

The effect of some non-ionic surfactants and a polyoxyethylene glycol on the dissolution rate of griseofulvin

P. H. ELWORTHY AND F. J. LIPSCOMB

Measurements of the dissolution rate of griseofulvin in water, four non-ionic surfactants, and a polyoxyethylene glycol have been made. These results are analysed in terms of a zero order rate constant (k_1) for transfer of the drug from the crystal to the bulk of the solution, and a first order constant (k_2) for the reverse process. Surfactants greatly increase the dissolution rate, increasing k_1 and decreasing k_2 . Polyoxyethylene glycol is not so effective as the surfactants at increasing dissolution rates. In an attempt to interpret k_1 and k_2 , it appears that both chemical and transport processes are involved in the dissolution, the presence of surfactant decreasing the energy change for transferring griseofulvin molecules from the crystal to the solution.

ONLY a few studies on the effect of surfactants on the dissolution rate of solids have been published. Parrott & Sharma (1967) have shown that surfactants increase the dissolution rate of benzoic acid, while Wurster & Seitz (1960) and Levy & Gumtow (1963) also observed an increased dissolution rate in the presence of sodium lauryl sulphate. The dissolution rate of griseofulvin is increased by the presence of surfactants (Bates, Lin & Gibaldi, 1967, Bates, Gibaldi & Kanig, 1966).

As surfactants are commonly used in pharmaceutical formulation, it is of interest to study their action on the dissolution rate in detail, to gain some understanding of the underlying mechanisms. The dissolution rate can be the rate-limiting step in the absorption of a drug, and the possibility of increasing it by the use of surfactants may have applications in formulation work. In the present study, griseofulvin was chosen as the insoluble drug, and its dissolution studied in a range of non-ionic surfactants. The solubility of this compound in various solvents and in surfactant solutions has already been reported (Elworthy & Lipscomb, 1968a, 1968b).

Experimental

The physical properties of the griseofulvin used have been reported (Elworthy & Lipscomb, 1968a). The surfactants used were commercial samples based on hexadecanol with varying numbers of ethylene oxide units e.g. $\text{Me}[\text{CH}_2]_{15}[\text{O}\cdot\text{CH}_2\cdot\text{CH}_2]_x\text{OH}$ where $x = 22, 38,$ and 50 (abbrev. to HEx); the octylphenol containing surfactant $\text{Me}_3\text{C}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{C}_6\text{H}_4[\text{O}\cdot\text{CH}_2\cdot\text{CH}_2]_{10}\text{OH}$, (Abbrev. to OE10), and polyoxyethylene glycol 400 (Elworthy & Lipscomb, 1968b). Deionization of these compounds did not affect the results.

Viscosities of solutions relative to water were measured in Ostwald capillary viscometers.

The dissolution apparatus consisted of a thermostated 1 litre glass jar which contained the dissolution medium. All measurements were made at $25^\circ \pm 0.01^\circ$ unless otherwise stated. A magnetic follower at the bottom of the jar was driven by a magnetic stirrer mounted below the thermostat.

From the Department of Pharmaceutical Technology, University of Strathclyde, Glasgow, C.1, Scotland.

A series of synchronous motors provided stirring speeds of between 5 and 600 rev/min. A glass tripod, with a "gauze" made of fine glass fibres, supported the tablet of griseofulvin in the dissolution medium. The tablets were prepared on a hydraulic press, and were washed before use to remove any loose particles of griseofulvin dust.

An experiment was commenced by placing the tablet on its tripod in the dissolution medium. Samples (5 ml) of the medium were withdrawn at noted time intervals, and assayed by measuring their extinction in the 294–296 $m\mu$ region (the position of λ_{max} depended on the surfactant being used). When surfactants or polyoxyethylene glycol (PG) 400 was present, extinctions were measured against blank solutions containing the appropriate concentrations of these materials. After each sampling, an equal volume of fresh dissolution medium was added. Examination of solution in an ultramicroscope did not reveal any particles of griseofulvin to be present. Because of the small extinction measured in some experiments, it was necessary to check that there was no significant adsorption of griseofulvin on glassware. None could be detected.

Results and discussion

INTERPRETATION OF RESULTS

With the method adopted, the solubilities of griseofulvin in the dissolution media are so small that the surface area of the tablet does not change significantly during the experiment.

The dissolution is regarded as consisting of two processes, occurring simultaneously:

1. A zero order reaction for the transfer of griseofulvin molecules from the solid surface into the solution, with rate constant k_1 .
2. A first order reaction for the deposition of solute from solution to the solid surface, with rate constant k_2 .

The rate of increase of concentration in solution:

$$\frac{dc}{dt} = k_1 - k_2c \quad \dots \quad \dots \quad \dots \quad (1)$$

The solution to this equation with the condition that at $t = 0, c = 0$ is

$$c = \frac{k_1}{k_2} \cdot \left(1 - e^{-k_2 t}\right) \quad (2)$$

Expanding the exponential term and rearranging gives

$$\frac{c}{t} = k_1 - \frac{k_1 k_2 t}{2} + \frac{k_1 k_2^2 t^2}{6} - \frac{k_1 k_2^3 t^3}{24} + \dots$$

At fairly early times in the dissolution process, terms in t^2 and t^3 etc. can be neglected giving:

$$\frac{c}{t} = k_1 - \frac{k_1 k_2 t}{2} \quad (3)$$

A plot of c/t vs. t will have an intercept k_1 and a slope $k_1 k_2/2$, enabling both constants to be evaluated. Trial calculations show that equation (3) gives 1% error in c compared to the exact equation (2) provided the $k_2 t$ term does not exceed 0.25.

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Equation 2 reduces to the Noyes-Whitney equation (Noyes & Whitney, 1897). When equilibrium is reached, i.e. a steady state between dissolving and redeposition

$$\frac{dc}{dt} = 0 = k_1 - k_2c_s$$

where c_s is the saturation solubility.

$$c_s = k_1/k_2 \quad (4)$$

and from equation (2)

$$c = c_s (1 - e^{-k_1 t})$$

or,

$$k_2 = \frac{1}{t} \cdot \ln\left(\frac{c_s}{c_s - c}\right) \quad (5)$$

which is the more usual form of the Noyes-Whitney equation. The rate constant of equation (5) thus appears to be the first order constant arising in the consideration of the dissolution-redeposition process. Equation (3) is useful if the saturation solubility is not known; when it is, equation (4) can be used to evaluate one constant when the other has been determined from (3) or (5).

The experimental results reported later are interpreted in terms of k_1 and k_2 .

EFFECT OF EXPERIMENTAL CONDITIONS ON STUDY OF DISSOLUTION RATE

In the development of the apparatus already described, the effect of a number of experimental conditions on the observed dissolution rate was examined.

1. *Position of tablet.* Three tripods were constructed to hold the tablet, which in each experiment was placed in the centre of the gas jar; the lowest tripod gave a distance from the top of the stirrer bar to the bottom of the tablet of 0.3 cm, the medium tripod a distance of 1.6 cm, and the highest tripod one of 2.5 cm. (Thickness of stirrer bar = 0.76 cm.) Using a tablet prepared at a compaction pressure of 10 ton/inch², a stirring rate of 250 rev/min, and an initial volume of water of 300 ml, from which 5 ml portions were removed at timed intervals for the measurement of absorbance gave results which showed that at this stirring speed, the height of the tablet appears to make little difference to the amount of griseofulvin dissolving. The highest tripod was used in all subsequent experiments, as it placed the tablet equidistant between the surface of the water and the bottom of the jar, giving the minimum disturbances from rotation of the stirrer bar, or the development of a vortex at the surface (particularly when stirring rates exceeding 250 rev/min were used).

2. *Volume of water.* Using a stirring rate of 250 rev/min and a tablet compacted as before, the effect of using initial volumes of 200 and 500 ml of water was examined. In these experiments 5 ml portions were withdrawn for assay at timed intervals, and the results are shown in Fig. 1 in terms of the weight of griseofulvin per 100 ml of water released by the tablet.

Some authors, e.g. Bates, Lin, & Gibaldi (1967), have added an equal volume of fresh dissolution medium when each sample is withdrawn for

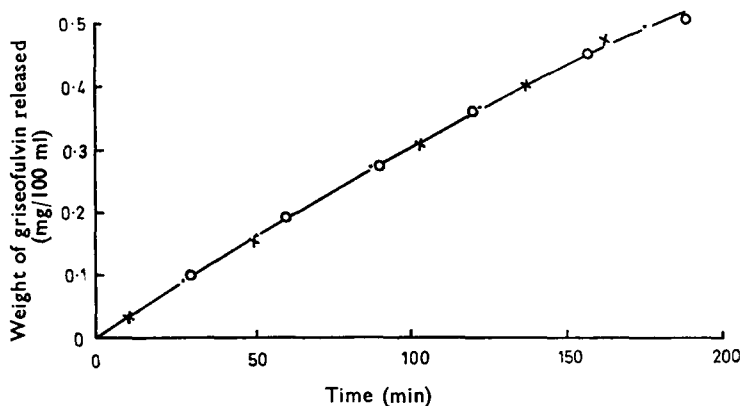


FIG. 1. Effect of different volumes of dissolution medium on the amount of griseofulvin dissolving. ○ = 200 ml. × = 500 ml. • = 300 ml, with replacement (see text).

assay. The results of such an experiment are shown in Fig. 1. All results have been corrected to allow for the amount of griseofulvin removed from the system for assay purposes. The different volumes and techniques of sampling do not appear to have a significant effect on the results. In all other experiments, an initial volume of 300 ml of water was used, together with replacement of withdrawn water with an equal volume of pure solvent.

3. *Rate of stirring.* Using a tablet compressed at 10 ton/inch², the effect of stirring rate on the rate of dissolution was determined. The results for k_1 and k_2 are given in Table 1. In both cases the rate constants increased with the rate of stirring.

According to Bircumshaw & Riddiford (1952) a plot of $\log k$ vs. \log (stirring rate) should be linear with a slope of 0.5, if the dissolution process is diffusion controlled. Graphs of this type for both k_1 and k_2 are reasonably linear, considering the large experimental errors involved in measuring small extinctions in the 5 and 10 rev/min experiments, and have a slope of 0.54. 250 rev/min seemed to be a suitable stirring speed for further work, as the rate of solution was fairly high, and the tablet showed no signs of moving on its support, which was a difficulty in some experiments at 600 rev/min.

4. *Compression of tablet.* The mean values of k_1 were 1.07, 1.14 and

TABLE 1. EFFECT OF RATE OF STIRRING ON k_1 AND k_2

Rate of stirring* (rev./min)	$10^6 k_1$ †	$10^6 k_2$ ‡
5	0.11	0.43
10	0.19	0.78
60	0.38	1.5
250*	1.12	4.6
600	1.58	6.5

* From standard runs.
 † moles litre⁻¹ min⁻¹ cm⁻²
 ‡ min⁻¹ cm⁻²

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1.12 and of k_2 were 4.4, 4.6, 4.6 for 5, 10 and 15 ton/inch² using 300 ml water and a stirring rate of 250 rev/min and thus appear to show little variation when the tablets are compressed at these pressures.

5. *Other experimental conditions and the standard runs.* The following were adopted as standard experimental conditions: 300 ml initial volume of dissolution medium, withdrawal of 5 ml samples, replaced by 5 ml fresh medium; high tripod supporting tablet; rate of stirring 250 rev/min; compaction of tablets at 10 ton/inch²; weight of tablets between 340 and 350 mg. Measurements on three representative tablets of weight 346.2, 348.0, and 341.8 mg, using a Cambridge Universal Measuring machine, gave diameters enabling the geometrical surface areas of 3.451, 3.450, and 3.463 cm² to be calculated. From these figures the apparent density of griseofulvin when compressed at 10 ton/inch² is 1.355. The diameter of the tablets will not vary with their weight, but their thicknesses will. Using weights of 340 and 350 mg, the density, and the observed diameter of 1.304 cm, the surface areas are 3.445 and 3.465 cm² respectively. Hence the weight of tablets was controlled between 340 and 350 mg, giving a maximum variation in geometrical surface area of about 0.6%. Values of k_1 and k_2 have been corrected to an area of 1 cm², using 3.45 cm² as the mean area of the tablet. The error introduced by using 3.45 cm² instead of the specific tablet area is considered to be small compared with other errors.

The results of five experiments made under the standard conditions detailed above are:

for 10^3k_1 : 1.18, 1.21, 1.09, 0.99, 1.23, mean 1.14:

for 10^4k_2 : 7.5, 3.8, 7.5, 9.6, 6.7. (From slopes.)

for 10^4k_2 : 4.84, 4.79, 4.97, 4.06, 5.03, mean 4.63. (From solubility.)

The experimental data were treated as follows. Observed extinctions were plotted against time, and the best line drawn through the points using a french curve. Values of extinctions and time were read from the smoothed curve and plotted as (extinction)/time against time. The intercept of this graph gives k_1 (Fig. 2), which was converted to absolute units using the $E(1\%, 1 \text{ cm})$ of griseofulvin and the volume of the solution.

The column giving k_2 evaluated from the slope of the (extinction)/time vs. time plots shows much variation, so k_2 was evaluated using k_1 and the solubility data (Elworthy & Lipscomb, 1968b), giving much more reproducible results. The standard deviation of k_1 is 0.091, and that of the

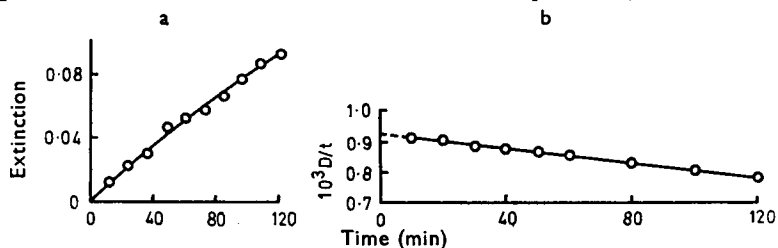


FIG. 2. (a) Extinction (in 1 cm cells) of solutions during dissolution of griseofulvin under standard conditions. (b) Extinction/time against time derived from the smoothed curve in (a).

second k_2 is 0.38 both corresponding to 8% of the mean value. In view of the precautions taken, this reproducibility was somewhat disappointing. The main part of the error probably arises in the measurement of small extinctions; under standard conditions the extinction reaches 0.1 (2 cm cells) in about 60 min. A further source of error may be the fracturing off of very small particles of griseofulvin from the tablet surface. Experiments in which the solution was filtered through 5/3 glass sintered disks, did not give any better reproducibility, so if particles become detached they must be small enough to pass through the filter. Also, we are interested in the value of k_1 , which is the initial slope of the concentration-time graph, and which is not easy to estimate, due to the very small extinctions (at 10 min, extinction \approx 0.03 in 2 cm cells). The advantage of equation 3 is that it enables results taken at longer times to be used in an extrapolation to zero time.

No significant difference in the results was found when a tablet was used in three or four experiments. After this amount of use, the tablet was discarded in case repeated handling had affected the surface area. In all subsequent experiments, in view of the error of a single experiment, three repeat experiments were made, the results graphed on an extinction vs. time plot, and the best curve drawn through the points. The quoted results are thus a mean of three experiments.

6. *Effect of temperature.* The results of the determination of k_1 and k_2 at 25°, 35° and 45° were: $10^8 k_1$ 1.14, 2.29, 5.02 and $10^4 k_2$ 4.6, 6.5, 8.2 respectively.

Increase of temperature has a much larger effect on k_1 than on k_2 , thus the total amount of griseofulvin going into solution in a given time is increased. Plots of $\log k_1$ and k_2 vs. $1/T$ are reasonably linear, and activation energies (E_a) of 14.2 kcal and 5.4 kcal for the zero order and first order reactions respectively were obtained.

Edwards (1951) states that according to the Stokes-Einstein equation, the energy of a diffusion process (E_D) should depend only on the viscosity of the solvent. Over the temperature range 25°–45°, the mean E_D value is 4.4 kcal/mole. Considering the experimental error involved, the value of the activation energy for k_2 , is fairly close to E_D , indicating that the control of this rate constant is very largely due to diffusion. The diffusion energy is only about one-third of the activation energy for the k_1 rate constant. As the rate of stirring experiments have shown an apparent diffusion control, it appears that other factors are involved in this dissolution step. The principal factor is probably the energy change in transferring a molecule of griseofulvin from the crystal to the solution.

EFFECT OF NON-IONIC SURFACTANTS AND POLYOXYETHYLENE GLYCOL ON DISSOLUTION RATE

Measurements of k_1 and k_2 were made as a function of concentration for cetomacrogol, HE38, HE60, OE10 and polyoxyethylene glycol-400.

Before discussing in detail the effect of surfactants on the velocity constants, an overall picture of their action in promoting the dissolution of griseofulvin is given. Fig. 3 shows the amount of drug dissolved at 100 min

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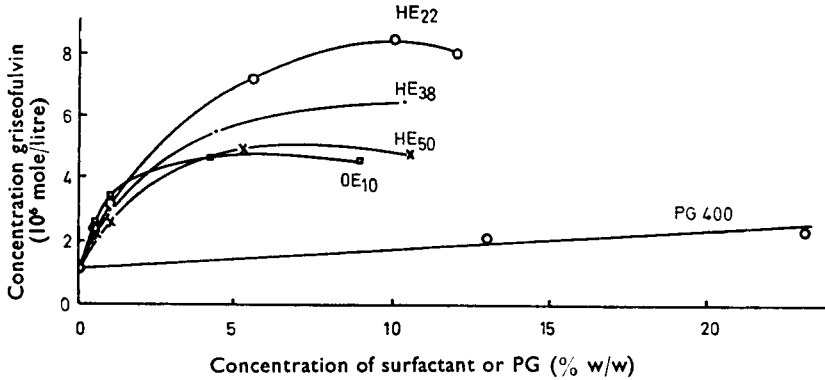


Fig. 3. Amount of griseofulvin dissolved after 100 min in contact with various surfactant and polyoxyethylene glycol solutions.

after the beginning of an experiment, calculated from the k values given in Table 2. There is a rapid increase of the amount dissolved with detergent concentrations, and 1% surfactant solutions give an increase of 2.5–3 times the amount dissolved in pure water. Higher surfactant concentrations give an increase of 5–8 times over the level in water. The polyoxyethylene glycol is not nearly so effective as the surfactants at increasing the dissolution rate, when the compounds are compared on a percentage basis.

All the surfactant concentrations used are well above the CMC, so that both wetting of the griseofulvin surface and adsorption of surfactant at it can be considered constant over the range of measurements made.

The effect of temperature on the dissolution rate was determined in a cetomacrogol solution. 10^8k_1 values were 6.90, 10.6, 18.58 and 10^4k_2 values were 0.841, 1.15, 1.87 for 25°, 35° and 45° respectively.

TABLE 2. DISSOLUTION OF GRISEOFULVIN IN SURFACTANT OR POLYOXYETHYLENE GLYCOL-400 SOLUTIONS AT 25°

Surfactant	Concentration % w/w	10^8k_1	10^4k_2	
Cetomacrogol (HE22)	0.497	2.40	2.29	
	0.959	3.16	1.71	
	1.000	3.19	1.63	
	4.654	6.9	0.84	
	5.500	7.2	0.75	
	10.00	8.5	0.49	
	10.10	8.3	0.47	
	12.00	7.7	0.37	
	HE38	0.514	2.16	3.07
		1.047	3.22	2.48
4.337		5.5	1.09	
10.36		6.4	0.55	
HE50	0.494	2.18	3.62	
	0.985	2.68	2.36	
	5.208	4.96	0.90	
	10.53	4.52	0.33	
OE10	0.501	2.66	2.08	
	0.940	3.54	1.61	
	4.148	4.52	0.50	
	8.960	4.90	0.24	
	Polyoxyethylene glycol-400	12.96	2.17	3.16
23.10		2.38	1.51	
34.85		3.33	0.82	
45.03		3.77	0.40	
54.29		4.93	0.25	

Both k_1 and k_2 increase with temperature, as they did in pure water. However, the activation energy for k_1 was 9.2 kcal/mole and for k_2 7.5 kcal/mole in 4.65% cetomacrogol solution, compared with values of 14.2 and 5.4 kcal/mole in pure water. Hence the presence of surfactant leads to a decrease in activation energy for the zero order reaction, and an increase for the first order one. This result will be considered further.

TABLE 3. EFFECT OF STIRRING RATE ON VELOCITY CONSTANTS IN CETOMACROGOL SOLUTIONS AT 25°

	Stirring rate rev/min		
	40	250	600
0.497% w/w cetomacrogol			
10 ⁹ k ₁	0.68	2.40	4.49
10 ⁴ k ₂	0.65	2.29	4.29
10.10% w/w cetomacrogol			
10 ⁹ k ₁	2.04	8.32	17.5
10 ⁴ k ₂	0.11	0.47	0.98

The effect of stirring rate on the velocity constants measured in 0.497% and 10.13% cetomacrogol solutions was evaluated (Table 3). Plots of log k_1 or k_2 against log of stirring rate gave a slope of 0.75 in both cases. This value differs from those found in pure water, and may indicate a different mechanism for dissolution in the surfactant solutions.

A further factor likely to influence the rate constants is the viscosity of the solutions. The relative viscosities are given in Fig. 4; the viscosities increase markedly at high concentrations of surfactants. When the rate constants for dissolution in surfactant solutions are plotted against concentration (Figs 5 and 6), at high surfactant concentrations both constants do not change sharply with concentration. This seems likely to be due to the rapidly rising viscosities of the solutions slowing the rate of diffusion of dissolved griseofulvin, and of griseofulvin being transported in a solubilized state. In the hexadecyl series of surfactants HE50 solutions have higher viscosities than HE22 solutions, while k_1 in HE22 is larger than k_1 in HE50 solutions. The viscosity of PG400 solutions increases in a roughly linear manner with concentration, while k_1 increases and k_2

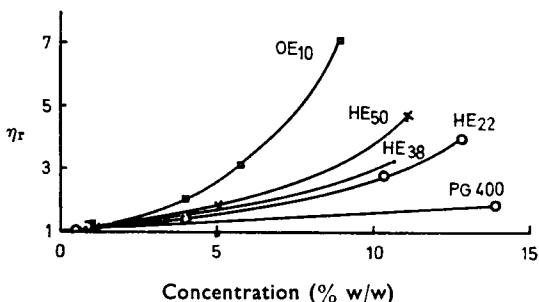


FIG. 4. Relative viscosities (η_r) of surfactant and PG400 solutions. (Experimental points at 0.5 and 1% cannot all be shown).

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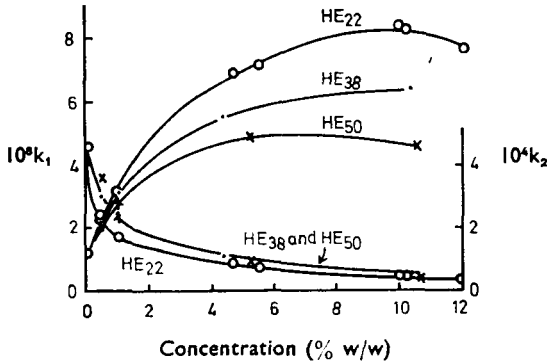


FIG. 5. Variation of k_1 (upper three curves) and k_2 (lower curves) with surfactant concentration for the hexadecyl containing surfactants.

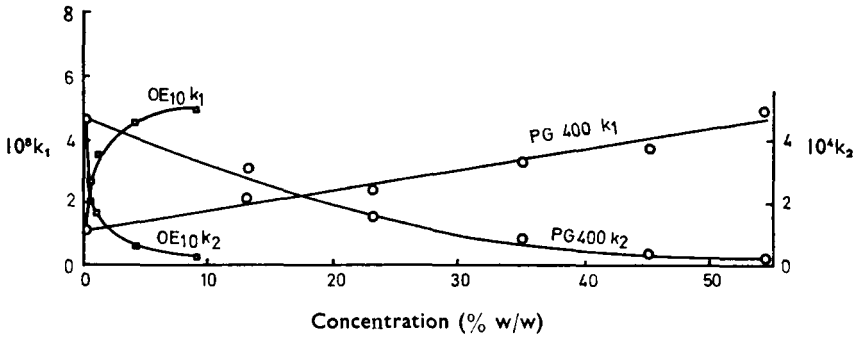


FIG. 6. Variation of k_1 and k_2 with solution concentration of OE10 and PG400.

decreases with concentration in the same way. The surfactants have a much more pronounced effect on the rate constants than the polyoxyethylene glycol.

It is not easy to interpret the rate constants in terms of fundamental quantities, and the interpretation given here is deliberately speculative.

It has been suggested (e.g. Bircumshaw & Riddiford, 1952) that for a dissolution controlled by a transport process, the velocity constant of the Noyes-Whitney equation (our k_2) can be written

$$k_2 = DA/V\delta \tag{6}$$

where D is the diffusion coefficient of the solute, A the area of the surface in contact with a volume, V , of solution, and δ is the thickness of the diffusion layer. From the Stokes-Einstein equation, the diffusion coefficient will be inversely proportional to the solvent viscosity i.e. to $1/\eta$. There is no theoretical foundation for interpreting the zero order constant, k_1 , but it seems reasonable to assume that this is proportional to DA/δ .

Using the solution viscosities (interpolated from graphs of $\log \eta_r$ against concentration), $k_1\eta$ and $k_2\eta$ were calculated. $k_1\eta$ gave a linear plot against

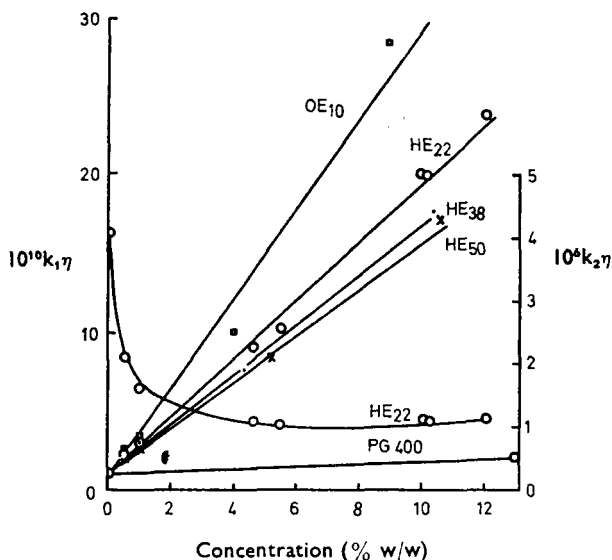


FIG. 7. Product of rate constant and viscosity of solution plotted against concentration. The straight lines refer to the $k_1\eta$ axis, while only one representative curve (for HE22) is shown as a plot of $k_2\eta$.

surfactant concentrations, instead of the type of graph shown in Figs 5 and 6. Also the different surfactants gave lines of different slopes (Fig. 7). Graphs of $k_2\eta$ against concentration are not linear. It seems necessary to account for the term V in equation 6. Although results have been expressed in terms of moles/litre, when we compare k_2 found in water with that in a surfactant solution, the capacities of the two "solvents" for griseofulvin are different. Hence the effective volume, V_e , was evaluated, being the volume of water to dissolve the amount of griseofulvin soluble at a particular surfactant concentration. Graphs of $k_2\eta V_e$ against surfactant concentration are linear, but again the slopes vary for the different compounds used. This treatment of k_2 is of course tentative.

Although there is some evidence from the rate of stirring experiments that diffusion does affect the velocity constant, there appears to be no sharp dividing line between those dissolution processes controlled by diffusion and those whose rate limiting step is a chemical reaction. A number of dissolution reactions seem to depend on both types of processes (see Bircumshaw & Riddiford, 1952), and on the relative magnitude of the energy changes involved. It seems likely that the presence of surfactants or polyoxyethylene glycol facilitates the transfer of a molecule of griseofulvin from the crystal surface into the solution, as the activation energy for this reaction is lower in cetomacrogol solution than in pure water. Also, the lowered energy of this process must be greater than any increase of activation energy due to increased viscosity effects.

In the case of k_2 the activation energy when surfactants are present is increased over that in water, which probably reflects the viscosity increase,

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and also the possibility that the energy change involved in redepositing a griseofulvin molecule on a surface with an adsorbed film of detergent present may differ from that involved in removing it from the vicinity of other griseofulvin molecules.

To obtain an idea of the free energy change on dissolution, ΔG , we can ignore activity coefficients and write

$$\mu (\text{solid}) = (\text{saturated solution}) = \mu_0 + RT \ln m$$

where m is the molality at saturation, hence

$$\Delta G = \mu_0 - \mu (\text{solid}) = -RT \ln m.$$

As we are only concerned with comparing the surfactants and polyoxyethylene glycol, molalities are used in place of mole fraction, and ΔG can be calculated from the solubilities already reported (Elworthy & Lipscomb, 1968b). ΔG has the value of -6.3 kcal/mole* in water, -5.4 and -5.1 kcal/mole respectively in 0.5 and 1% cetomacrogol solutions. Increase of cetomacrogol concentration to 4.7% decreases ΔG to -4.2 kcal/mole, while in 12% cetomacrogol solutions, ΔG has fallen to -3.7 kcal/mole. When these figures are compared with the value of k_1 given in Table 2, it seems likely that the rapid initial increase of k_1 with surfactant concentration may be related to the effect of the surfactant on the free energy of dissolution. There is a smaller effect (per unit of surfactant concentration) on ΔG at higher cetomacrogol concentrations, and also the viscosity of the solutions increased. The overall effect is a small variation of k_1 with surfactant concentration above the 4–5% region. It seems likely that the rate constants are related to both the transport properties of the solute, and to the energy changes in removing molecules of griseofulvin from the crystal to the bulk of the solution. A number of factors, like activity coefficients, the assumption that the diffusion coefficient of solute is governed solely by viscosity, and the fact that thickness of the diffusion layer can also be related to the viscosity (Bircumshaw & Riddiford, 1952), have been neglected in the above discussion.

The present results indicate that surfactants can significantly influence the dissolution rate of an insoluble drug.

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References

- Bates, T. R., Lin, S. L. & Gibaldi, M. (1967). *J. pharm. Sci.*, **56**, 1492–1493.
Bates, T. R., Gibaldi, M. & Kanig, J. L. (1966). *Nature, Lond.*, **210**, 1331–1333.
Bircumshaw, L. L., & Riddiford, A. C. (1952). *Q. Rev.*, **6**, 157–185.
Edwards, L. J. (1951). *Trans. Faraday Soc.*, **47**, 1191–1210.
Elworthy, P. H. & Lipscomb, F. J. (1968a), *J. Pharm. Pharmac.*, **20**, 790–792.
Elworthy, P. H. & Lipscomb, F. J. (1968b), *Ibid.*, **20**, 817–824.
Levy, G. & Gumtow, R. H. (1963). *J. pharm. Sci.*, **52**, 1139–1144.
Noyes, A. A., & Whitney, W. R. (1897). *J. Am. chem. Soc.*, **19**, 930–934.
Parrott, E. L. & Sharma, U. K. (1967). *J. pharm. Sci.*, **56**, 1341–1343.
Wurster, D. E. & Seitz, J. A. (1960). *Ibid.*, **49**, 335–338.

* ΔG is negative due to the choice of standard state.