viscosity of the dissolution medium and K'' is a constant. Effective diffusion coefficients were calculated according to Gibaldi & others (1970), using a mean micellar diffusion coefficient from our data.

The coefficients in Table 3 were obtained by linear multiple regression analysis using our data from both the stirred beaker and rotating disc methods. The dependence of dissolution on the effective diffusion coefficient is about 0.5 for both stirred beaker and rotating disc methods at pH 1.0 to 3.0. Thus, it would appear that the mechanism of dissolution for both methods is similar. The dependence on viscosity increases as the pH is increased from 1.0 to 3.0 for both dissolution methods. This increased dependency reflects the increase in solute concentration and viscosity with increasing pH and polysorbate 20 concentration (Rees & Collett, 1974). The viscosity coefficients for the rotating disc method are less than those for the stirred beaker method at all pH levels indicating a lesser dependence of dissolution rate on viscosity. Other workers investigated the effect of viscosity on dissolution and reported exponents between -0.25 and -0.8 (Wurster & Taylor, 1965). However, in general these values relate to fully ionized systems.

The data of Singh & others (1968) can also be analysed according to equation (8) and the coefficients obtained are shown in Table 3. The dependence of dissolution rate on D_{eff} indicates that the mechanism operating in their system is similar to that in ours. The dependence on viscosity is similar at all stirring speeds using both a stirred beaker and a rotating disc type method. However, the viscosity of the polysorbate 80—benzocaine system up to 4% w/v polysorbate 80 is less than that of our

Table 3. Coefficients obtained from linear multiple regression of equation (8) and of data of Singh & others (1968).

	pH						From Singh & others (1968)			
	1.0		2.0		3.0		rev min ⁻¹			
	a	b	a	b	a	b	50	60	150	300
K ⁿ	-6.56	-6.38	-6.75	-6.65	-6.83	-6.64	-0.54	-0.55	-0.33	-0.23
log D _{eff}	0.53	0.62	0.47	0.54	0.47	0.56	0.53	0.47	0.51	0.49
log viscosity	-0.41	-0.19	-0.49	-0.30	-0.67	-0.43	-0.96	-1.2	-1.07	-1.26
Multiple correlation coefficient	0.99	0.99	0.98	0.99	0.99	0.98				

a—stirred beaker. b—rotating disc.

salicylic acid—polysorbate 20 systems. The dependency on viscosity may have become apparent at higher polysorbate 80 concentrations but the authors reported non-linearity of log D_{eff} against log (dr/C_t). Thus, the present work and that of Singh & others (1968) indicate that the mechanism of dissolution in the stirred beaker and rotating disc methods can be described by the same mechanism with a significant contribution from viscosity.

The value of the log D_{eff} coefficient in all cases was approximately 0.5, which may indicate a Danckwerts' type mechanism (1951). Toor & Marchello (1958) have suggested that the mechanisms described in the diffusion layer theory and Danckwerts' theory are not separate unrelated concepts but limiting cases of a more general model. They proposed a dissolution model indicating that mass transfer in dissolution occurs by two simultaneous processes; one involving a stagnant film in which steady state molecular transfer occurs and the other involving non steady state molecular transfer into eddies existing in the surface region. At the extremes this model reduces to the diffusion layer theory or Danckwerts' theory. When conditions are such that the rate of renewal of the surface and the rate of diffusion of the dissolving species are comparable then the transfer characteristics are intermediate between the diffusion layer and Danckwerts' theory predictions. Huang & Kuo (1963) further developed this dissolution model to show that the exponent relating dissolution rate to the diffusion coefficient exponent can have any value between 0.15 and 1.0. Even though values of log D_{eff} in the present work indicate that dissolution may be described by Danckwerts' theory, the possibility that we have chosen limiting conditions cannot be ruled out. Nonetheless the observation that dissolution is dependent on viscosity should be borne in mind when designing *in vitro* dissolution tests.

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