species of Mycobacteria, *S. cerevisiae*, *C. albicans*, and *G. candidum*. None showed appreciable inhibition of any test organisms at concentrations of 100 mcg./ml.

None of the compounds had surface anesthetic activity when tested in the rabbit's eye.

Intracutaneous injection of a 0.25% solution of compound 13 (Table I) in guinea pigs caused anesthesia of 30 min. duration.

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Keyphrases

1,3-dioxolanes, basically substituted—synthesis
1,3-dioxanes, basically substituted—synthesis
Azeotropic distillation reaction—acid catalyzed
Microbiological screening
Anesthesia, local—screening

Dissolution Rates in Surfactant Solutions Under Stirred and Static Conditions

By M. GIBALDI, S. FELDMAN, R. WYNN, and N. D. WEINER*

The dissolution rate of benzoic acid was determined in water and solutions of polyoxyethylene (23) lauryl ether by the rotating disk and static disk methods. The results under stirred and static conditions substantially deviated from the Noyes-Whitney equation. Dissolution rates in surfactant solutions were much less than anticipated on the basis of solubilization data. The ratios of dissolution rate in surfactant solution to that in pure solvent were found to be significantly greater under static conditions as compared to the ratios determined under stirred conditions, suggesting a possible change in dissolution mechanism. Certain aspects of dissolution rate theory are explored to explain this unusual phenomenon.

THE INFLUENCE of interacting colloids such as polymers or micellar aggregates on drug solubility has been investigated extensively and the literature contains numerous reports concerning drug solubilization in colloidal systems. However, only a limited amount of information is available on the influence of solubilization on dissolution rate.

Taylor and Wurster (1) found significant increases in both the solubility and dissolution rate of various forms of prednisolone in 0.1% solutions of sodium lauryl sulfate. Since this concentration is considerably below the critical micelle concentration (CMC) and since the extent of solubiliza-

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tion appeared to be related to the activity of the crystal form, the authors suggested that a cooperative phenomenon was responsible for the increased solubility. Furthermore, a major factor in the increased dissolution rate appeared to be an apparent increase in the interfacial rate constant by virtue of the surfactant assisting in the release of surface molecules through interfacial tension lowering. Hence, the influence of micellar solubilization, if any, on the dissolution rate of prednisolone is this study cannot be assessed.

Bates, Gibaldi, and Kanig (2) reported substantial increases in the dissolution rates of griseofulvin and hexestrol in micellar solutions of bile salts. In each case, because of the extremely low solubility of both drugs, dissolution rate was followed in a concentration region which was above the saturation solubility in water.

Until recently the influence of interacting colloids on dissolution rate in a drug concentration region below saturation solubility had received only theoretical consideration. Higuchi (3) presented a theoretical analysis pertinent to the dissolution of solids in colloidal solutions. The equations resulting from this analysis predict that the effect on dissolution rate as a function of colloidal solubilizer concentration will be far less than the effect predicted by the Noyes-Whitney relationship (4). The latter suggests a direct proportionality between dissolution rate and total solubility. The Higuchi equations (3) further predict that substantial effects on dissolution rate will be observed only when the drug concentration in solution approaches or exceeds saturation solubility. This prediction is in agreement with the findings of Bates *et al.* (2) and the earlier findings of Wurster and Polli (5).

Experimental evidence confirming the theoretical predictions were presented in a recent review (6). The dissolution rate of benzocaine in various concentrations of polysorbate 80[1] was found to be in agreement with the diffusional model proposed by Higuchi rather than the Noyes-Whitney equation. Higuchi (6) has further suggested that the magnitude of effects of interacting colloids on dissolution rates could be used for the differntiation of dissolution mechanism.

The present report concerns a study of the solubilization and dissolution rate of benzoic acid in solutions of a nonionic ether-type surfactant. Dissolution rate was followed under stirred and static conditions. It is the purpose to demonstrate that the effect of micellar solubilization on dissolution rate cannot be predicted by the Noyes-Whitney equation and to propose that different mechanisms of dissolution may be operative under stirred and static conditions.

[1] Tween 80, Atlas Chemical Industries, Wilmington, Del.

EXPERIMENTAL

Materials—Baker analyzed reagent benzoic acid was used as the dissolving solid and polyoxyethylene (23) lauryl ether,[2] served as the solubilizing agent.

Solubility Determinations—Benzoic acid solubility was determined in a series of aqueous solutions containing various concentrations of polyoxyethylene (23) lauryl ether. In each case, an amount of benzoic acid in excess of the amount required for saturation solubility was added to the surfactant solutions contained in 25-ml. culture tubes. The tubes were sealed, placed in a Metabolyte incubator shaker (New Brunswick Scientific Co., N.J.), and equilibrated at 37° for 3–5 days. Equilibrium was determined by repetitive sampling.

Determination of Dissolution Rate—Dissolution rates were determined at 37° by the rotating disk (7, 8) and static disk (9) methods, using 300 ml. of water or aqueous solutions of polyoxyethylene (23) lauryl ether. Speed of rotation for the rotating disk experiments was 100 r.p.m.

Assay—Aliquot samples were passed through a Millipore filter (0.45 μ pore size), when necessary, and appropriately diluted with 0.1 *N* HCl. Benzoic acid concentration was determined spectrophotometrically at 230 mμ using a Beckman DB-G recording spectrophotometer. In each case, an appropriate concentration of surfactant was contained in the blank to avoid interference.

RESULTS AND DISCUSSION

Figure 1 shows the saturation solubility of benzoic acid as a function of surfactant concentration. The results describe a typical solubilization curve with a linear relation between solubility and polyoxyethylene (23) lauryl ether concentration above the CMC. Solubilization studies at low surfactant concentrations indicate a CMC of less than 0.1 Gm./100 ml.

According to the Noyes-Whitney relationship (4), under sink conditions and with constant surface area, dissolution rate (*d.r.*) may be described by the following equation:

$$d.r. = KC_s \qquad \text{(Eq. 1)}$$

where K is a constant and C_s is the solubility. In nonmicellar systems, $K = D/h$ where D is the solute molecule diffusion coefficient, and h is the effective diffusion layer thickness. If one assumes that both D and h remain invariant if the drug is dissolved in a medium containing colloidal solubilizer, then it may be deduced from Eq. 1 that

$$R = \frac{Cs^*}{Cs} \qquad \text{(Eq. 2)}$$

where R is the ratio of dissolution rate in surfactant solution to that in pure solvent and Cs^* is the drug solubility in surfactant solution.

Using the solubility data obtained in the present

[2] Brij 35 SP, Batch No. 1340B, generously supplied by Atlas Chemical Industries, Wilmington, Del.

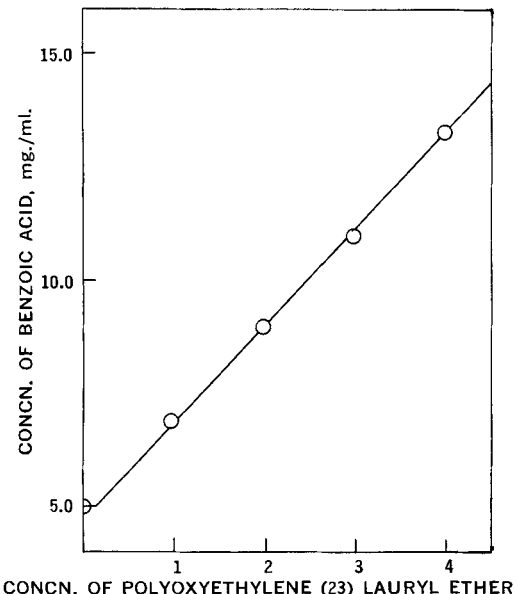

Fig. 1—Saturation solubility of benzoic acid as a function of surfactant concentration.

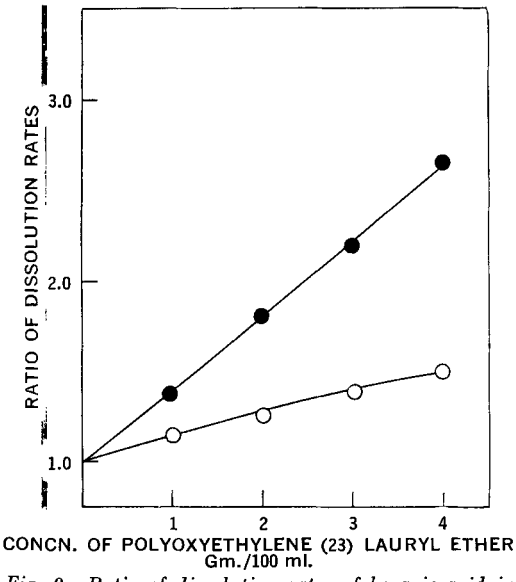

Fig. 2—Ratio of dissolution rates of benzoic acid in surfactant solution to that in water. Key: ●, upper curve was constructed by means of the Noyes-Whitney equation and solubility data: ○, lower curve represents experimental dissolution rate data.

study the theoretic dissolution rate ratios employing Eq. 2 were determined. The results are shown in Fig. 2 in contrast to the experimental dissolution rate ratios determined at 100 r.p.m. The curves in Fig. 2 clearly demonstrate that the Noyes-Whitney relation fails to predict dissolution behavior in systems containing colloidal solubilizers. Dissolution rates of benzoic acid in solutions containing polyoxyethylene (23) lauryl ether are substantially less than anticipated on the basis of solubilization data and the application of the Noyes-Whitney equation.

The dissolution of a drug in the presence of an interacting colloid such as a micelle involves consideration of two diffusing species, *viz.*, the free drug and the drug–micelle interaction product (3). In view of the large difference in molecular weight between the drug molecule and the micellar species, one anticipates a significant difference with respect to the diffusion coefficient of each species. For this situation, the diffusion layer theory gives the following equation (3):

$$d.r. = \frac{DCs}{h} + \frac{D'Cs'}{h} \qquad \text{(Eq. 3)}$$

where D' is the diffusion coefficient of the micelle-solubilized drug and Cs' is the solubility increase due to solubilization. If we assume that h, D, and D' are independent of the concentration of colloidal solubilizer then the following ratio (R) of dissolution rate in surfactant solution to that in pure solvent is predicted by diffusion layer theory.

$$R = \frac{DCs + D'Cs'}{DCs} \qquad \text{(Eq. 4)}$$

As indicated in Eq. 4 the greater the difference between D and D' the greater the negative deviation of R from the ratio value predicted by the Noyes-Whitney equation.

If one assumes that the data under stirred conditions adheres to the diffusion layer theory, a theoretic diffusion coefficient for the micelle-solubilized drug may be determined. Using the experimental R values, the appropriate solubilization data, and a value of 1.2×10^{-5} cm.²/sec. as the diffusion coefficient for benzoic acid (10), an apparent mean diffusion coefficient of 3.8×10^{-6} cm.²/sec. for the micelle-solubilized benzoic acid was calculated.

The ratios predicted by the diffusion layer theory are shown as the dashed line in Fig. 3. The predicted curve fits the experimental data reasonably well. The fit suggests, in agreement with Higuchi (3, 6), that a diffusion layer model can be used to explain the effect of colloidal solubilizers on dissolution rate.

The dissolution studies under static conditions were prompted by the possibility that different mechanisms of dissolution exist under extremely low agitation conditions and under stirred conditions. The results of these studies were used to calculate dissolution rate ratios which are plotted in Fig. 3. At each polyoxyethylene (23) lauryl ether concentration studied the ratio under static conditions was significantly higher than the ratio under stirred conditions.

An advantage of studying dissolution in systems involving interacting materials which result in diffusing species with significantly different diffusion coefficients is the possibility of mechanism differentiation (6). For example, if hydrodynamic conditions are maintained constant, dissolution rate ratios as a function of solubilizer concentration will be the same regardless of the intensity of agitation. A change in the magnitude of a dissolution rate ratio suggests a change in the hydrodynamics of the system and a possible change in the dissolution mechanism. Thus, the difference in dissolution rate ratios observed under static conditions provides evidence for the existence of different dissolution mechanisms.

An alternative to the diffusion layer theory to consider in describing dissolution rate mechanism

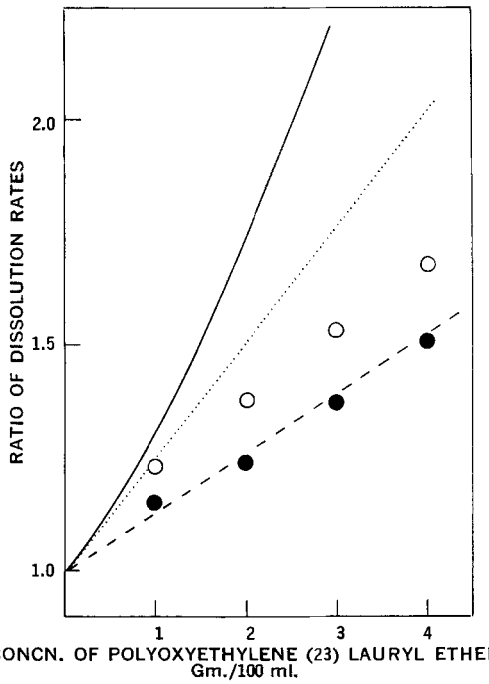

Fig. 3—Ratio of dissolution rates of benzoic acid in surfactant solution to that in water under static (○) *and stirred conditions* (●). *Key: theoretical ratios predicted by Noyes-Whitney theory* (——); *Danckwerts' theory* (· · ·); *and diffusion layer theory* (– – –).

under static conditions is one originally proposed by Danckwerts (11) to describe dissolution phenomenon under turbulent conditions. This model envisions macroscopic packets of solvent impacting the solid-liquid interface by eddy diffusion. Uptake of solute into the packet occurs upon impaction and these saturated surface elements are continually replaced by new packets of solvent. Although the Danckwerts' model was proposed originally to explain dissolution under turbulent conditions, a type of eddy diffusion may exist under static conditions and a transference of concept may be possible.

The appropriate rate expression for dissolution rate per unit area under sink conditions in accord with the Danckwerts' model is

$$d.r. = S^{1/2}D^{1/2}Cs \qquad \text{(Eq. 5)}$$

where S is the mean rate of production of fresh surface. When considering dissolution of a material in a medium of colloidal solubilizer, Higuchi (6) has shown that Danckwerts' theory leads to the following rate equation:

$$d.r. = S^{1/2}\sqrt{(Cs + Cs')(DCs + D'Cs')} \qquad \text{(Eq. 6)}$$

where the terms have the same meaning as previously described. If we assume that S, D, and D' are independent of concentration of solubilizer, then the following ratio of dissolution rate in surfactant solution to that in pure solvent is predicted by Danckwerts' theory.

$$R = \frac{\sqrt{(Cs + Cs')(DCs + D'Cs')}}{D^{1/2}Cs} \qquad \text{(Eq. 7)}$$

Theoretical values of R were calculated from Eq. 7 using an apparent mean diffusion coefficient of 3.8×10^{-6} cm.²/sec. for the micelle-solubilized benzoic acid. The theoretical relation of R and concentration of surfactant is shown as the dotted line in Fig. 3. It is apparent that the Danckwerts' model fits the static dissolution data only at the 1% level. At higher concentrations of polyoxyethylene (23) lauryl ether, progressive deviation is observed.

Several possibilities may be explored to rationalize the lack of agreement of the experimental data with the model. One possibility is that surface renewal rate is dependent on the surfactant concentration, *i.e.*, $S^{1/2} \alpha 1/(\text{surfactant})$. The dependence could involve viscosity or some other physical-chemical property of the system which is a function of polyoxyethylene (23) lauryl ether, concentration.

A second possibility is that the mechanism of dissolution under static conditions involves a combination of the diffusion layer and Danckwerts' models. Such a combination has been termed the film-penetration model (12). This model is similar to the Danckwerts' model except that solvent packets impact a diffusion layer rather than the solid-liquid interface. Interestingly, the film-penetration model has been shown to predict dissolution under turbulent conditions, more accurately than the Danckwerts' model (12).

A further possibility which cannot be ruled out is that dissolution under static conditions actually adheres to Dankwerts' theory, while dissolution under stirred conditions (under the present experimental conditions) manifests negative deviation from the results predicted by this model. The evidence, to date, that dissolution under stirred conditions follows diffusion layer theory is strictly empirical. There has been no independent verification of the model, as for example, by the independent determination of the diffusion coefficient of the drug-micellar species. Hence, the various possibilities cannot be resolved without further investigation.

BIOLOGIC IMPLICATIONS

The present report describes certain dissolution phenomena which may have an important bearing on dissolution in the gastrointestinal tract as well as on the general area of *in vivo-in vitro* correlation. The most successful methodology employed to date to relate *in vitro* dissolution rate with *in vivo* absorption has been described by Levy (13–15) and appears to involve a dissolution mechanism describable by diffusion layer theory. By means of this dissolution method Levy *et al.* (16) have reported quantitative correlation of gastrointestinal absorption in man of aspirin from three markedly different types of dosage forms. The correlation may be expressed as

$$\%\text{ – absorbed at time } T = \%\text{ – dissolved in } \frac{T - \text{lag time}}{2}$$

There is no doubt as to the precision of the correlation. However, in terms of absolute amounts, about twice the amount of drug was dissolved *in vitro* than was absorbed *in vivo* over the same time period. Correlation was observed at 50–60 r.p.m. and failed to exist at higher or lower r.p.m. Thus, it is not possible to correct the correlation in absolute

terms by simply decreasing the agitation rate.

It is proposed that the problem we face in developing *in vivo-in vitro* correlations could involve the mechanism of dissolution as well as the intensity of agitation. The nature of the dissolution mechanism in the gastrointestinal tract is not at all clear. In view of the type of agitation a dissolving solid encounters in the tract as a result of gastrointestinal motility, it is quite conceivable that dissolution will not follow pure diffusion layer theory. The process may be obscured by periodic and irregular diffusion currents which could result in a highly complex dissolution mechanism. Perhaps a combination of diffusion layer and Danckwerts' mechanisms may be operative. A great deal of further experimentation on dissolution is required to resolve these questions.

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Keyphrases

Benzoic acid dissolution rates
Surfactant solution—benzoic acid solubility
Stirred conditions—dissolution rates
Static conditions—dissolution rates

Kinetics of Reaction of Dehydroacetic Acid II

Reaction With Primary Amines

By S. GOTO, A. KONO, and S. IGUCHI

It was concluded that the conversion of 2,6-bis-(phenethylamino)-2,5-heptadiene-4-one (BPH) into *N*-phenethyl-lutidone (PL) in 80 percent ethanol is accounted for in terms of aminolysis reaction. In general, the aminolysis reaction proceeds *via* a two-step reaction path involving a *gem*-diamine as an intermediate. The first step in the above reaction of BPH becomes reversible by the addition of excess β-phenethylamine (PE-NH). The mechanistic pathway was discussed. Moreover, it was supported with kinetic investigation using an analog computer that BPH is the most important intermediate in the conversion of 3-(1-phenethylamino)ethylidene-6-methyl-3*H*-pyran-2,4-dione (Schiff's base) to PL in the presence of large excess PE-NH.

IN A PREVIOUS paper (1), the kinetic study of Schiff's base formation between dehydroacetic acid (DHA) and β-phenethylamine (PE-NH) has been shown. A further kinetic investigation on the transformation of Schiff's base to *N*-phenethyllutidone (PL)[1] is described, and also an attempt was made to confirm kinetically the reaction mechanism that was proposed by Iguchi *et al.* (2).

EXPERIMENTAL

Materials—Ethanol of superior special grade for precision analysis was used. PE-NH (Wako pure reagent) was redistilled twice (b.p. 178–179°). DHA (Taito Pfizer Co.) was recrystallized from ethanol–water, m.p. 109–110°. Commercial acetic acid was redistilled, and sodium acetate and sodium chloride of pure reagent grade were used for the kinetic studies.

Preparation of 3-(1-Phenethylamino)ethylidene-6-methyl-3H-pyran-2,4-dione (Schiff's Base)—DHA (10 Gm.) was dissolved in 15 ml. ethanol solution containing an equivalent mole of PE-NH and the solution was warmed on a steam bath. After 30 min. the solvent of reaction mixture was distilled *in vacuo*, the residue was washed once with ethyl ether, and recrystallized from ethyl ether–benzene, m.p. 89–91°.

Preparation of 2,6-Bis-(phenethylamino)-2,5-heptadiene-4-one (BPH)—To 5 ml. of ethanol solution of DHA (3.4 Gm.) was added an excess of

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[1] The final product of this series of the reaction.