

Effect of Various Parameters upon Diffusion-Controlled Dissolution of Benzoic Acid

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Abstract □ Under stirred and sink conditions the dissolution of benzoic acid in aqueous solutions of polysorbate 80 is shown to occur in accord with the diffusion layer model. Since dissolution is diffusion controlled, the diffusion coefficients were measured by the method of quasisteady-state cell in micellar solutions with constant and uncontrolled viscosity. The experimental diffusion coefficient is decreased as the concentration of the surfactant is increased. The effective thickness of the diffusion layer was determined, and the micellar diffusion coefficient was calculated. The micellar diffusion coefficient is decreased as the quantity of solubilized species in solution is increased, presumably due to changes in the size and weight of the solubilized species. The observed dissolution rate is described in terms of the contribution of the molecular and solubilized species to the dissolution rate. The influence of solubilization, viscosity, and diffusion coefficients on the dissolution rate is discussed.

Keyphrases □ Solubility-diffusion coefficient-dissolution rate-relationship at constant viscosity, benzoic acid-aqueous polysorbate 80 solutions □ Benzoic acid, dissolution in aqueous polysorbate 80 solutions—micellar diffusion coefficient calculated, constant and uncontrolled viscosity, determination of diffusion layer thickness □ Diffusion coefficient, micellar—calculated for dissolution of benzoic acid in aqueous polysorbate 80 solutions, constant and uncontrolled viscosity □ Micellar diffusion coefficient—calculated for dissolution of benzoic acid in aqueous polysorbate 80 solutions, constant and uncontrolled viscosity

Comprehensive reviews of the dissolution rate of solids were presented by Higuchi (1), Wagner (2), and Wurster and Taylor (3). Probably the earliest physical model for the dissolution of a solid was the diffusion layer model proposed by Nernst (4). In the diffusion layer model, it is assumed that there is a liquid layer of effective thickness (h) in which there is a negligible velocity component in the direction perpendicular to the surface. At a distance from the surface of the solid greater than h , mixing occurs so rapidly that no concentration gradients exist in this region. At the solid-liquid interface, a solid-solution equilibrium exists. Then the rate of solute movement and, therefore, the dissolution rate are determined entirely by Brownian diffusion of the molecules in the liquid diffusion layer.

When a one-component, single-phase solid of macroscopic dimensions and of low to moderate solubility dissolves without disintegration and without chemical reaction into a dissolution medium under mild to high agitation conditions, the dissolution rate may be expressed:

$$R = \frac{D}{h} (C_s - C) \quad (\text{Eq. 1})$$

where R is the weight of solute dissolved per unit surface per unit time, D is the diffusion coefficient of the solute molecule, C_s is the solubility, and C is the concentration of the solute.

Since the definition of any diffusional process or model requires the determination of the diffusion coefficient, one purpose of this investigation was to deter-

mine independently the experimental diffusion coefficients and the dissolution rates of benzoic acid in aqueous solutions of various concentrations of polysorbate 80 so that the relationship between diffusion and dissolution could be studied. In a previous investigation the concomitant and individual effects of solubilization and viscosity on dissolution rate were reported (5). Although at constant viscosity the dissolution rate was roughly proportional to the total solubility, as depicted by the Noyes-Whitney relation, this investigation sought to study the deviation in terms of the contribution of the diffusion coefficient of benzoic acid and the diffusion coefficient of solubilized benzoic acid to the observed dissolution rate in various concentrations of polysorbate 80.

EXPERIMENTAL

Determination of Diffusion Coefficients—A diagram of the Plexiglas cell used to determine diffusion coefficients is shown in Fig. 1. The volume of each cell compartment was accurately determined by weight using distilled water at 25°. Access to the contents of the cell was through 9.5-mm. ports, which were sealed with threaded nylon plugs. Glass spheres were used in the cell compartments to provide sufficient agitation so that there were no stagnant layers of solution and diffusion occurred only across the membrane. A metallic silver membrane¹, having a thickness of 50 μ and a pore size of 1.2 μ , was used. The advantage of the silver membrane was that the same membrane was used for all determinations because of its tensile strength and ability to provide reproducible results (6). The cell was mounted eccentrically 8 cm. from the shaft, which was rotated at 13 r.p.m. Tests revealed no absorption of benzoic acid by the components of the cell.

The cell constant (L) was initially determined for a diffusion time of 4 hr. using a standard solution of potassium chloride. The experimental diffusion coefficient at 25° for benzoic acid in distilled water was determined using a diffusion time of 4 hr. The experimental value of 1.082×10^{-5} cm.²/sec. was in good agreement with the values of King and Brodie (7) and King and Cathcart (8).

It was found later that a diffusion time of 8 hr. was required, because a diffusion time of 4 hr. was insufficient for the determination of diffusion coefficients in dissolution media with high viscosity. Quasisteady-state conditions were maintained during the 8 hr., while sufficient benzoic acid diffused across the membrane to provide an accurate analysis of the solution. The cell constant was determined using a 0.010 M solution of benzoic acid and a diffusion time of 8 hr. by means of the relationship:

$$L = \frac{G}{D(C_1 - C_2)} \quad (\text{Eq. 2})$$

where G is the rate of mass transport from cell compartment 1 to cell compartment 2, D is the diffusion coefficient of benzoic acid in water as reported by King and Brodie (7), and C_1 and C_2 are the concentrations of benzoic acid at 8 hr. in compartments 1 and 2, respectively. After 8 hr. it was found that $C_1 = 1.060$ mg./ml., $C_2 = 0.159$ mg./ml., and $G = 84.70 \times 10^{-5}$ g./sec. The

¹ Flotronics Membrane, Selas Flotronics, Spring House, Pa.

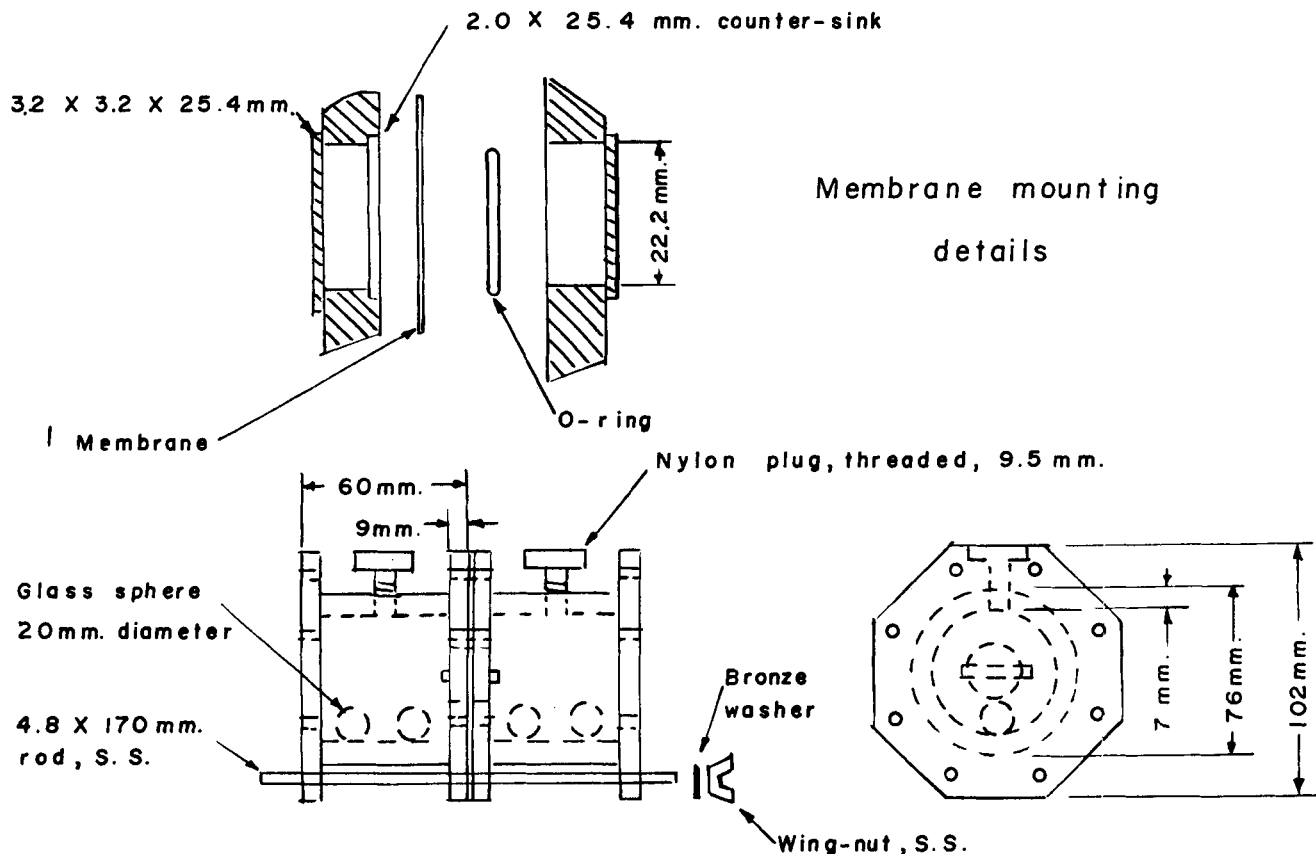


Figure 1—Diffusion cell used for determination of diffusion coefficient with quasisteady-state diffusion.

cell constant:

$$L = \frac{84.7 \times 10^{-5}}{1.11 \times 10^{-5} \times 0.901} = 84.69 \text{ cm.} \quad (\text{Eq. 3})$$

The value of the cell constant was confirmed periodically.

In the determination of the diffusion coefficients after 8 hr., the cell was removed from the water bath at $25 \pm 0.05^\circ$ and rotated

rapidly by hand to ensure a homogeneous solution in each cell compartment. The nylon plug was removed from compartment 1, and three 5.0-ml. samples were withdrawn by pipet. The pipets were allowed to drain for 5 min. into volumetric flasks. Each 5.0-ml. sample was diluted to 200 ml. with distilled water. The solutions were analyzed spectrophotometrically for benzoic acid.

The experimental diffusion coefficients (D_{exp}) of benzoic acid were determined using Eq. 2. The solutions were prepared 24 hr. prior to the measurement and maintained at 25° . Each determination required the dissolution medium and a solution of 0.0100 M benzoic acid in the corresponding dissolution medium. All determinations were in triplicate. For D_{exp} of approximately $0.1 \times 10^{-5} \text{ cm.}^2/\text{sec.}$, the estimated error was approximately 10%; for D_{exp} of $0.5 \times 10^{-5} \text{ cm.}^2/\text{sec.}$ and greater, the error was approximately 2%. Typical data are given in Table I.

Other Parameters—All determinations were made at 25° . The dissolution rate of benzoic acid was determined by means of a spherical tablet with an initial diameter of 0.953 cm. in 2 l. of dissolution medium stirred at 324 r.p.m. The techniques of dissolution rate determination and tablet production were previously described (9). The determination of solubility and the adjustment of viscosity also were reported earlier (5).

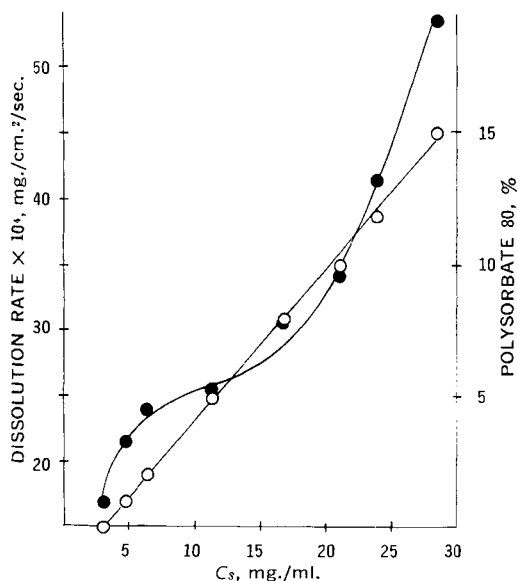


Figure 2—Relationship of total solubility of benzoic acid to dissolution rate and concentration of polysorbate 80 in aqueous solutions adjusted with sucrose to a relative viscosity of 3.95. Key: ●, rate; and ○, concentration (5).

Table I—Diffusion Coefficients (D_{exp}) of Benzoic Acid at 25° in Aqueous Polysorbate 80 Solutions Adjusted with Methylcellulose to a Relative Viscosity of 6.72

Concentration, % w/v	C_1 , mg./ml.	C_2 , mg./ml.	$C_1 - C_2$, mg./ml.	$10^5 G$, mg./sec.	$10^5 D_{\text{exp}}$, $\text{cm.}^2/\text{sec.}$
0	1.142	0.078	1.064	41.56	0.462
1	1.150	0.070	1.080	37.35	0.408
2	1.158	0.062	1.096	33.14	0.357
3	1.168	0.052	1.116	27.88	0.295
4	1.174	0.046	1.128	24.73	0.259
5	1.180	0.041	1.140	21.57	0.223

^a 1500 cps.

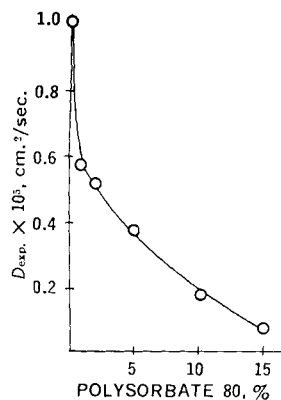


Figure 3—Experimental diffusion coefficient of benzoic acid at 25° in aqueous polysorbate 80 solutions.

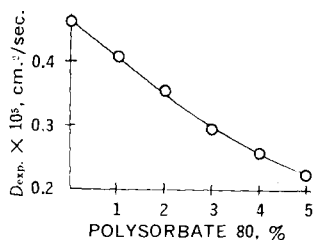


Figure 4—Experimental diffusion coefficient of benzoic acid in aqueous polysorbate 80 solutions adjusted with methylcellulose to a relative viscosity of 6.72.

RESULTS AND DISCUSSION

In an investigation of the dissolution kinetics of benzoic acid in micellar solutions, the relationship of dissolution rate, solubilization, and viscosity was determined (5). As shown in Fig. 2, when the viscosity is maintained constant, the dissolution rate of benzoic acid in aqueous solutions of polysorbate 80 is increased as the total solubility is increased. Under these conditions the relationship between dissolution rate and total solubility is not linear, as depicted by the Noyes-Whitney equation; therefore, factors in addition to viscosity influence the dissolution rate. Since dissolution was considered to be a diffusion-controlled process (10), it was necessary to investigate the dissolution rates in relation to diffusion coefficients, which were determined experimentally in various concentrations of the surfactant.

In an aqueous micellar solution, the dissolved solute exists as a molecular species and as a solubilized species. The mass transport of each species is dependent on its diffusion coefficient. The contribution of each species to the observed dissolution rate is dependent on the diffusion coefficient of each species and the solubility of the solute in each phase. Higuchi (11) proposed that the dissolution rate in micellar solutions could be represented by the equation:

$$R = \frac{D_0 C_0}{h} + \frac{D_m (C_s - C_0)}{h} \quad (\text{Eq. 4})$$

where R is the dissolution rate, h is the thickness of the effective diffusion layer, C_0 is the solubility of the solute, $C_s - C_0$ is the increase of solubility due to solubilization, and D_0 and D_m are the diffusion coefficients for the molecular species and the solubilized species, respectively. The report of Singh *et al.* (12) on the dissolution rate of benzocaine in polysorbate 80 solutions supports the diffusion layer model.

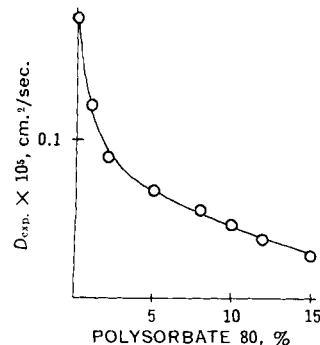


Figure 5—Experimental diffusion coefficient of benzoic acid in aqueous polysorbate 80 solutions adjusted with sucrose to a relative viscosity of 3.95.

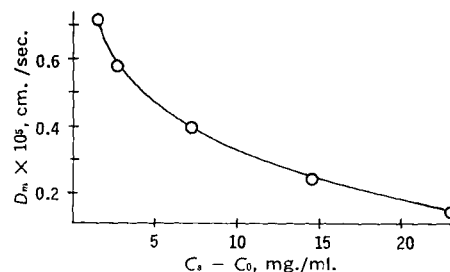


Figure 6—Relationship of micellar diffusion coefficient of benzoic acid to its micellar solubility in aqueous polysorbate 80 solutions.

Solubilization and Diffusion Coefficients—The D_{exp} of benzoic acid in aqueous solutions of polysorbate 80 at 25° is shown in Fig. 3 as a function of the concentration of polysorbate 80. As in many cases, it was found that the diffusion coefficient is not constant and is not a linear function of concentration. The D_{exp} decreases rapidly as the concentration of polysorbate 80 is increased to 2%. The slope of the curve in Fig. 3 or the rate of change of the diffusion coefficient with a change of concentration then becomes less as the concentration of polysorbate 80 is increased to values greater than 2%.

The values of D_{exp} of benzoic acid in aqueous polysorbate 80 solutions adjusted with methylcellulose to a relative viscosity of 6.72 are shown in Fig. 4 as a function of the concentration of polysorbate 80. An inverse relationship between the diffusion coefficient and viscosity is described by the Stokes-Einstein equation:

$$D = \frac{RT}{6\pi\eta N} \sqrt{\frac{4N}{3M\bar{v}}} \quad (\text{Eq. 5})$$

As predicted by Eq. 5, D_{exp} (0.462×10^{-5} cm.²/sec.) in aqueous solution adjusted to a relative viscosity of 6.72 is less than D_{exp} (1.082×10^{-5} cm.²/sec.) of benzoic acid in distilled water. As the concentration of polysorbate 80 is increased in the dissolution medium adjusted to a relative viscosity of 6.72, the rate of decrease of D_{exp} with a change of concentration tends to be less.

The aqueous polysorbate 80 solutions adjusted with sucrose to a relative viscosity of 3.95 provide a large concentration range in which to study the behavior of the diffusion coefficient of benzoic acid with respect to the change in concentration of polysorbate 80 under conditions of a constant viscosity. Even though the viscosity is constant, as shown in Fig. 5, the value of D_{exp} is decreased as the concentration of polysorbate 80 is increased. Similar to the above system, D_{exp} is initially decreased at a rapid rate as the concentration of surfactant is increased; and as the concentration of polysorbate 80 is further increased, the rate of change of D_{exp} with a change of concentration of surfactant becomes progressively less.

The decrease in the magnitude of the diffusion coefficients caused by increasing the concentration of polysorbate 80 in solutions having a constant viscosity indicates that micellar solubilization has a significant role in the dissolution rates of benzoic acid in micellar solutions. If it is assumed that the diffusion coefficient of molecular benzoic acid in the aqueous phase of a dissolution medium at constant viscosity is unchanged by the addition of a surfactant, the diffusion coefficient of the solubilized species contributes significantly to the total dissolution rate and depends on the concentration of the surfactant.

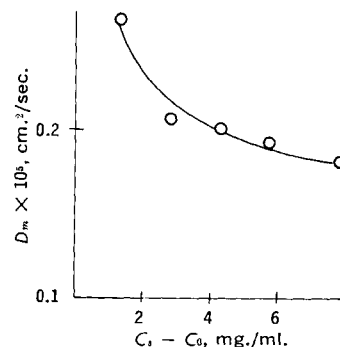


Figure 7—Relationship of micellar diffusion coefficient of benzoic acid to its micellar solubility in aqueous polysorbate 80 solutions adjusted with methylcellulose to a relative viscosity of 6.72.

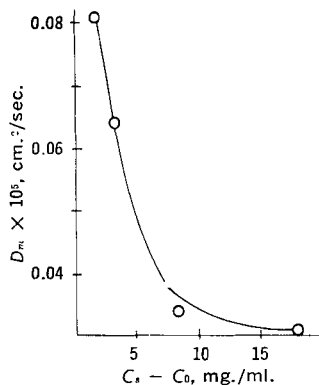


Figure 8—Relationship of micellar diffusion coefficient of benzoic acid to its micellar solubility in aqueous polysorbate 80 solutions adjusted with sucrose to a relative viscosity of 3.95.

The thickness of the effective diffusion layer was evaluated by experimentally measuring the dissolution rate, solubility, and diffusion coefficient in distilled water at 25°, and:

$$h = \frac{D_0 C_0}{R} = \frac{1.082 \times 10^{-5} \times 3.43}{127.14 \times 10^{-4}} = 0.00291 \text{ cm.} \quad (\text{Eq. 6})$$

In a similar manner, h in aqueous methylcellulose and sucrose solutions was found to be 30.2 and 32.0 μ , respectively. These values are within approximately $\pm 5\%$ variation from their average, and they are within the 20–50- μ range proposed by Nernst (4). By another technique the thickness of the diffusion layer for benzoic acid dissolving in distilled water was reported to be 32.8 μ (13).

Since all terms, except for the diffusion coefficient (D_m) of the solubilized species, were determined experimentally, D_m may be calculated by rearrangement of Eq. 4 to:

$$D_m = \frac{R - D_0 C_0/h}{(C_s - C_0)h} \quad (\text{Eq. 7})$$

For example, the D_m of benzoic acid in an aqueous 2% polysorbate 80 solution is:

$$D_m = \frac{(170.22 \times 10^{-4}) - (1.082 \times 10^{-5} \times 3.42)/29.1 \times 10^{-4}}{(6.06 - 3.42)/29.1 + 10^{-4}} = 0.475 \times 10^{-5} \text{ cm.}^2/\text{sec.} \quad (\text{Eq. 8})$$

The relationship between D_m and the micellar solubility ($C_s - C_0$) in an aqueous polysorbate 80 solution is shown in Fig. 6. As the concentration of the surfactant is increased and a greater quantity of benzoic acid is transported as the solubilized species, D_m becomes less. Inspection of Eq. 5 shows that an increase in viscosity results in a decrease in the diffusion coefficient. As the concentration of the surfactant is increased and the viscosity of the dissolution medium is simultaneously increased, the diffusion coefficient is decreased.

The values of D_m in aqueous polysorbate 80 solutions adjusted to a relative viscosity of 6.72 and 3.95 are shown in Figs. 7 and 8, respectively, as a function of micellar solubility. In all experiments, D_m decreased as the quantity of solubilized species was increased. In aqueous polysorbate 80 solutions with uncontrolled viscosity, the magnitude of the change in D_m for a given change in micellar solubilization was greater than in dissolution media with controlled viscosity. Using the Stokes–Einstein equation, Gibaldi *et al.* (14) calculated a mean micellar diffusion coefficient for benzoic acid

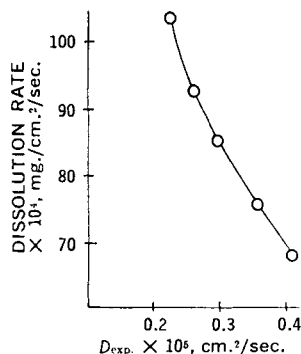


Figure 9—Relationship of dissolution rate of benzoic acid to its experimental diffusion coefficient in aqueous polysorbate 80 solutions adjusted with methylcellulose to a relative viscosity of 6.72.

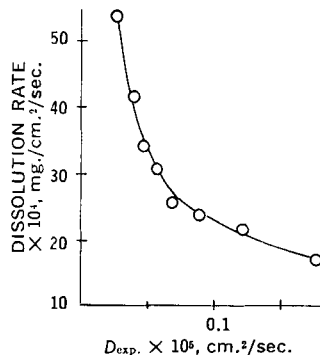


Figure 10—Relationship of dissolution rate of benzoic acid to its experimental diffusion coefficient in aqueous polysorbate 80 solutions adjusted with sucrose to a relative viscosity of 3.95.

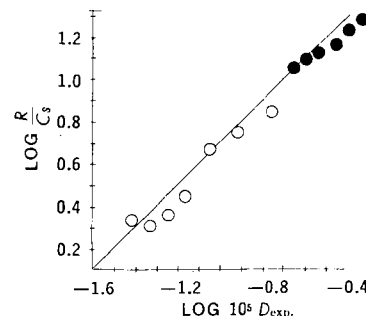


Figure 11—Comparison of experimental data with a theoretical slope of 1.0 for the diffusion layer model as predicted by Eq. 9. Key: ●, $\eta_{rel.} = 6.72$; and ○, $\eta_{rel.} = 3.95$.

in an aqueous solution of a nonionic surfactant. As shown in Fig. 7, D_m decreases as the concentration of surfactant and the quantity of the solubilized species are increased. Thus, a mean micellar diffusion coefficient is not representative of the diffusional environment (15). With a constant viscosity, the change of D_m with a change in concentration of surfactant is related to the weight of the solubilized species and the specific volume occupied by the solubilized species, as represented by M and v , respectively, in Eq. 5.

Dissolution Rate and Diffusion Coefficient—The dissolution rate may be described by the equation:

$$R = \frac{D_{exp.} C_s}{h} \quad (\text{Eq. 9})$$

where C_s is the total solubility of the solute. The relation between the observed dissolution rate of benzoic acid and its $D_{exp.}$ in aqueous polysorbate 80 solutions with a relative viscosity of 6.72 and 3.95 is shown in Figs. 9 and 10, respectively.

As discussed by Singh *et al.* (12), the relationship of dissolution rate, total solubility, and diffusion coefficient may be used to determine the type of diffusion model by which a dissolution process occurs. One test of the dissolution model can be made by plotting $\log R/C_s$ against $\log D_{exp.}$. The slope of the line is equal to a critical exponent, which indicates the type of dissolution model. In Fig. 11 the theoretical line with a slope of 1, as predicted by the diffusion layer model, is drawn. The experimental points for the dissolution of benzoic acid in micellar solutions of polysorbate 80 are given at two constant viscosities. By using values of dissolution rate and $D_{exp.}$ determined by independent experimental procedures, the

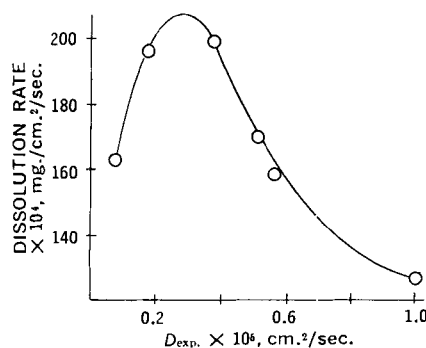


Figure 12—Relationship of the dissolution rate of benzoic acid to the experimental diffusion coefficient in aqueous polysorbate 80 solutions.

Table II—Observed Dissolution Rate, Dissolution Rate Calculated by Use of Experimental Diffusion Coefficient, and Dissolution Rate Calculated by Use of Micellar Diffusion Coefficient in Various Concentrations of Polysorbate 80 at 25°

Polysorbate 80, % w/v	$10^4 R$, mg./cm. ² /sec.	$10^5 D_{exp.}$, cm. ² /sec.	$\frac{10^4 D_{exp.} C_s}{h}$, mg./cm. ² /sec.	$10^5 D_m$, cm. ² /sec.	$\frac{10^4 D_0 C_0}{h} + \frac{10^4 D_m (C_s - C_0)}{h}$, mg./cm. ² /sec.
0	127.2	1.082	127.2	—	127.2
1	158.7	0.572	96.3	0.620	127.2 + 31.6
2	170.2	0.516	107.5	0.475	127.2 + 43.1
5	198.7	0.382	139.5	0.289	127.2 + 71.5
10	196.4	0.177	108.9	0.139	127.2 + 69.3
15	162.6	0.078	70.8	0.045	127.2 + 35.5

experimental points fit a slope of 1 and confirm that dissolution occurs according to the diffusion layer model.

The dissolution rate is described in Eq. 4 in terms of the summation of the contribution to the rate by the molecular species in the aqueous phase and the contribution to the rate by the solubilized species. If it is assumed that the contribution of the molecular species in the aqueous phase remains constant, changes in the dissolution rate of benzoic acid as the concentration of surfactant is changed are due to changes in the micellar dissolution rate, which is represented by the second term in Eq. 4.

It was reported (5) that in each of the dissolution media of constant viscosity, the solubility is a linear function of the concentration of polysorbate 80. As $D_{exp.}$ is increased, the dissolution rate is slowed. At low concentrations of polysorbate 80, the experimental and the micellar diffusion coefficients are relatively large, and diffusion occurs primarily in the aqueous phase. As the concentration of polysorbate 80 is further increased, the experimental and micellar diffusion coefficients are decreased; however, the dissolution rate is increased because the total solubility (or the quantity of solubilized species) is increased at a greater rate than the diffusion coefficients are decreased by the change in concentration of polysorbate 80. Thus, at a constant viscosity, solubilization is the chief factor in increasing the dissolution rate.

In dissolution media with uncontrolled viscosity, the relationship between $D_{exp.}$ and dissolution rate is different (Fig. 12). At low concentrations of polysorbate 80, the changes in viscosity of the dissolution medium caused by the addition of the surfactant do not greatly affect the dissolution rate. At low concentrations of polysorbate 80, the experimental and micellar diffusion coefficients are relatively large, and diffusion occurs primarily in the aqueous phase. As the concentration of polysorbate 80 is increased, the experimental and micellar diffusion coefficients are decreased; however, the dissolution rate is increased due to the solubilization effect.

At concentrations greater than 8% polysorbate 80, the net result of the decrease in values of the experimental and micellar diffusion coefficients and the increase in solubilization is a slower dissolution rate. It is at concentrations of polysorbate 80 exceeding 8% that the viscosity of the dissolution medium is markedly increased. Thus, the combined effect of the increased viscosity and the decreased diffusion coefficient is greater than the solubilizing effect, and the dissolution rate is slowed.

A comparison of the observed dissolution rate, the dissolution rate calculated by Eq. 9 using $D_{exp.}$, and the dissolution rate calculated using D_m is given in Table II. The dissolution rate calculated using

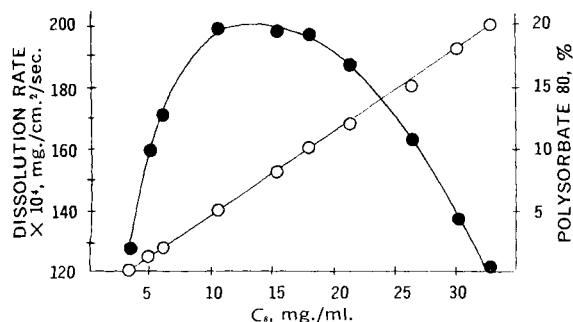


Figure 13—Relationship of the total solubility of benzoic acid to dissolution rate and concentration of polysorbate 80. Key: ●, rate; and ○, concentration (5).

$D_{exp.}$ is consistently slower than the observed dissolution rate. For example, in a 5% polysorbate 80 solution, the observed dissolution rate was 198.68 mg./cm.²/sec., and the dissolution rate calculated using $D_{exp.}$ of 0.382×10^{-5} cm.²/sec. was 139.54 mg./cm.²/sec. or 30% slower.

A similar situation exists in the dissolution media having a constant relative viscosity of 6.72 and 3.95 as shown in Tables III and IV, respectively. The difference between the observed dissolution rate and the rate calculated by means of $D_{exp.}$ is much smaller in the dissolution media in which the viscosity is constant than in the dissolution media with uncontrolled viscosity. For example, in 5% polysorbate 80 solutions adjusted to a relative viscosity of 3.95, the observed dissolution rate was 25.51 mg./cm.²/sec., and the dissolution rate calculated using $D_{exp.}$ of 0.068×10^{-5} cm.²/sec. was 24.3 mg./cm.²/sec. or 5% slower.

The relationship in Fig. 13 of the solubility of benzoic acid to the dissolution rate and the concentration of polysorbate 80 can now be explained in terms of the effects of viscosity, solubility, and the diffusion coefficients of the molecular and solubilized species.

The viscosity of the micellar solution is not greatly increased by the surfactant at low concentrations of polysorbate 80; however, at concentrations exceeding 8% polysorbate 80, the viscosity is greatly increased by the surfactant (5).

The diffusion coefficient is rapidly decreased due to the contribution of the slow diffusing, solubilized species to $D_{exp.}$ at concentrations less than 2% polysorbate 80. Since the solubility is linearly dependent on concentration of polysorbate 80, at low concentrations of the surfactant the dissolution rate is increased in accordance with the general concept of Noyes and Whitney. The maximum dissolution rate occurs at approximately 8% polysorbate 80, at which the solubilizing effect is large, the viscosity is low, and the diffusion coefficients are not greatly reduced. As the concentration of polysorbate 80 exceeds 8%, the large increase in viscosity and the decrease in diffusion coefficient act to decrease the dissolution rate to a greater extent than the increase in solubility acts to increase the dissolution rate; the net result is a decrease in dissolution rate.

When the factor of viscosity is maintained constant, the effects of solubilization and diffusion can be more easily seen. As shown in

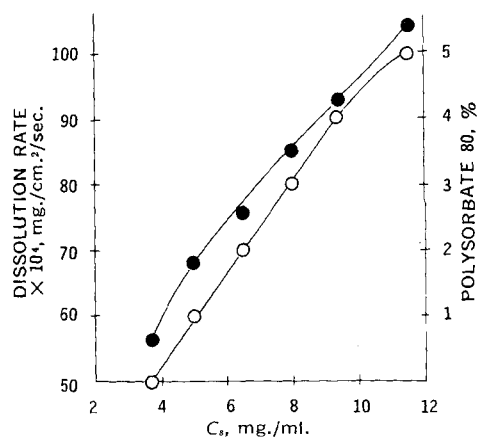


Figure 14—Relationship of total solubility of benzoic acid to dissolution rate and the concentration of polysorbate 80 in aqueous solutions adjusted with methylcellulose to a relative viscosity of 6.72. Key: ●, rate; and ○, concentration (5).

Table III—Observed Dissolution Rate, Dissolution Rate Calculated by Use of Experimental Diffusion Coefficient, and Dissolution Rate Calculated by Use of Micellar Diffusion Coefficient in Various Concentrations of Polysorbate 80 Solutions Adjusted with Methylcellulose to a Relative Viscosity of 6.72

Polysorbate 80, % w/v	$10^4 R$, mg./cm. ² /sec.	$10^5 D_{exp.}$, cm. ² /sec.	$\frac{10^4 D_{exp.} C_s}{h}$, mg./cm. ² /sec.	$10^5 D_m$, cm. ² /sec.	$\frac{10^4 D_0 C_0}{h} + \frac{10^4 D_m (C_s - C_0)}{h}$, mg./cm. ² /sec.
0	56.6	0.462	56.6	—	56.6
1	68.1	0.408	67.5	0.266	56.6 + 11.5
2	75.7	0.357	76.8	0.206	56.6 + 19.1
3	85.3	0.295	78.1	0.201	56.6 + 28.7
4	92.9	0.259	80.3	0.194	56.6 + 36.3
5	103.7	0.223	84.9	0.182	56.6 + 47.1

Table IV—Observed Dissolution Rate, Dissolution Rate Calculated by Use of Experimental Diffusion Coefficient, and Dissolution Rate Calculated by Use of Micellar Diffusion Coefficient in Various Concentrations of Polysorbate 80 Solutions Adjusted with Sucrose to a Relative Viscosity of 3.95

Polysorbate 80, % w/v	$10^4 R$, mg./cm. ² /sec.	$10^5 D_{exp.}$, cm. ² /sec.	$\frac{10^4 D_{exp.} C_s}{h}$, mg./cm. ² /sec.	$10^5 D_m$, cm. ² /sec.	$\frac{10^4 D_0 C_0}{h} + \frac{10^4 D_m (C_s - C_0)}{h}$, mg./cm. ² /sec.
0	17.2	0.177	17.2	—	17.2
1	21.6	0.122	18.5	0.0814	17.2 + 4.4
2	23.8	0.089	17.8	0.0643	17.2 + 6.6
5	25.5	0.068	24.3	0.0320	17.2 + 8.3
8	30.7	0.057	29.9	0.0316	17.2 + 13.5
10	34.2	0.047	31.0	0.0302	17.2 + 17.0
12	41.6	0.038	28.5	0.0373	17.2 + 24.4
15	53.7	0.026	23.1	0.4060	17.2 + 36.5

Fig. 14, the relationship of dissolution rate and total solubility approaches linearity. The $D_{exp.}$ does not sharply decrease with an increase in concentration of polysorbate 80 (Fig. 4). Thus, the effects of the gradual decrease in the diffusion coefficient and of the linear relationship of solubility to concentration of polysorbate 80 combine to provide a relation of the dissolution rate to solubility that only slightly deviates from the Noyes-Whitney concept.

As illustrated in Fig. 2, when the viscosity is maintained constant, similar effects of solubilization and diffusion can be seen over a large range of concentration of polysorbate 80. Although the relationship of dissolution rate to total solubility does not rigorously conform to the Noyes-Whitney equation, no maximum dissolution rate is observed at a constant viscosity and the moderately sigmoidal curve representing the relationship of dissolution rate to solubility can, within reasonable limits, be superimposed on the straight line representing the relationship of concentration of surfactant to total solubility. At least it appears that solubilization is a major factor influencing dissolution rate and that in micellar solutions the dissolution rate is approximately proportional to the total solubility when the factor of viscosity is properly considered.

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