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Hydrodynamic and Diffusional Considerations in Assessing the Effects of Surface Active Agents on the Dissolution Rate of Drugs[1]

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The influence of a non-ionic surface active agent on the dissolution rate of benzoic and salicylic acids has been investigated and dissolution mechanisms have been examined as a function of the hydrodynamics of the system. Clearly, the dissolution rate of a solid in a micellar solution is not proportional to the solubility of the compound in the dissolution medium. Evaluation of dissolution rate data and theories has led to the conclusion that, depending upon hydrodynamic conditions, the dissolution rate of a solid will be proportional to the effective diffusion coefficient raised to a power between 0.5 and 1.0.

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.[3–5] However, only a limited amount of information is available on the influence of solubilization on dissolution rate.

Bates, Gibaldi and Kanig[6] reported substantial increases in the dissolution rates of griseofulvin and hexestrol in micellar solutions of bile salts. Bates, *et al.*[7] have also shown that physiologic concentrations of lysolecithin, a biologic surfactant, produce an increase in the solubility and dissolution rate of hexestrol, dienestrol and griseofulvin. In each case, because of the extremely low solubility of the drugs, dissolution rate was followed in a concentration region which was above the saturation solubility in water.

During the course of the present study, Parrott and Sharma[8] reported that surfactants increase the dissolution rate of benzoic acid. More recently, Elworthy and Lipscomb[9] studied the dissolution rate of griseofulvin in water and aqueous solutions of four non-ionic surfactants and found that the surfactants significantly increase the dissolution rate of the drug.

Higuchi[10] has 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.[11] The latter suggests a direct proportionality

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3) O. Blanpin, *Prod. Pharm.*, **13**, 425 (1958).
4) M.E.L. McBain and E. Hutchinson, eds., "Solubilization and Related Phenomena," Academic Press Inc., New York, N.Y. 1955.
5) B.A. Mulley, in "Advances in Pharmaceutical Sciences," Vol. I, H.S. Bean, A.H. Beckett., and J.E. Carless, eds., Academic Press Inc., New York, N.Y., 1964, p. 86.
6) T.R. Bates, M. Gibaldi, and J.L. Kanig, *Nature*, **210**, 1331 (1966).
7) T.R. Bates, S.L. Lin, and M. Gibaldi, *J. Pharm. Sci.*, **56**, 1492 (1967).
8) E.L. Parrott and V.K. Sharma, *J. Pharm. Sci.*, **56**, 1341 (1967).
9) P.H. Elworthy and J.L. Lipscomb, *J. Pharm. Pharmac.*, **20**, 923 (1968).
10) W.I. Higuchi, *J. Pharm. Sci.*, **53**, 532 (1964).
11) A.A. Noyes and W.R. Whitney, *J. Am. Chem. Soc.*, **19**, 930 (1897).

between dissolution rate and total solubility. The Higuchi equations[10] further predict that substantial effects on dissolution rate will be observed only when the drug concentration in solution approaches or exceeds saturation solubility. The large effects on dissolution rate predicted above saturation are evident in the works of Bates, *et al.*[6,7] and Wurster and Polli.[12] Experimental evidence confirming the theoretical predictions as to the effect of interacting colloids on initial dissolution rate was presented in a recent review.[13] The dissolution rate of benzocaine in various concentrations of polysorbate 80 was found to be in agreement with the diffusional model proposed by Higuchi[10] rather than the Noyes–Whitney equation.[11]

Higuchi[13] has further suggested that the magnitude of effects of interacting colloids on dissolution rates could be used for the differentiation of dissolution mechanisms, *i.e.* the dependence of dissolution rate on the diffusion coefficients of the diffusing species. Among the recognized dissolution mechanisms which are diffusion controlled are the following.

Diffusion Layer Theory

Higuchi[13] has disscussed the one-dimensional diffusion layer model developed by Brunner,[14] and applied it to the dissolution of a pure solid in a stirrred medium containing a colloidal solubilizing agent. The dissolution model assumes that an equilibrium exists between the solid and the solution at the solid–solution interface and that the rate is controlled by the diffusion of the free and solubilized solute across a stagnant liquid diffusion layer of thickness, h. Equilibrium between the free and solubilized solute is assumed at every point in the diffusion layer as well as in the bulk.

These assumptions lead to the following equation for the diffusion layer model in a system of colloidal solubilizer under constant surface area and sink (*i.e.*, the concentration of drug in solution does not exceed 10% of the saturation solubility) conditions:

$$\mathrm{dr}=(DC_S/h)+(D_MC_M/h) \qquad \text{(Eq. 1)}$$

where dr is the dissolution rate per unit area of dissolving solid, D_M is the diffusion coefficient of the micelle solubilized drug and C_M is the increase in solubility of the drug due to the presence of the surfactant. It is assumed that the diffusion layer thickness, h, is identical for each species.

Higuchi[13] has also discussed the concept of an effective diffusion coefficient (D_{eff}) which is particularly useful in systems with more than one diffusing species. In the present system, D_{eff} is given by

$$D_{eff}=\frac{DC_S+D_MC_M}{C_T} \qquad \text{(Eq. 2)}$$

where $C_T=C_S+C_M$ Introducing Eq. 2 into Eq. 1 yields

$$\mathrm{dr}=D_{eff}\cdot C_T/h \qquad \text{(Eq. 3)}$$

See Attached Rotating Disk Theory

Levich[15] has proposed a convective diffusion theory for the rate of mass transport to or from the face of a rotating disk. The equations derived by Levich are based upon the exact solution to the hydrodynamic problem as derived by Cochran.[16]

The equation for the dissolution rate of a solid in a medium containing a solubilizing agent according to the rotating disk theory is:[17]

12) D.E. Wurster and G.P. Polli, *J. Pharm. Sci.*, **50**, 403 (1961).
13) W.I. Higuchi, *J. Pharm. Sci.*, **56**, 315 (1967).
14) E. Brunner, *Z. Physik. Chem.*, **47**, 56 (1904).
15) V.G. Levich, "Physicochemical Hydrodynamics," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1962.
16) W.G. Cochran, *Proc. Camb. Phil. Soc.*, **30**, 365 (1934).
17) P. Singh, S.J. Desai, D.R. Flanagan, A.P. Simonelli, and W.I. Higuchi, *J. Pharm. Sci.*, **57**, 959 (1968).

$$dr = 0.621\gamma^{-1/6}\omega^{1/2}(D_{eff})^{2/3}C_T \quad \text{(Eq. 6)}$$

where γ and ω are the viscosity of the medium and the angular velocity of the rotating disk, respectively.

Relationship of Various Models

Inspection of the various dissolution rate models indicates that a plot of the cumulative amount of drug in solution *versus* time for the dissolution of the drug in the presence or absence of colloidal solubilizer under sink conditions yields a linear relation regardless of hydrodynamics. What is clearly different in the various models is the dependence of the dissolution rate on the diffusion coefficients of the species involved.

Since the micellar species of the drug would have a much higher molecular weight than the free drug, and therefore a much lower diffusion coefficient, the greater the dependence of dissolution rate on the diffusion coefficient the smaller will be the effect of the colloidal solubilizer on dissolution rate. Hence, the effect of the colloidal solubilizer will depend on the mechanism of dissolution in the experimental system, which in turn may be related to the hydrodynamics of the system.

Since the effects of the colloidal solubilizer may depend on the hydrodynamics of the system, it was desirable to examine a number of *in vitro* dissolution methods and attempt to define the dissolution mechanism (s) operative in each of these *in vitro* dissolution rate tests.

Experimental

Materials——Baker analyzed reagent benzoic acid and Fisher certified reagent grade salicylic acid were used as the dissolving solids. Polyoxyethylene (23) lauryl ether (POE (23) lauryl ether) served as the solubilizing agent.

Solubility Determinations——The solubility of benzoic acid was determined in a series of aqueous solutions containing various concentrations of POE (23) lauryl ether. The solubility of salicylic acid was determined in 0.1N HCl and various concentrations of POE (23) lauryl ether dissolved in 0.1N HCl. In each case, an amount of benzoic or salicylic 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 $37 \pm 0.25°$ for 3—5 days. Equilibrium was determined by repetitive sampling. Five per cent POE (23) lauryl ether did not change the pH of a saturated solution of benzoic acid in distilled water nor alter the pH of a saturated solution of salicylic acid in 0.1N HCl.

Determination of Dissolution Rates——Dissolution rates of benzoic or salicylic acid from non-disintegrating tablets, prepared by compression of pure drug in a Carver model B hydraulic press at 10000 p.s.i. were determined at 37° using the following methods

a) Rotating Disk Method[19]: Benzoic acid tablets were mounted in a plexiglass holder with the aid of paraffin as previously described.[19] The apparatus was attached to a Servodyne constant torque unit. A 500 ml round bottom 3-neck flask, containing 300 ml of distilled water or aqueous solutions of POE (23) lauryl ether was maintained at $37 \pm 0.1°$ by immersion in a constant temperature water bath. The plexiglass holder and tablet was rotated at 100 rpm and placed in the dissolution fluid. One ml samples were withdrawn at appropriate intervals and retained for analysis.

The pH of the pure solvent and aqueous solutions of POE (23) lauryl ether ranged between pH 5.2 and pH 5.4. Measurement of the pH at the conclusion of each dissolution rate determination revealed no significant change in the pH of the dissolution medium.

b) Static Disk Method[20]: Benzoic acid tablets were affixed and the plexiglass assembly was placed in the solvent for known periods of time. Sampling was accomplished by removing the assembly from the dissolution medium, stirring the solution, and removing a known volume for assay. The tablet surface was lightly dabbed with tissue to remove adhering solvent and the rest of the assembly wiped dry. The assembly was then placed in the dissolution medium for the next time period. Initial studies showed that the total amount of benzoic acid dissolved by exposing the tablet to the dissolution medium, for example, for six five minute periods was identical to the amount dissolved when the tablet was exposed to the dissolution

19) G. Levy and B.A. Sahli, *J. Pharm. Sci.*, **51**, 58 (1962).
20) G. Levy, *J. Pharm. Sci.*, **52**, 1039 (1963).

medium for a continuous 30 minute period. This indicated that the surface of the tablet was not altered by repetitive drying procedures and that the dissolution rates determined by this method were an accurate indication of the dissolution rate over the entire time period studied.

c) Stirred Beaker Method[20]: Stirring was provided by a 3 inch Teflon blade and shaft attached to a stirring motor. The blade and shaft were inserted into the center neck of a 500 ml round bottom 3-neck flask. The stirring motor was controlled by a Servodyne constant torque unit which also served to provide a direct read-out of speed of rotation.

One hundred and fifty milliliters of either 0.1N HCl or various concentrations of POE (23) lauryl ether dissolved in 0.1N HCl was placed in the flask and permitted to equilibrate to 37°. The stirring blade was immersed in the dissolution medium to a constant depth and accurately centered by means of a guide. The stirrer was rotated at a speed of 50 rpm and three 1.0 g salicylic acid tablets were placed in the dissolution medium by dropping them through the side neck. The tablets rested on the bottom, on one face, and remained in this position throughout the experiment.

d) Static Beaker Method: This method involved the following procedure: Fifteen milliliters of either 0.1N HCl or varying concentrations of POE (23) lauryl ether in 0.1N HCl was equilibrated at 37° by placing the solution into 25 ml Erlenmeyer flasks in a constant temperature oven. After the solutions had come to thermal equilibrium, one non-disintegrating tablet (prepared as described previously) weighing 1.0 g was dropped into each flask. At specific time intervals, a flask was rapidly emptied of its fluid contents. An aliquot was immediately removed and retained for analysis. Dissolution rate determinations were run at least in duplicate and the individual rates were averaged.

Assay Procedures——Aliquot samples of the dissolution or solubilization medium were passed through a Millipore filter (0.45 μ pore size), when necessary, and appropriately diluted with 0.1N HCl for the determination of benzoic acid or with acidified methanol (1:100, 0.1N HCl–methanol) for the determination of salicylic acid. Benzoic acid concentration was determined spectrophotometrically at 230 mμ and salicylic acid at 302 mμ using a Beckman DB-G recording spectrophotometer. In each case, an appropriate concentration of surfactant was contained in the blank to avoid interference.

Calculation of the Micellar Diffusion Coefficient——The reported literature values for the diffusion coefficients of benzoic acid[21] and salicylic acid[20] are 12×10^{-6} cm^2/sec and 11.3×10^{-6} cm^2/sec, respectively. According to the Stokes–Einstein relationship the diffusion coefficient of a solute may be calculated by means of the following equation:[22]

$$D=\frac{RT}{6\pi\eta N}\cdot\sqrt[3]{\frac{4\pi N}{3M\bar{v}}} \qquad \text{(Eq. 7)}$$

where R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent, N is Avogadro's number, M is the molecular weight and $\bar{v}$ is the partial specific volume. As can be seen from equation 7, the Stokes–Einstein relationship predicts an inverse cube root relationship between the diffusion coefficient and molecular weight, *viz.* $D\propto(1/M^{1/3})$. The mean micellar diffusion coefficient for the POE (23) lauryl ether micelle was calculated from the following relationship:

$$\frac{D_{\text{drug}}}{D_{\text{micelle-drug}}}=\frac{(M)^{1/3}_{\text{micelle-drug}}}{(M)^{1/3}_{\text{drug}}} \qquad \text{(Eq. 8)}$$

Becher[23] has reported the anhydrous micellar molecular weight of POE (23) lauryl ether as approximately 46000 at 35°. Taking into account the water of hydration (4.69 moles water per ethylene oxygen) an apparent molecular weight of 113500 was calculated for the surfactant micelle. Assuming that incorporation of benzoic acid or salicylic acid into the micelle does not change the shape, size or hydration of the micellar species, a mean micellar diffusion coefficient (D_M) of 1.23×10^{-6} cm^2/sec may be calculated by means of equation 8.

Treatment of Data——To determine the dependence of dissolution rate under various hydrodynamic conditions on the diffusion coefficients, a generalized form of the dissolution rate equation was employed; *viz.*

$$\mathrm{dr}=(D_{\text{eff}})^{1/n}C_T\cdot K^* \qquad \text{(Eq. 9)}$$

where $1/n$ is the diffusion coefficient exponent and K^* refers to all other parameters such as viscosity, speed of rotation, etc. It is then possible to derive the following equation

21) W.I. Higuchi, N.A. Mir, and S.J. Desai, *J. Pharm. Sci.* **54**, 1405 (1965).
22) A.N. Martin, "Physical Pharmacy," Lea & Febiger, Philadelphia, Pa., 1960, p. 525.
23) P. Becher and H. Arai, *J. Colloid Interface Sci.*, **27**, 634 (1968).

$$\log(\mathrm{dr}) = \frac{1}{n}\log D_{\mathrm{eff}} + \log C_{\mathrm{T}} + \log K^{*} \qquad \text{(Eq. 10)}$$

Rearrangement of equation 10 yields

$$\log \frac{(\mathrm{dr})}{C_{\mathrm{T}}} = \frac{1}{n}\log D_{\mathrm{eff}} + \log K^{*} \qquad \text{(Eq. 11)}$$

Therefore, a plot of log $(\mathrm{dr})/C_{\mathrm{T}}$ *versus* log D_{eff} theoretically should give a straight line, with the slope of the line being equal to the exponent $(1/n)$ of the diffusion coefficient.[19]

Results

Figure 1 shows the saturation solubilities of benzoic acid and salicylic acid as a function of surfactant concentration. The results describe typical solubilization curves with a linear relation between solubility and POE (23) lauryl ether concentration above the critical micelle concentration (CMC). Solubilization studies at low surfactant concentration indicate a CMC of less than 0.1 g/100 ml. The linearity of the plots suggest that the micellar participation

Table I. Solubility of Benzoic and Salicylic Acids at Various Surfactant Concentrations at 37° and Effective Diffusion Coefficients Calculated from Solubility Data Using Eq. 2

% POE(23) lauryl ether	Benzoic acid solubility (mg/ml)[a]	D_{eff}-Benzoic acid data ($\mathrm{cm^2/sec} \times 10^6$)
0	5.00	12.0
1	6.84	9.10
2	8.95	7.25
3	10.97	6.14
4	13.25	5.29
5	15.44	4.72
% POE(23) lauryl ether	Salicylic acid solubility (mg/ml)[b]	D_{eff}-Salicylic acid ($\mathrm{cm^2/sec} \times 10^6$)
0	2.62	11.3
1	4.58	6.99
2	6.68	5.18
3	8.65	4.28
4	10.67	3.70
5	12.50	3.34

a) determined in distilled water mean of 2 or moredeterminations
b) determined in 0.1N HCl mean of 2 or more determinations

Table II. Dissolution Rates of Benzoic Acid at 37° determined by the Rotating Disk and Static Disk Methods[a]

% POE (23) lauryl ether	Dissolution rate[b] rotating disk, 100 rpm ($\mu\mathrm{g/min/cm^2}$)	Ratio	Dissolution rate[b] static disk ($\mu\mathrm{g/min/cm^2}$)	Ratio
0	633	1.00	131	1.00
1	728	1.15	161	1.23
2	784	1.24	181	1.38
3	869	1.37	201	1.53
4	957	1.51	220	1.68
5	975	1.54	236	1.80

a) The dissolution medium consisted of distilled water or distilled water with various concentrations of surfactant.
b) Mean values of 2 or more determinations.

to the solubilization process increases linearly with increasing surfactant concentration over the entire range of surfactant concentration studied. The mean solubilities of benzoic and salicylic acids as a function of surfactant concentration are listed in Table I. Also included in this table are the values of D_{eff} calculated from solubility data by means of equation 2.

Figure 2 represents a typical set of dissolution runs from the rotating disk at 100 rpm at varying concentrations of POE (23) lauryl ether. The average dissolution rates at various surfactant concentrations from the static disk method are shown in Fig. 3. All date are tabulated in Table II. The excellent linearity in the cumulative amount in solution *versus* time plots is evidence for the maintainance of sink conditions and constant surface area during the dissolution rate determination.

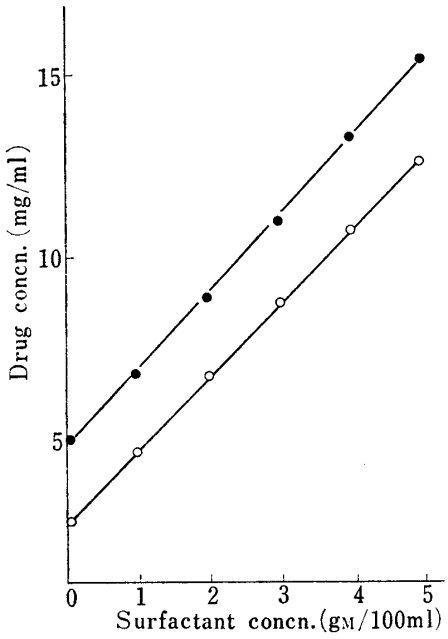

Fig. 1. Effect of POE(23) Lauryl Ether on the Solubility of Salicylic Acid (○) in 0.1N HCl and of Benzoic Acid (●) in Water, at 37°

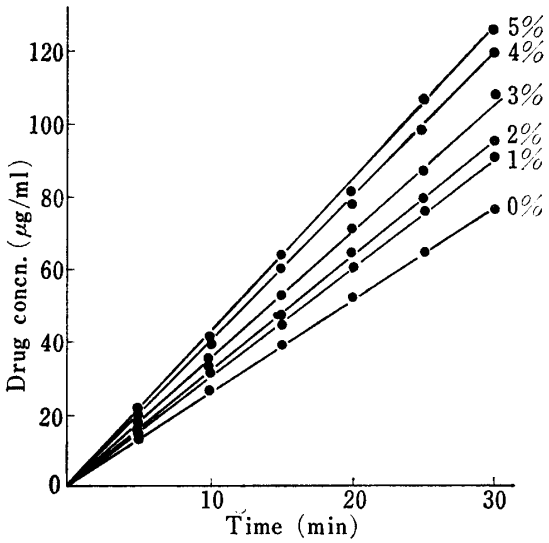

Fig. 2. Dissolution of Benzoic Acid in Water containing Various Concentrations (% w/v) of POE (23) Lauryl Ether at 37° using the Rotating Disk Method at 100 rpm

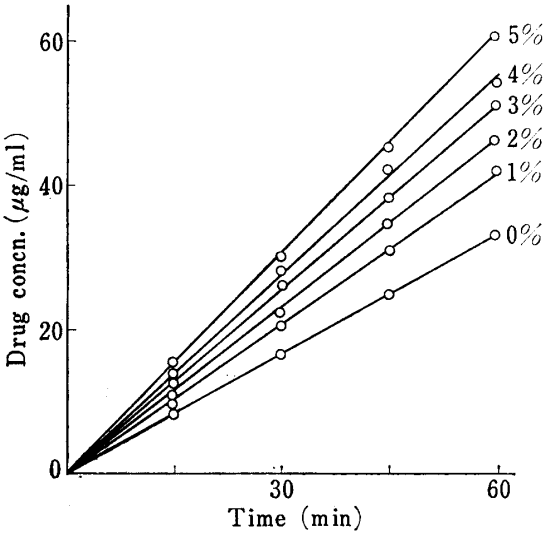

Fig. 3. Dissolution of Benzoic Acid in Water containing Various Concentrations (Per Cent w/v) of POE (23) Lauryl Ether at 37° using the Static Disk Method

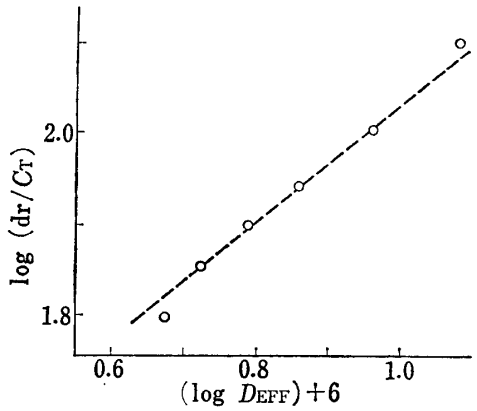

Fig. 4. log–log Plot of Dissolution Rate of Benzoic Acid in Surfactant Solutions using Rotating Disk Method (dr) Dirided by the Solubility of the Drug in the Dissolution Medium (C_T) *versus* calculated (D_{eff})
key : ·····, slope=0.667 according to the Levich equation

Plots of the amounts of salicylic acid dissolved *versus* time using both the stirred and static beaker methods also demonstrated excellent linearity providing that drug concentration did not exceed 10 per cent of solubility. In each case the slope of the linear portion of the curve yields the apparent zero order dissolution rate constant. These data are reported in Table III.

Table III. Rate Constants for Dissolution of Salicylic Acid at 37° Using the Stirred and Static Beaker Methods[a]

Stirred (beaker) method % POE (23) lauryl ether	k_0[b] (mg/min)	Ratio
0	4.5	1.00
1	5.41	1.20
2	6.55	1.46
3	7.50	1.67
4	8.53	1.90
5	8.91	1.98
Static beaker Method % POE(23) lauryl ether	**k_0[b] (mg/min)**	**ratio**
0	0.71	1.00
1	0.87	1.22
3	1.19	1.69
5	1.37	1.93

a) The dissolution medium consisted of 0.1N HCl or 0.1N HCl with various concentrations of surfactant.
b) Apparent zero order dissolution rate constant calculated from initial dissolution rate data, mean of 2 or more determinations.

Analysis of the Dissolution Data

Figure 4 is a plot of log (dr/C_T) *versus* log D_{eff} for the data obtained from the rotating disk experiments with benzoic acid. The dashed line represents a theoretical line with a slope equal to 0.667 as predicted by the Levich equation. A least squares analysis of the data points from 0 to 5% POE (23) lauryl ether concentration yields a slope of 0.732 which is in fairly good agreement with the theoretical slope. This finding confirms the work of Singh, *et al.*[19] who reported that the dissolution of benzocaine from a rotating disk into polysorbate 80 solutions could be closely approximated by the Levich equation.

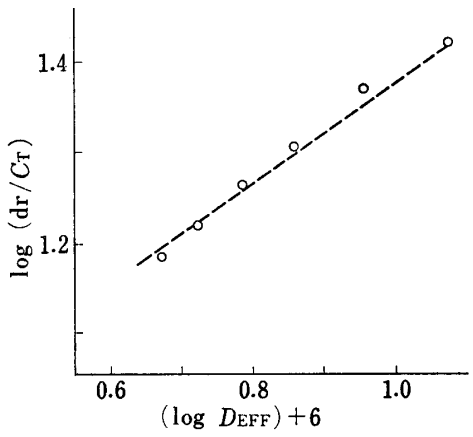

Fig. 5. Log–Log Plot of Dissolution Rate of Benzoic Acid in Surfactant Solutions using the Static Disk Method (dr) divided by the Solubility of the Drug in the Dissolution Medium (C_T) *versus* Calculated Values of the Effective Diffusion Coefficient (D_{eff})

key:····· , slope=0.5 according to the Danckwerts' equation

A similar plot of log (dr/C_T) *versus* log D_{eff} for the data obtained from the static disk experiments can be seen in Figure 5. A least squares fit of the data points yields a slope of 0.586. The results suggest that dissolution from a hanging disk under static conditions adheres to the kinetics predicted by the Dankwerts' model.

The data obtained by the beaker methods were also well described by log–log plots. The slopes of these plots were 0.697 and 0.725 for the stirred and static beaker methods respectively.

Discussion

The results obtained with the rotating disk method supports the thesis that the magnitude of effects of interacting colloids on dissolution rates may be used for the differentiation of dissolution mechanism. Hence, it was quite surprising to find a 0.5 power dependency of dissolution rate from a static disk on D_{eff}. As noted previously, this dependecny is predicted by the Danckwerts' model. However, this mechanism does not appear to be applicable to the hydrodynamic conditions imposed by the static disk method. While the Danckwerts' equation has heretofore been restricted to turbulent systems, it is based upon the existence of eddy diffusion and the possibility exists that this type of diffusion is predominant in the hanging disk method where no forced convection is introduced. Certainly, further investigation is needed to clarify the matter of mechanism.

The data obtained by the beaker methods yielded unexpected results since unlike the situation observed using the disk dissolution methods, where each type of stirring resulted in a different dependency on diffusion coefficient, the dependency on diffusion coefficient with the two beaker methods was apparently the same. Moreover, these data could not be fit to a reasonable theoretical equation. Although the slope of a log (dr/C_T) *versus* log D_{eff} plot for the data obtained with the beaker methods was in the order of 2/3, it is inappropriate to suggest that the data can be approximated by the Levich equation, since this equation was derived *strictly* for the dissolution of a solid from a rotating disk.

The possibility must be considered that the calculated salicylic acid POE (23) lauryl ether micellar diffusion coefficient is markedly different from the actual value in the experimental system. To test this possibility it was decided to study the dissolution rate of benzoic acid in surfactant solution using the stirred beaker method. It is assumed that the calculated benzoic acid–POE (23) lauryl ether micellar diffusion coefficient is in good agreement with the actual experimental value since 1) the observed dependency of dissolution rate on D_{eff} using the rotating disk method is in good agreement with the Levich equation and 2) the observed dependency of dissolution rate on D_{eff} using the static disk method is in excellent agreement with results of Singh, *et al.*[19] who used a benzocaine–polysorbate 80 system and were able to determine experimentally the appropriate diffusion coefficients. The average apparent zero-order dissolution rates of benzoic acid at various surfactant concentrations in 300 ml water at 37° and 50rpm using 1 g non-disintegrating tablets in the stirred beaker assembly are listed in Table IV. Also shown in the table are the experimental ratios of dissolution rate in surfactant solutions to that in pure solvent. Least squares analysis of a plot of log (dr/C_T) *versus* log D_{eff} for the data obtained from stirred beaker experiments with benzoic acid yields a slope of 0.691 which is in excellent agreement with the value of 0.697 calculated with the salicylic acid using the stirred beaker method. Hence, the present findings suggest that the influence

Table IV. Dissolution Rates of Benzoic Acid at 37° determined by the Stirred Beaker Method[a]

% POE (23) lauryl ether	k_0[b] (mg/min)	Ratio
0	2.41	1.00
1	2.89	1.20
2	3.16	1.31
3	3.41	1.42
4	3.67	1.52
5	3.99	1.65

a) The dissolution medium consisted of distilled water or distilled water with various concentrations of surfactant.
b) Apparent zero order rate constant. mean values of 2 determinations

of a colloidal solubilizer on the dissolution process under the hydrodynamic condition imposed by either the stirred or static beaker methods cannot be adequately predicted by any single dissolution model.

The lack of agreement of the data obtained by the beaker method in the present study with conventional dissolution rate models leads one to conclude that an alternate model is needed to explain the experimental results. One such model has been derived by Toor and Marchello[25] and represents a combination of the diffusion layer theory[14] and the surface renewal concept of Danckwerts.[16] Thier model known as the film–penetration model, suggests that under most hydrodynamic conditions mass transfer occurs by two simultaneous processes; one involving a stagnant film in which steady state molecular transfer is controlling and the other involving non–steady state molecular transfer into eddies existing in the surface region. According to the model derived by Toor and Marchello[25] and later by Huang and Kuo[26] at the extremes *i.e.* when surface renewal is very rapid or very slow and therefore, unimportant, the model reduces to the Danckwerts' model or the diffusion layer theory, respectively. When conditions are such that the rate of the renewal of the surface and the rate of diffusion of the dissolving species are comparable then the transfer characteristics are intermediate between the diffusion layer and Danckwerts' theory predictions.

The film–penetration model of Toor and Marchello[25] predicts a dependence of the dissolution rate on the diffusion coefficients which can be any value between 0.5 and 1.0. Therefore, depending upon the hydrodynamic conditions, the exponent of the diffusion coefficients will fall somewhere between 0.5 and 1.0.

A further explanation for the results obtained with the beaker methods is to consider that they are consistent with a special case of the diffusion layer theory. Singh, *et al.*[19] have studied the dissolution of benzocaine using methodology similar to the stirred beaker method with the exception that only one face of the tablet surface was exposed to the dissolution medium rather than exposing surfaces and edges as in the present study. They proposed that dissolution followed diffusion layer theory and found that the effective diffusion coefficient had an exponent dependence of 0.811 at 150 rpm comparing favorably to the theoretical value of unity. The discussion presented by Levich[17] also suggests that the diffusion layer theory should apply to the dissolution process in the stirred and static beaker methods provided that no edges are exposed. According to Levich[17] protrusions above the surface of a solid body as well as the corners or edges of that body will change the nature of the flow passed that surface very materially. While the surface may be exposed to laminar flow the existence of an edge will create turbulent flow in the immediate area. Hence, an intense agitation of the fluid occurs at the lateral surface of the tablet. Consequently, dissolution in this zone occurs more rapidly than dissolution at the face of the tablet. The net result is that the dependence of log dissolution rate on log of the effective diffusion coefficient will be less than unity but larger than 0.5, in agreement with experimental findings. From a kinetic point of view, the special case of the diffusion layer model in the presence of protrusions or edges on the surfaces of the dissolving solid is essentially identical to the more simplistic film penetration model.[25]

25) H.L. Toor and J.M. Marchello, *A.I. Ch. E.J.*, **4**, 97 (1958).
26) C.J. Huang and C.H. Kuo, *A.I. Ch. E.J.*, **9**, 161 (1963).