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Keyphrases

Polymeric membranes—drug diffusion
Silastic membranes—aminophenones, diffusion
Diffusion, steady state—membrane, pH, temperature, ethanol effect
Aminophenones, concentration—diffusion rate
Quasi-steady-state diffusion
Nonsteady-state diffusion

Mechanistic Study of the Influence of Micelle Solubilization and Hydrodynamic Factors on the Dissolution Rate of Solid Drugs

By P. SINGH*, S. J. DESAI*, D. R. FLANAGAN, A. P. SIMONELLI, and W. I. HIGUCHI

The influence of micelle-drug solubilization on the dissolution rate has been investigated. The dissolution rates predicted by the diffusion layer model, the Danckwerts theory, and by the rotating disk theory were calculated and compared with experimental data obtained for the benzocaine–polysorbate 80 system. All the parameters involved were independently determined. The different conditions under which each of these theories is applicable have been discussed. Different kinds of dissolution experiments were designed to produce the conditions under which each theory would apply. The theoretical and experimental procedures involved in these studies provide a unique method for distinguishing mechanisms and should be useful in future studies, *e.g.*, in studies of the effects of agitation on mechanisms of interphase transport.

As PART of the authors' program on drug release rates it was decided to conduct experiments on the influence of micelle-drug solubilization on the dissolution rate behavior. There were two reasons for carrying out these studies. First, there has been relatively little work reported in the literature on the effects of solubilization by colloids upon the dissolution rate. Therefore, establishing a relationship between solubilization and dissolution rate appeared to be a worthwhile endeavor. Secondly, as will be seen, the different theories for dissolution rates based upon different hydrodynamic models predict significantly different rate relationships when a solubilizing agent is present. Experimental tests of such theories by other methods (1, 2) are extremely difficult, and, in the authors' opinion, past attempts have not led to convincing results. Thus meaningful information on the hydrodynamical aspects of the dissolution rate process might be obtained by the proposed method of study involving colloidal solubilizing agents.

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THEORETICAL

Diffusion Layer Theory—Recently (3) Higuchi discussed the one-dimensional diffusion layer model for the dissolution rate of a pure solid in a stirred medium containing a colloidal solubilizing agent. The model assumes that equilibrium exists between the solid and the solution at the solid-solution interface, and that therefore the rate is controlled by the diffusion of the free and solubilized solute across an effectively stagnant liquid diffusion layer of thickness, h. Equilibrium between the free and the solubilized solute is assumed at every point in the diffusion layer.

These assumptions lead to the following equation for this model:

$$G = \frac{1}{h}\left(D_1C_1 + \sum_i D_iC_i\right) \qquad \text{(Eq. 1)}$$

Here G is the initial dissolution rate per cm.^{2} for the solid in the medium containing the solubilizing agent, D_1 is the diffusion coefficient of the free molecule in solution, C_1 is the contribution to the total solubility by the free solute, D_1 is the diffusion coefficient of the solubilized species, i, and S_i is the contribution of species, i, to the total solubility. Equation 1 reduces to

$$G = \frac{1}{h}(D_1C_1 + D_MC_M) \qquad \text{(Eq. 2)}$$

where the solubilization involves only a single solubilized species.

The Danckwerts Theory—The eddy diffusion model proposed by Danckwerts (4) assumes that fresh elements of liquid continually replace the aged ones at the solid-liquid interface. While at the interface, the elements absorb solute according to nonsteady-state diffusion laws. Thus the rate of dissolution may be visualized as being a function of the surface renewal rate and the diffusion rate.

When a colloidal solubilizing agent is present, the Danckwerts model gives

$$G = s^{1/2}\sqrt{(D_1C_1 + D_MC_M)(C_1 + C_M)} \qquad \text{(Eq. 3)}$$

Here s is the surface renewal rate constant, which is a function of the agitation rate, the viscosity and density of the medium, and the dimensions of the system. The derivation of Eq. 3 assumes that equilibrium between the free drug and the solubilized drug exists everywhere, and that the ratio of the free to solubilized drug is constant at all drug concentrations for a given concentration of the solubilizing agent.[1] Olander (5) has given the derivation for Eq. 3 although he presented it for the general situation that can be characterized by any equilibrium of the type, reactant $\overset{K}{\rightleftarrows}$ product.

It can be seen that Eq. 3 differs from Eq. 2 in the dependence of G upon the diffusion coefficients. The former predicts a square root dependence upon the effective diffusion coefficient, while the latter depends upon the first power of the effective diffusion coefficient. The effective diffusion coefficient can be written as:

$$D_{eff} = \frac{D_1C_1 + D_MC_M}{C_1 + C_M} \qquad \text{(Eq. 4)}$$

The Rotating Disk Theory—Levich (6) has provided a convective diffusion theory for the rate of mass transport to or from the face of a rotating disk. The equations are based upon Cochran's (7) exact solution to the hydrodynamic problem. As a result this situation represents one of the few instances where a physically well-defined picture can be presented mathematically.

The appropriate rotating disk equation for the dissolution rate of a solid in a medium containing a solubilizing agent is

$$G = 0.62(D_1C_1 + D_MC_M)^{2/3}\nu^{-1/6}\omega^{1/2}(C_1 + C_M)^{1/3} \qquad \text{(Eq. 5)}$$

where ν and ω are the viscosity of the medium and the angular velocity of the rotating disk, respectively. It is assumed, as was done in Eqs. 2 and 3, that equilibrium exists between the free and the solubilized drug and that the ratio of the two species is constant for all drug concentrations. Equation 5 differs from Eqs. 2 and 3 in that a two-thirds power dependence upon the effective diffusion coefficient is predicted.

The Noyes-Whitney Theory—This empirical theory simply predicts that the dissolution rate would be proportional to the total solubility. As the differences between the free drug and the solubilized drug diffusion coefficients are ignored, these parameters do not enter into this theory.

GENERAL CONSIDERATIONS IN THE DESIGN OF EXPERIMENTS

As mentioned earlier the object of these studies was twofold: first, to establish the role of colloid solubilization in dissolution rate processes and, secondly, to study the various theories that differ primarily in the assumptions regarding the interaction between hydrodynamics and molecular diffusion. In order to achieve these goals it was necessary to select a system that would provide a sufficiently large solubility increase and a sufficiently small D_M while not increasing the solvent viscosity and density appreciably with increasing solubilizing agent concentration. As will be seen, the system, benzocaine (ethyl *p*-aminobenzoate) in aqueous polysorbate 80,[2] generally satisfied these requirements and was therefore selected for this work.

Several hydrodynamic situations were selected. A tablet mounted in a beaker with a propeller stirrer, a rotating tablet in a disk mount, and a tablet mounted with no agitation were the three selections employed in the present study.

In addition to the dissolution rate experiments additional independent data were necessary for examining Eqs. 2, 3, and 5. Thus suitable solubility, diffusion coefficient, viscosity, and density experiments were considered and carried out.

EXPERIMENTAL

Dissolution Rates—Dissolution rates were carried out in both a propeller-driven stirrer apparatus and a rotating disk apparatus.

[1] Other experiments indicate that this assumption is approximately valid. In order to vigorously account for any deviations due to nonconstancy, more complex equations must be used, but should not otherwise affect our present interpretation.

[2] Marketed as Tween 80 by Atlas Chemical Industries, Wilmington, Delaware.

Propeller-Driven Stirrer Apparatus—The drug powder (<70 mesh) was compressed into a tablet in a 9.5-mm. ($^3/_8$-in.) die at 2,400 lb. using a Carver press[3] so that the tablet surface was flush with the die surface. The back of the die was then sealed with a cork stopper. The die was mounted directly in a Plexiglas holder in a water-jacketed beaker containing 400 ml. of solvent at 30°. Stirring was achieved by a Teflon-coated stirrer attached to a Hurst synchronous motor[4] mounted on the beaker cover. The stirrer was positioned so that the blade in its closest proximity to the tablet surface was 6 mm. away. The Plexiglas sample holder was also mounted on the cover so that (*a*) all components could be simultaneously introduced into the solvent as an entire unit, and (*b*) the hydrodynamics could be reproduced and maintained constant. Samples were withdrawn at known time intervals and spectrophotometrically assayed on the Perkin-Elmer Hitachi spectrophotometer at 286 mμ. These studies were conducted under stirring speeds of 50 r.p.m. and 150 r.p.m.

Rotating Disk Apparatus—The dissolution studies with the rotating disk were carried out by using an aluminum assembly similar to the one previously reported by Wood *et al.* (8). The powder was compressed in a 1.1-cm. ($^7/_{64}$-in.) die using a Carver press in the same manner as described before. The apparatus was attached to a Bodine motor[5] and started before immersion into the solvent. A 3-L. beaker, containing 950 ml. of solvent was immersed in a water bath maintained at 30°. The rotating disk and the Bodine motor were mounted on a beaker cover as before.

The diameter of the rotating disk was 4.5 cm. and that of the beaker was 15.5 cm.; the apparatus was maintained 5 cm. above the bottom of the beaker. The dissolution runs were conducted over a period of 30 min. at 60 and 300 r.p.m.

For the runs at 0 r.p.m. a different method was employed. The tablet was compressed in the die and the apparatus immersed in the solvent for a known period of time. Sampling was accomplished by removing the apparatus entirely from the solvent, stirring the solution, and removing a known volume for assay. The surface of the tablet was lightly dabbed with tissue to remove adhering solvent and the rest of the apparatus was also quickly dried. The entire apparatus was then immersed in fresh solvent with as little agitation as possible and timing started from zero. Essentially, each time the apparatus was immersed, the tablet was considered to be a new one. The release rate as a function of time was obtained by successively immersing the tablet for proportionally longer periods of time. The validity of this technique was proven by the reproducibility of the dissolution rates for the same solvent system using different tablets with different immersion times, showing that the release rate was independent of the past history of the tablet.

Diffusion Coefficient[6]—The method employed to determine the diffusion coefficients is essentially similar to the one reported earlier (9). The diffusion cell was modified by using a Gelman Versapor[7] filter in place of the porous sintered-glass disk. Also, the apparatus was not water-jacketed so that the two halves could be separated and the filter mounted between them. One Teflon gasket was placed on either side of the filter and the joints were clamped together. A step, 0.6 mm. deep, was made in one of the Teflon gaskets so that the filter could be fitted into it. Once the apparatus was assembled, this procedure insured that leakage from the filter was completely prevented. The filter had a diameter of 37 mm., pore size of 0.9 μ, and a thickness of 0.635 mm.

The filter was initially soaked in a 50:50 ethanol–distilled water solution for 1 day and then in distilled water for 2 days, to remove all soluble components present. Diffusion experiments were then carried out by a similar procedure to that described in *Ref.* 9. Since the diffusion cell was not water-jacketed, it was immersed in a water bath maintained at 30°. Into one compartment of the diffusion cell the aqueous solution of benzocaine in polysorbate 80 was added and the rate of diffusion into the other compartment containing the same polysorbate 80 concentration was determined.

The Versapor filter is made of glass fibers reinforced with epoxy, and its inherent strength enabled it to be used repeatedly without any change in surface area (not true of several other filters tried). In order to check possible changes that might occur in the filter, a benzoic acid standard was run between every two diffusion coefficient determinations.

Other Parameters—Solubility measurements were made as reported earlier (9). The viscosities of all solutions used in this study were measured at 30° using the Ostwald viscometer. The densities of these solutions were measured using a pycnometer.

RESULTS

Dissolution rates of benzocaine were determined in water and five concentrations of polysorbate 80 using both the propeller-driven stirrer and the rotating disk methods. The dissolution rate data obtained from the propeller-driven stirrer apparatus at 50 r.p.m. and 150 r.p.m. and that obtained from the rotating disk apparatus at 60 r.p.m. and 300 r.p.m. were highly reproducible, as can be seen by a typical set of data obtained at 150 r.p.m., shown in Fig. 1. These dissolution rates are tabulated in Column 3 of Table I. Figure 2, illustrating the dissolution rates obtained without stirring, shows, as expected, a larger experimental fluctuation between the data points of each curve. The resulting slopes, however, were in good agreement with theory. The rotating disk dissolution rates are tabulated in Table II.

The data from the diffusion rate experiments are plotted in Fig. 3. It should be pointed out here that each diffusion experiment had a positive intercept (since sampling was started only after steady-state had been reached) which has been subtracted in order to pass all lines through the origin, permitting better comparison. This procedure does not alter the slope of the line, and only the desired steady-state slope is needed in the calculations (9). These diffusion coefficients, along with the respective solubilities and relative viscosities, are presented in Table III.

[3] Carver Laboratory Press, Model B, Fred S. Carver, Inc., Summit, New Jersey.
[4] Model CA, Hurst Mfg. Corp., Princeton, Indiana.
[5] Type KYC-23RB, Bodine Electric Co., Chicago, Illinois.
[6] In diffusion coefficient determination experiments of this type, there is some uncertainty arising from the assumption that there is an effective diffusion layer adjacent to the membrane. Thus it is assumed that through this apparent stagnant film only molecular diffusion is important. It is estimated from calculations that the effect of some corrective transport should be small compared to the uncertainty in the overall experiment.
[7] Gelman Instrument Co., Ann Arbor, Michigan.

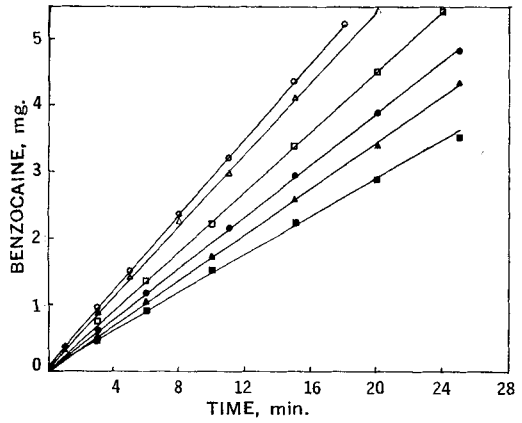

Fig. 1—Dissolution data for benzocaine in different concentrations of polysorbate 80 using the propeller-driven stirrer apparatus at a stirring speed of 150 r.p.m. Key: Polysorbate concn.—○, 6%; △, 4%; □, 2%; ●, 1%; ▲, 0.5%; ■, 0%.

Figure 4 illustrates the solubilization curve for benzocaine in polysorbate 80 solutions. The linearity obtained by plotting the amount solubilized against the concentration of polysorbate 80 suggests that the apparent individual micellar participation remains relatively constant over the entire range of surfactant concentrations.

Analysis of Data Obtained with Propeller-Driven Stirrer Apparatus—By using the definition for the effective diffusion coefficient, as given by Eq. 4, Eq. 2 can now be rewritten as

$$G = \frac{1}{h} D_{eff} C_T \qquad \text{(Eq. 6)}$$

where C_T is the total solubility. Similarly, Eq. 3 may be expressed as:

$$G = s^{1/2} D_{eff}^{1/2} C_T \qquad \text{(Eq. 7)}$$

The independently determined parameters listed in Table III can now be used to calculate the dissolution rates predicted by Eqs. 6 and 7 to test the diffusion layer and Danckwerts models, respectively. In order to eliminate the constants present in the two equations, the data were compared to the theories by taking the ratio of the dissolution rate in the surfactant solution to that in water.

Consequent to the above discussion, the final equation used to test the diffusion layer model is:

$$\frac{G'}{G_{H_2O}} = \frac{D_{eff} C_T}{D_1 C_1} \qquad \text{(Eq. 8)}$$

Similarly, for the Danckwerts model:

TABLE I—DISSOLUTION RATES (mg./min./cm.²) FOR THE BENZOCAINE–POLYSORBATE 80 SYSTEM USING THE PROPELLER-DRIVEN STIRRER APPARATUS

Polysorbate 80, % w/v	Stirrer Speed, r.p.m. 50	150
0	0.145	0.199
0.5	0.163	0.236
1.0	0.180	0.270
2.0	0.211	0.306
4.0	0.254	0.379
6.0	0.278	0.402

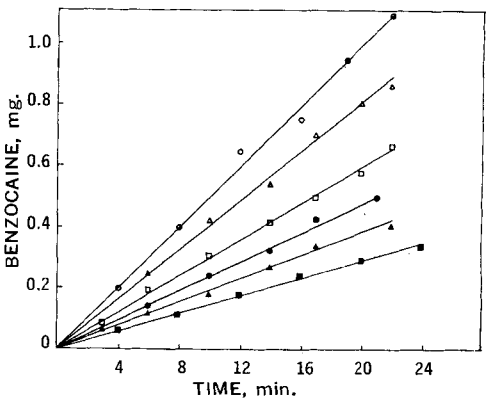

Fig. 2—Dissolution data for benzocaine in different concentrations of polysorbate 80 under nonstirring conditions. Key: polysorbate concn.—○, 6%; △, 4%; □, 2%; ●, 1%; ▲, 0.5%; ■, 0%.

TABLE II—DISSOLUTION RATES (mg./min./cm.²) FOR THE BENZOCAINE–POLYSORBATE 80 SYSTEM USING THE ROTATING DISK APPARATUS

Polysorbate 80, % w/v	Rotation Speed, r.p.m. 0	60	300	300/60
0	0.0151	0.105	0.223	2.12
0.5	0.0201	0.125	0.272	2.18
1.0	0.0242	0.145	0.312	2.14
2.0	0.0299	0.169	0.362	2.14
4.0	0.0415	0.199	0.415	2.08
6.0	0.0495	0.219	0.465	2.13

$$\frac{G'}{G_{H_2O}} = \left(\frac{D_{eff}}{D_1}\right)^{1/2} \frac{C_T}{C_1} \qquad \text{(Eq. 9)}$$

Here G' is the dissolution rate in the surfactant solution.

The theoretical ratio of rates predicted by Eqs. 8 and 9 have been drawn as smooth curves in Fig. 5. The graphical points illustrate the experimental ratio at both 50 r.p.m. and 150 r.p.m., as obtained from Table I. It can be readily seen that the diffusion layer theory gives a much closer fit than the Danckwerts model. Further examination of Fig. 5 reveals that the fit between the experimental data and the diffusion layer prediction is extremely good

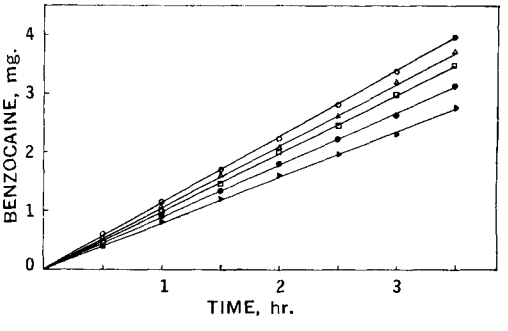

Fig. 3—Diffusion data for benzocaine in different concentrations of polysorbate 80. Key: Polysorbate concn.—○, 4%, 6%; △, 2%; □, 1%; ●, 0.5%; ▲, 0%.

TABLE III—PHYSICAL CONSTANTS DETERMINED FOR THE BENZOCAINE–POLYSORBATE 80 SYSTEM

Polysorbate 80, % w/v	C_T, Gm./ml. × 10^2	ν_{rel} Cps.	D ± σ[a] cm.²/sec. × 10^6
0	0.120	1.00	9.86 ± 0.19
0.5	0.184	1.04	7.61 ± 0.46
1.0	0.247	1.04	6.28 ± 0.33
2.0	0.371	1.06	4.53 ± 0.19
4.0	0.580	1.20	3.15 ± 0.39
6.0	0.810	1.35	2.31 ± 0.20

[a] The standard deviation was estimated to be 0.30, determined by considering all 48 experimental values.

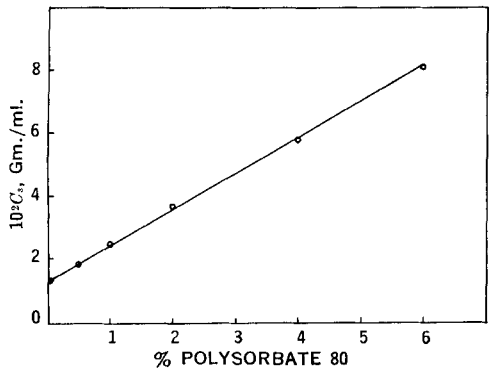

Fig. 4—Solubilization data for benzocaine in different concentrations of polysorbate 80.

at the lower concentrations of polysorbate 80. It was felt that the deviations of the data from the theory at the higher concentrations of polysorbate 80 may be due to some nonlaminar hydrodynamic condition near the tablet surface. In order to test this, a Plexiglas plate was attached to the front of the tablet surface at a distance of about 2 mm. This would ensure laminar solvent flow past the tablet surface. However, the dissolution rate ratios under these conditions were not significantly changed from those without the plate

Analysis of Data Obtained with No Agitation—In Fig. 6, a comparison of the theoretical curves has been made with the experimental dissolution rate data obtained by the rotating disk assembly un-

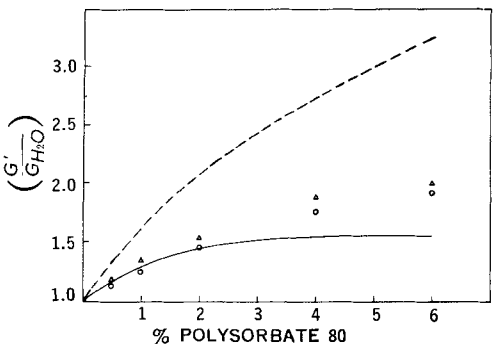

Fig. 5—Comparison of the theoretical ratio of dissolution rates as predicted by Eqs. 8 and 9 (smooth curves) and the experimental ratios obtained from the propeller-driven stirrer apparatus. Key: 0, 50 r.p.m.; △, 150 r.p.m.; – – –, Danckwerts model; —, diffusion layer model.

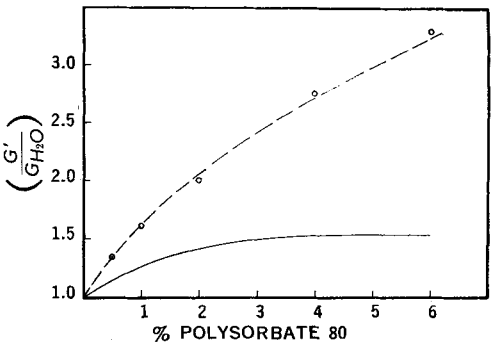

Fig. 6—Comparison of the theoretical ratio of dissolution rates as predicted by Eqs. 8 and 9 (smooth curves) and the experimental ratio obtained under nonstirring conditions. Key: – – –, Danckwerts model; ——, diffusion layer model.

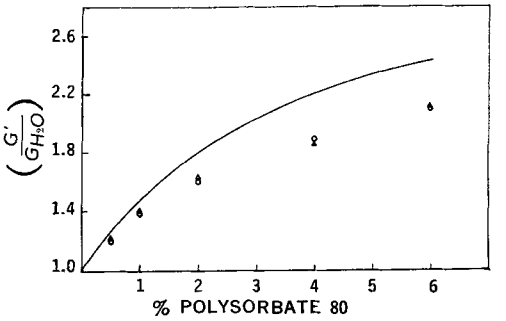

Fig. 7—Comparison of the theoretical ratio of dissolution rates as predicted by Eq. 10 (smooth curve) and the experimental ratios obtained from the rotating disk apparatus. Key: 0, 60 r.p.m.; △, 300 r.p.m.

der nonstirring conditions (see Column 2 of Table II). Here it is evident that the experimental data no longer fit the diffusion layer model but show excellent agreement with the Danckwerts model. It is of interest to point out that Gibaldi *et al.* (10) in their studies of the dissolution rates of benzoic acid in polyoxyethylene ether[8] solution have shown that under no forced convection conditions their data fit the Danckwerts predictions more closely than under stirring conditions.

Analysis of the Rotating Disk Data—Following the same general procedure as before, the fit of the rotating disk theory with the experimental dissolution data can be made by taking ratios of the dissolution rates. Then, under identical conditions of agitation, Eq. 5 becomes

$$\frac{G'}{G_{H_2O}} = \left(\frac{D_{eff}}{D_{H_2O}}\right)^{2/3} \frac{C_T}{C_1} \frac{1}{\nu_{rel}^{1/6}} \qquad \text{(Eq. 10)}$$

The theoretically predicted ratios of rates from Eq. 10 have been drawn as a smooth curve in Fig. 7. While it can be seen that the data are in approximate agreement with theory, the deviations observed may be significant.

DISCUSSION OF THE RESULTS

A further examination of the data with the theories can be made in the following manner. Since the

[8] Marketed as Brij, Atlas Chemical Industries, Wilmington, Del.

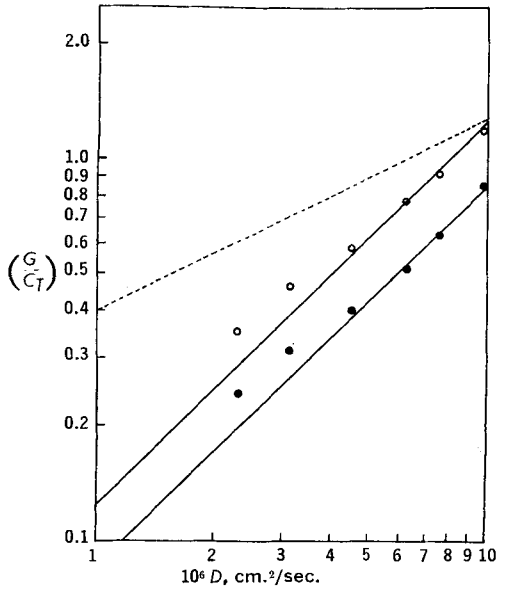

Fig. 8—Comparison of the theoretical slopes of 1.0 as predicted by Eq. 6 and the theoretical slope of 0.5 as predicted by Eq. 7 with experimental data. Key: - - -, 0.5; —, 1.0; ○, 150 r.p.m.; ●, 50 r.p.m.

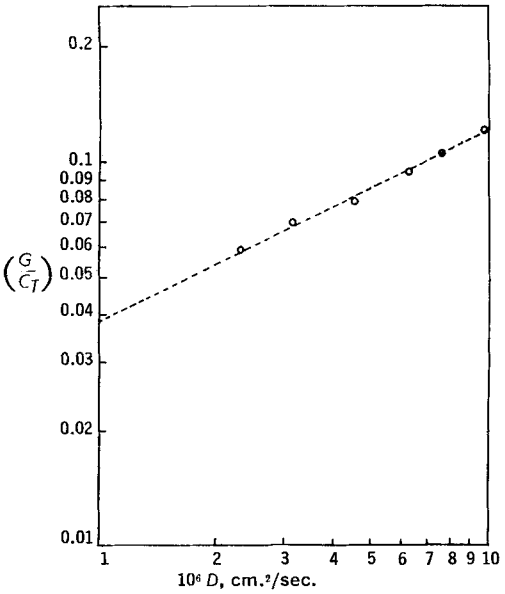

Fig. 9—Comparison of the theoretical slope of 0.5, 0 r.p.m., as predicted by Eq. 7 with experimental data.

main point of difference between these theories is in the exponent of the diffusion coefficient, a more stringent test can be made by plotting log (G/C_T) against log D_{eff}. By this means, the slope of the line in each case would be equal to the critical exponent, and would be a direct indication of the validity of the theory.

In Fig. 8, a theoretical line of slope = 0.5 (as predicted by the Danckwerts theory), and two theoretical lines of slope = 1.0 (as predicted by the diffusion layer model) have been drawn. The experimental data points for surfactant concentrations up to 2% (from Tables I and III) appear to fit a slope of one, which is in good agreement with the diffusion layer theory. The 4.0 and 6.0% polysorbate 80 points deviate from theory. Further studies are needed before an unambiguous reason for the deviations can be presented. However, it can be seen from Table III that the viscosities of the polysorbate 80 solutions begin to increase appreciably at 4.0%. As it has been assumed that viscosity changes are unimportant in comparing Eqs. 8 and 9 with data, the deviations of the 4.0 and 6.0% data from the diffusion layer theory may reside here.

Despite the deviations exhibited by the 4.0 and 6.0% polysorbate 80 data, the plot clearly shows the diffusion layer model best describing the situation with the propeller-driven stirrer apparatus. A least squares analysis was done on the data for both sets of experimental points. For the 50 r.p.m. data, by considering only the data up to 2.0% polysorbate 80, the slope of the line was calculated to be 0.965, whereas for the 150 r.p.m. data, the corresponding slope was 0.890. However, by considering all the data (up to 6.0% polysorbate 80), the slopes were 0.838 and 0.811, respectively.

A similar plot (Fig. 9) for the nonstirring dissolution rate experiment (from Tables II and III) shows that the experimental data give a slope of 0.5. This shows that the Danckwerts predicted dependence on the square root of the diffusion coefficient is applicable under conditions of no agitation.

Finally, a plot of log $G_\nu^{1/6}/C_T$ against log D_{eff} can be made for a test of the rotating disk theory (from Tables II and III). Figure 10 shows that the data for the 60 r.p.m. and 300 r.p.m. are in fair agreement with the predicted slope of 0.667, although somewhat higher—0.722 and 0.736, respectively. More work is needed to establish whether or not this

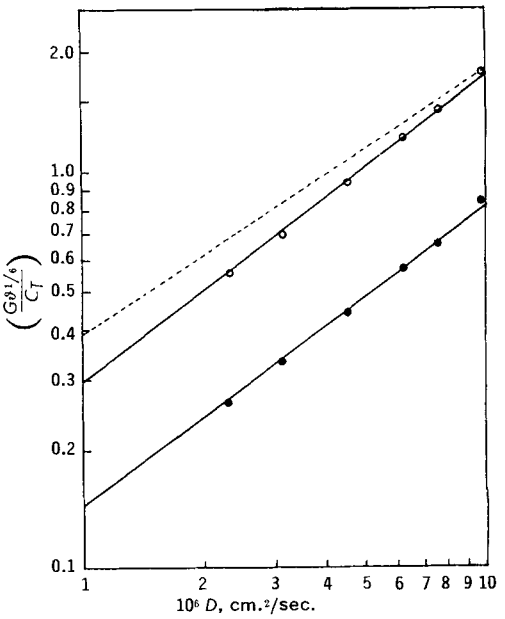

Fig. 10—Comparison of the theoretical slope of 0.667 as predicted by Eq. 5 with experimental data: Key: - - -, slope = 0.667; —○, slope = 0.736, 300 r.p.m.; —●, slope = 0.722, 60 r.p.m.

difference is really a breakdown of the theory. It is noteworthy that the stirring rate dependence obtained with the rotating disk apparatus (Column 5 of Table II) is very close to the theoretical square root prediction of 2.23.

PHARMACEUTICAL SIGNIFICANCE

These studies provide a firm quantitative basis for studying and establishing the particular mechanism of mass transport which is controlling a given dissolution experiment. The need for explicitly describing the hydrodynamics, under which such dissolution takes place also has been shown to be of prime importance. Although a limited number of examples were utilized, it is apparant that large differences in mechanisms may exist among different dissolution processes.

In view of the widespread interest in the use of dissolution studies as a basis for comparison of release profiles of different dosage forms and the resultant need for meaningful comparison of dissolution studies of independent workers, it becomes increasingly apparent that experimental conditions must be ei her standardized or taken into consideration. In addition the results of this study clearly indicate that the use of *in vitro* dissolution rates as a basis of drug availability must consider and account for the differences in the environmental conditions which exist in the respective *in vitro* and *in vivo* systems. As an example, it is very possible that an *in vitro* test in which the diffusion layer model may be operative could be used to draw conclusions regarding an *in vivo* system in which the Danckwerts model may be functioning. Such a possible system may be drug absorption when the rate of diffusion in the intestinal lumen is rate controlling.

These results also demonstrated that the effective diffusion coefficient can be radically altered with changes in components of the transport medium. Depending upon the kind and the intensity of the agitation, the dependence upon the effective diffusion coefficient may range from a one-half power to a first power. The conception of increased apparent solubility leading to an increased dissolution rate can be thus seen to be faulty if overextended. As a matter of fact, recent dissolution studies by Parrott (11) showed that dissolution rates did not increase linearly with an increased solubility and may be explained on the basis of a reduced effective diffusion coefficient.

Various biopharmaceutical transport systems which have been studied involve species of widely differing sizes, *viz.* molecules, micelles, colloidal particles, emulsion droplets, *etc.* In such situations the effective diffusion coefficient may range over several orders of magnitude and the importance of understanding the predominant transport mechanism becomes apparent.

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Keyphrases

Dissolution rates—solid drugs
Micellar solubilization effect—dissolution rate
Stirrer, propeller-driven—dissolution apparatus
Rotating disk—dissolution apparatus
Diffusion coefficients