Dissolution of Hydrocortisone

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Abstract □ Equations for use in studies of dissolution are derived from simple Noyes–Whitney kinetics. In one model the amount of drug added to the test system, W_o, is equal to the saturation capacity of the system, W_s. In the second model an equation is derived for use when $W_o \neq W_s$. It was found that the dissolution of hydrocortisone, in both distilled water and nonionic surfactant solutions, obeyed Model I equations up to about 40% saturation. The results obtained using Model II equations showed considerable variation in the dissolution rate constant. The effect of low concentrations of an *n*-alkyl polyoxyethylene surfactant upon the dissolution of hydrocortisone was investigated. It is shown that the plot of the dissolution rate constant against the surfactant concentration shows a pronounced maxima at the region of the CMC. Possible reasons for this finding are discussed.

Keyphrases □ Hydrocortisone dissolution—effect of low concentrations of nonionic surfactant (*n*-alkyl polyoxyethylene) □ Surfactant effect, nonionic—hydrocortisone dissolution □ Dissolution, hydrocortisone—effect of low concentrations of nonionic surfactant

In recent years, investigations of the dissolution of pharmaceutical powders and dosage forms have attracted considerable interest. For sparingly soluble drugs, such as many steroids, dissolution can be the rate-determining step controlling absorption. Biopharmaceutical aspects of dissolution rates were discussed by Gibaldi (1).

The original Noyes–Whitney law for application to dissolution kinetics (2) was modified by a number of workers, notably Nernst and Brunner (3), Hixson and Crowell (4), and Dankwerts (5). Another noteworthy paper about dissolution theory is that of Higuchi and Hiestand (6).

A number of workers have presented reports showing how substances used as pharmaceutical adjuvants can affect drug dissolution rates (7–11). For example, Finholt and Solvang (12) demonstrated that the rate of dissolution was modified by polysorbate 80; the changes were attributed to changes in interfacial tension rather than solubilization effects. Weintraub and Gibaldi (13) pointed out that while the influence of micellar solubilization has been extensively studied, the effect of concentrations below the CMC has been given only limited attention.

In the present paper the derivations and applications of some dissolution equations are reported; the mathematical approach used is fundamentally similar to that used by a number of other workers (4, 6, 14, 15). Solutions of the Noyes–Whitney law are described for two cases: (*a*) when $W_o = W_s$, and (*b*) when $W_o \neq W_s$. By using model equations, the dissolution of hydrocortisone in a number of systems containing an *n*-alkyl polyoxyethylene surfactant was investigated. The dissolution results are compared with solubilization data to elucidate the mechanisms whereby the surfactant modifies the dissolution process. In these investigations, the beaker method, which was recently subjected to some critical appraisal (16, 17), was used. However, the apparatus needed to overcome some of the difficulties associated with the beaker method is rather complex and, as Hersey (18) pointed out, this method is simple and adaptable and thus has much to commend it.

THEORY

Model I—The discussion is based on the equation:

$$\frac{dC}{dt} = KA(C_s - C) \qquad \text{(Eq. 1)}$$

where C = concentration of the drug in solution at time t, C_s = saturation concentration of the drug, A = surface area of undissolved drug exposed to the solvent at time t, and K = the rate constant of dimensions $T^{-1}L^{-2}$.

If V = volume of the system, and $Z = VC$ = the mass of solute dissolved at time t, then:

$$W_s = VC_s \qquad \text{(Eq. 2)}$$

where W_s is the mass of solute required to saturate the volume V. Moreover, W_o = the mass of undissolved solute at initial time, t_o; then Eq. 2 may be written in terms of the amount of dissolved solid, Z:

$$\frac{dZ}{dt} = KA(W_s - Z) \qquad \text{(Eq. 3)}$$

A shape factor, η, is defined for the particles (assumed identical) by: $A = \eta(W_o - Z)^{2/3}$. If it is assumed further that the particles are spherical and remain so during dissolution:

$$\eta = AW^{-2/3} = \left[\frac{6\sqrt{\pi}}{P}\right]^{2/3} \qquad \text{(Eq. 4)}$$

where P is the solute density.

By substituting in Eq. 3, recalling that $W_s = W_o$, and integrating, $\int(W_o - Z)^{-5/3}dZ = K\eta t + Y$. By using the initial condition $Z = 0$ at $t = 0$ to evaluate the integration constant, after integration:

$$(W_s - Z)^{-2/3} - W_s^{-2/3} = 2/3K\eta t \qquad \text{(Eq. 5)}$$

A plot of the left-hand side based on experimental values of Z at known times t should give a straight-line graph (Fig. 2). From its slope σ, K is calculated: $K = [3e^2/32\pi]^{1/3} \times \sigma$, where Eq. 4 has been substituted for η.

Model II—It is not always experimentally convenient to arrange $W_s = W_o$ as demanded by Model I. The modification required for the case $W_s > W_o$ is therefore given. It is convenient to rewrite Eq. 3 in the form:

$$\frac{dW}{dt} = -K\eta W^{2/3}(W_s - W_o + W) \qquad \text{(Eq. 6)}$$

where $W = W_o - Z$ is the mass of solute undissolved at time t.

By letting $W = u^3$ and $W_s - W_o = F^3$, Eq. 6 becomes:

$$\frac{du}{dt} = -K(u^3 + F^3) \qquad \text{(Eq. 7)}$$

By using a standard integral from Dwight (19):

$$-\eta K(t_2 - t_1) = 3\int_{u(t_1)}^{u(t_2)} (u^3 + F^3)^{-1}du \qquad \text{(Eq. 8a)}$$

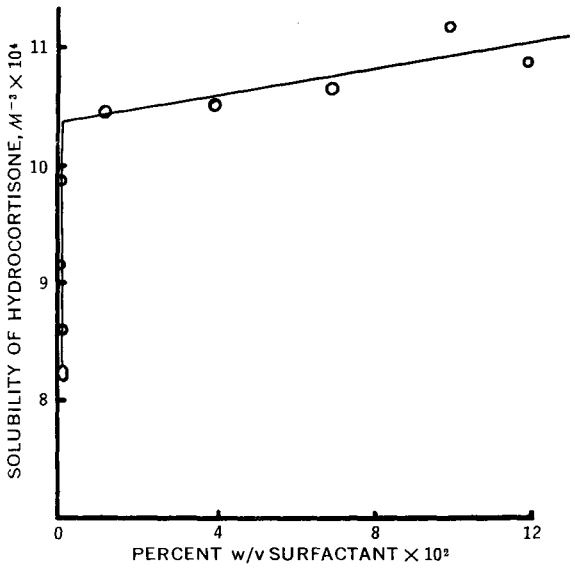

Figure 1—*Solubility of hydrocortisone as a function of surfactant concentration (0–0.12% w/v).*

$$= \left[\frac{1}{2} F^{-2} \log_e \frac{(u+F)^2}{F^2 + u^2 - Fu} + \sqrt{3}F^{-2} \arctan \frac{2u - F}{F^3}\right]_{t=t_1}^{t=t_2} \quad \text{(Eq. 8b)}$$

$$= [I\{u(t)\}]_{t=t_1}^{t=t_2} \quad \text{(Eq. 8c)}$$

for any two times t_1 and t_2 ($t_2 t_1$)

Thus:

$$K = \frac{1}{(t_2 - t_1)} [IW^{1/3}(t_2) - IW^{1/3}(t_1)] \quad \text{(Eq. 9)}$$

By calculating η from Eq. 4 and determining $W = W_o - Z$ experimentally at different times t_1 and t_2, I and thus K are obtained from Eq. 9.

EXPERIMENTAL

Materials—A nonionic *n*-alkyl polyoxyethylene surfactant[1] was used. This material, which was characterized previously (20), has an average of 16 carbon atoms in the alkyl chain and 30 polyoxyethylene groups. Hydrocortisone[2] (m.p. 212°), glass-distilled water, and immersible stirring units[3] were used.

Hydrocortisone Assay—Hydrocortisone was assayed in distilled water by UV spectrometry at 248 nm. The molar absorptivity for hydrocortisone at this wavelength was 1.61×10^4, and the Beer–Lambert law was obeyed. Surfactant solutions were used as blanks when required.

Solubility Determinations—An aqueous suspension of hydrocortisone, plus the appropriate amount of surfactant, was stirred for 1 week at 25 ± 0.1° until equilibrium was reached. Samples were filtered through 0.22-μm. Millipore filters.

Determination of Dissolution Rate—The dissolution rate was determined using the beaker method. The calculated amount of hydrocortisone was added, in powder form, to the center of the vortex in 200 ml. of the dissolution medium at time zero. The solution was stirred, using an immersible stirring unit, at 1200 r.p.m. Samples were withdrawn, through a 0.22-μm. Millipore membrane filter held in a filter adaptor (Swinney), at different times and diluted.

RESULTS AND DISCUSSION

The first attempt to quantify the rate of dissolution of a solid is usually attributed to Noyes and Whitney (2). They attributed the dissolution to a diffusion process, which they expressed by the equation:

$$\frac{dC}{dt} = \text{constant} \times (C_s - C) \quad \text{(Eq. 10)}$$

(where the symbols used are those of Model I). This Noyes–Whitney equation contains no explicit dependence of dissolution rate on solute surface area but seems to have been a fair description of the Noyes–Whitney experimental conditions. By using only large cylinders (8 cm. long and 2 cm. in diameter) of low solubility solids, these workers kept their solute surface area substantially unchanged. However, the assumption that surface area is not significantly reduced by time is hardly realistic for powdered solids.

In investigating solutes other than benzoic acid and lead chloride, to which the original Noyes–Whitney work was confined, Higuchi and Hiestand (6), Niebergall and Goyan (14), and Niebergall *et al.* (15) allowed in their respective theories for such a reduction, with time, of solute surface area. In Model I, the approach used is similar to that of Niebergall and Goyan.

It is appreciated that Eq. 5, though more explicit than the original Noyes–Whitney equation, is too crude for the purpose of distinguishing dissolution mechanisms. Equation 5 is used because of the convenience of the parameter K. In writing the concentration, $C(t)$, as a function of time alone, the space dependence normally to be expected from a diffusion process is suppressed. This is justified if it may be assumed that stirring renders the drug concentration uniform throughout the volume V. Otherwise stated, it is assumed that diffusion occurs across the solute–solvent interface and diffusion through the solvents is neglected.

No allowance in this paper has been made here for the effect of particle-size distribution.

A plot of the solubility of hydrocortisone against surfactant concentration takes the form of two straight lines intersecting at an apparent CMC of about 1×10^{-3}% w/v (Fig. 1). By the method of least squares, the slopes of the lines at both submicellar and supramicellar surfactant concentrations were evaluated. From the results shown in Table I, the value of W_s at any surfactant concentration between 5×10^{-5} and 1.2×10^{-1}% can be calculated.

Figure 2 shows the graph for the dissolution of hydrocortisone in distilled water. At 300 sec. the dissolution medium was 75% saturated. However, the line plotted from the experimental results deviates from linearity at about 50 sec. when the medium was 48% saturated. One reason for this finding may be a change in the value of η with time. Also, the simple dissolution model fails to take into account the possible change of the diffusion coefficient with concentration (21). A similar finding was made in the systems containing surfactant; Eq. 5 could only be applied to the first half of the dissolution process. Kabasakalian *et al.* (22) also reported a similar divergence between experimental results and theory when the saturation exceeds about 40%. Using an approach similar to that used by Wilhelm *et al.* (23), K was determined from dissolution results obtained from systems of 0–40% saturation (23).

Table I—Estimated Solubilities of Hydrocortisone in Solutions of an *n*-Alkyl Polyoxyethylene Surfactant

Surfactant, % w/v	Estimated Solubility of Hydrocortisone, × 10^4 M^{-3}	Characteristics of Lines Fitted to —Experimental Data in Fig. 1— Slope, M^{-3}/%	Intercept × 10^4 M^{-3}	Correlation Coefficient
Below apparent CMC of 1×10^{-3}				
0	8.33	0.1526	8.33	0.9856 (4 points)
5×10^{-5}	8.41			
1×10^{-4}	8.48			
5×10^{-4}	9.09			
1×10^{-3}	9.86			
Above apparent CMC				
1×10^{-3}	10.12	8.51×10^{-4}	10.11	0.8437 (5 points)
1×10^{-2}	10.20			
4×10^{-2}	10.45			
7×10^{-2}	10.71			
1×10^{-1}	10.96			
1.2×10^{-1}	11.13			

[1] Glover's Ltd., Leeds, England.
[2] Merck Sharp and Dohme Ltd., Hoddesdon, Herts, England.
[3] Rank Bros., Bottisham, Cambridge, England.

Table II—Dissolution Rate Constants of Hydrocortisone Powder in Various Concentrations of Surfactant

	Concentration of Surfactant, % w/v									
	0	5×10^{-5}	1×10^{-4}	5×10^{-4}	1×10^{-3}	1×10^{-2}	4×10^{-2}	7×10^{-2}	1×10^{-1}	1.2×10^{-1}
K, m.$^{-2}$ sec.$^{-1}$	205	290	384	247	216	276	263	279	300	306
Correlation coefficient	0.988	0.973	0.990	0.993	0.992	0.991	0.997	0.998	0.997	0.996
(number of points)	(8)	(13)	(7)	(9)	(9)	(7)	(9)	(9)	(9)	(9)

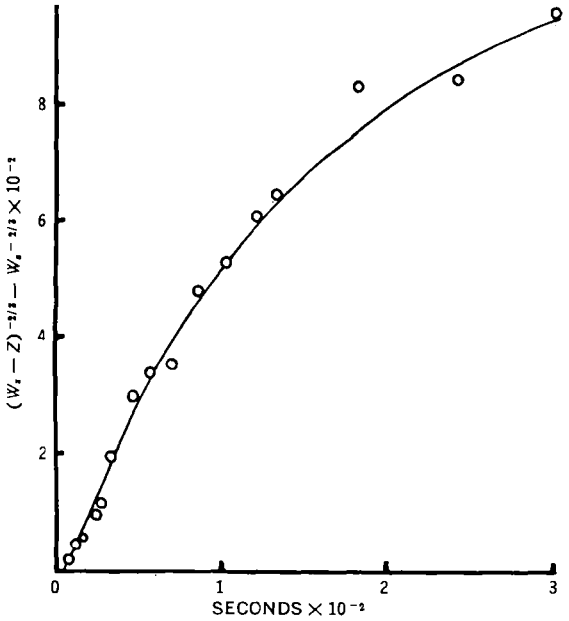

Figure 2—*Dissolution of hydrocortisone in distilled water as described by Model I.*

Table II shows the rate constants for the dissolution of hydrocortisone in various concentrations of surfactant. In all cases the correlation coefficients give strong evidence of linearity.

Figure 3 shows K as a function of surfactant concentration. The initial rise of K to a maximum, at a surfactant concentration of about 1×10^{-4}%, is of considerable interest. Although a number of workers reported significant changes in dissolution rates produced by surfactants, the existence of a peak value of K in the region of the apparent CMC does not appear to have been previously reported.

Figure 4 shows a plot of the solubility ratio (solubility of hydrocortisone in surfactant solution/solubility of hydrocortisone in water) and dissolution rate ratio (dissolution constant in surfactant solution/dissolution constant in water). An explanation of the use of such a graph was presented by Gibaldi *et al.* (24). Above the apparent CMC, the two curves are reasonably close to one another. However, whereas below the CMC the dissolution rate ratio shows a significant peak, no such maximum is evident on the solubility ratio curve. This indicates that the initial rapid rise in K could be due to a reduction in the interfacial barrier, a deaggregation effect, or a modification of the drug diffusion coefficient. This finding is supported to some extent by the results of Weintraub and Gibaldi (13). However, it is also of interest to compare Fig. 3 with a surface tension surfactant concentration graph (25). The shape of the dissolution K maximum is very similar to the surface tension minima commonly observed in such systems. Thus, it is suspected that the

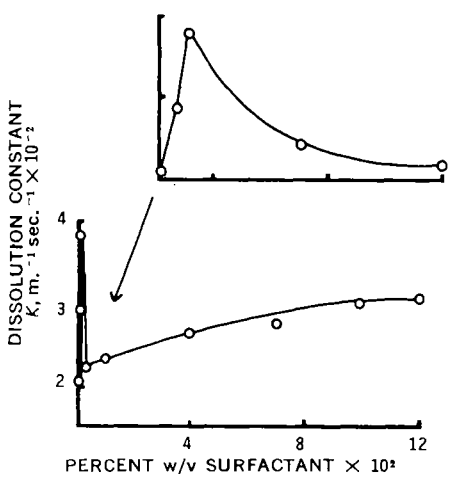

Figure 3—*Dissolution rate constant (Model I) of hydrocortisone as a function of surfactant concentration, 0–0.12%. (Insert shows 0–10^{-3}% expanded.)*

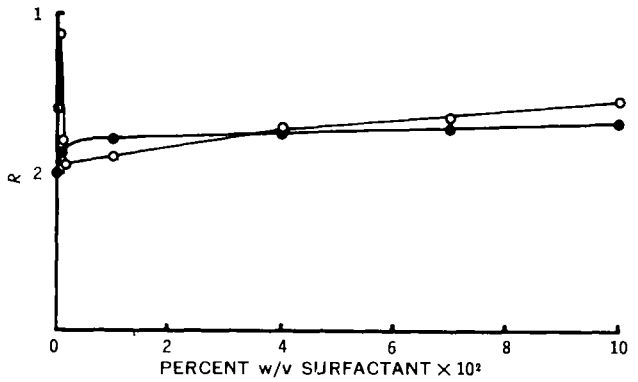

Figure 4—*Solubility ratio and dissolution rate ratio, R, of hydrocortisone as a function of surfactant concentration. Key: ○, dissolution rate ratio; and ●, solubility ratio.*

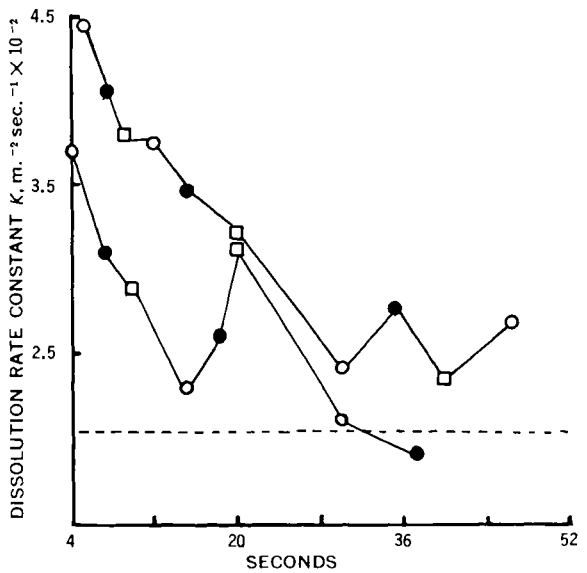

Figure 5—*Dissolution rate constants (Model II) of hydrocortisone as a function of time. Upper curve is for W_o = 0.6 W_s, and lower curve is for W_o = 0.1 W_s. Key: □, Run 1; ○, Run 2; and ●, Run 3. (The dotted line indicates the value of K obtained by use of Model I.)*

rise and fall of the dissolution K values in the vicinity of the apparent CMC may be due to a surface tension effect. Further information about the micellar molecular weight of the drug–surfactant complex would be required to identify fully the mechanism responsible for this finding.

Studies of the dissolution of hydrocortisone using Model II equations were performed in six separate experiments. In three experiments, W_o was equal to 0.1 W_s; in the other three, W_o was equal to 0.6 W_s. Values of K are shown as a function of time in Fig. 5. It is evident that in both series of experiments, K decreased significantly with time.

The values of K are average rate constants as t_1 was set to zero in Eq. 9. Although there is a good deal of scatter in the results, values of K at later times, 28 sec., appear to be approaching a limiting value of the same order of magnitude as that determined using Model I.

Thus, the results obtained using both Models I and II show that although simple Noyes–Whitney kinetics may be usefully applied in dissolution at low levels of saturation, a more elaborate theoretical model is needed for systems that are more than about 40% saturated. The results of the Model II experiments show that the dissolution process under nonsink conditions is not described by the equations derived in this report.

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Acetylcholinesterase Substrates: Acetoxymethylpyridines and Benzyl Acetate

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Abstract □ 2-Acetoxymethylpyridine (I) and 2-, 3-, and 4-acetoxymethylpyridinium methiodides (II, III, and IV, respectively) are spectrophotometrically useful substrates for acetylcholinesterase. Compounds III and IV are highly water soluble yet equal to phenyl acetate in resistance toward aqueous hydrolysis. Compound I and benzyl acetate are appreciably more stable. Kinetic constants for both enzymatic and nonenzymatic hydrolysis are reported. Comparison of the relative rates of acylation of acetylcholinesterase by Compounds I, III, and IV and phenyl acetate indicates considerable kinetic selectivity. Contrary to general expectations, the uncharged compounds, I and phenyl acetate, have the highest turnover rates.

Keyphrases □ Acetylcholinesterase substrates—acetoxymethylpyridines, benzyl acetate □ Hydrolysis rates, enzymatic, nonenzymatic—acetoxymethylpyridines □ Michaelis constants—acetoxymethylpyridines □ Acetoxymethylpyridine, methiodides—as acetylcholinesterase substrates, hydrolysis rates □ Benzyl acetate—as acetylcholinesterase substrate

As part of a program to develop spectrophotometrically useful substrates[1] for application in kinetic and mechanism studies with acetylcholinesterase (E.C. 3.1.1.7), results are reported here with four acetoxymethylpyridines (Table I) and benzyl acetate (V). The particular aim is to provide substrates having a range in kinetic constants, $K_{m(app)}$ and k_{cat}, and in useful wave-

[1] Earlier papers in this series include References 1 and 2.