

Dissolution Kinetics of Benzoic Acid in High Concentrations of Surface-Active Agents

By E. L. PARROTT and V. K. SHARMA

The dissolution kinetics of benzoic acid has been studied in the presence of certain surface-active agents. The addition of tyloxapol, polysorbate 80, sodium lauryl sulfate, and poloxakol to the dissolving fluid increased the apparent solubility of benzoic acid. In considering the experimentally determined dissolution rate as a function of solubility, it appears that the dissolution process in solutions of tyloxapol, polysorbate 80, and sodium lauryl sulfate concurs with the diffusion layer concept, while the dissolution process in the presence of poloxakol is best described by an interfacial barrier model.

IT IS WELL RECOGNIZED that the dissolution rate can be the rate-limiting step in the biological availability of drugs administered in the solid state. Wagner (1) has discussed the relation of dissolution kinetics to biological availability. Wurster and Taylor (2) have reviewed factors which influence the dissolution rate. In a recent review Higuchi (3) presented models for three mechanisms of dissolution rate behavior of solids.

Since surface-active agents are often a constituent of liquid and solid pharmaceuticals, a more complete understanding of the effect of surface-active agents on the dissolution rates of solids is of interest in the design of these dosage forms. Limited information has been published regarding the effect of surface-active agents on dissolution rate (4-7). Generally these investigations have been conducted in the region of the critical micelle concentration (CMC) of the surface-active agent employed. The purpose of this work is to investigate the effect of high concentrations of surface-active agent on dissolution rate of a relatively water-insoluble compound.

EXPERIMENTAL

Materials—The surface-active agents were commercial lots which were used without further purification. Poloxakol¹ is an oxyethylene polymer which contains 80% polyoxyethylene and has an approximate molecular weight of 8700. Tyloxapol² is a condensation product of *tert*-octylphenol with ethylene oxide having an average molecular weight of 2800. U.S.P. polysorbate 80³ and sodium lauryl sulfate;⁴ benzoic acid, citric acid, and disodium hydrogen phosphate were reagent grade.

Dissolution Rate Determinations—The procedure for tablet production and the dissolution apparatus were similar to that previously described (8). Spherical 3/8-in. diameter tablets of pure benzoic acid were used. All determinations were made at 25° and at a stirrer speed of 324 r.p.m. At hourly intervals the 2 L. of dissolving fluid was changed, and the tablet was weighed and its diameter measured with a micrometer. At each concentration of surface-active agent, the dissolution rate was de-

termined in triplicate with the rates falling within a 3% range.

Solubility Studies—An excess of benzoic acid and aqueous solutions of the surface-active agent were rotated in 50-ml. amber bottles in a constant-temperature bath at $25 \pm 0.1^\circ$ for 24 hr. An aliquot was withdrawn from each bottle using a pipet fitted with a filter. After diluting with distilled water, the absorbance was measured with a Beckman DU spectrophotometer, and the solubility of the benzoic acid was determined by means of a standard curve.

In the analysis of samples containing polysorbate 80, sodium lauryl sulfate, and poloxakol, distilled water was used as a blank since the samples were diluted 400-fold and there was no absorption by the surface-active agents. The absorbance was measured at 272.5 $m\mu$. The concentration of benzoic acid was determined from a standard curve prepared by measuring in known concentrations of surface-active agents the absorbances of known concentrations of benzoic acid which had been diluted in a similar manner.

The strong absorption of tyloxapol in the region of 280 $m\mu$ necessitated the use of an extraction procedure. In preparing a standard curve using chloroform as the solvent it was found that there was a shift in the absorption maximum of benzoic acid to 273.5 $m\mu$. In the analytical procedure a 10-ml. sample was diluted 100-fold with distilled water, and 25 ml. of this dilution was extracted with three 25-ml. portions of chloroform. The combined chloroform extract was filtered into a 100-ml. volumetric flask and adjusted to 100 ml. with chloroform. The absorbance was measured at 273.5 $m\mu$. The concentration of benzoic acid was determined from a standard curve prepared by measuring in known concentrations of tyloxapol the absorbances of known concentrations of benzoic acid which had been extracted in the manner described.

RESULTS AND DISCUSSION

Solubilization—In dilute aqueous solutions in which the surface-active agent is molecularly dispersed, compounds of low water solubility, such as benzoic acid, do not dissolve to a greater extent than they would in water; however, at concentrations of surface-active agent in excess of the CMC the total solubility is increased. The amount of benzoic acid solubilized by micellar interaction ($C_s - C_0$) is represented by the difference between the total solubility (C_s) in a solution of a surface-active agent and the solubility (C_0) in water (9). The quantity ($C_s - C_0$) is linearly dependent on the concentration of the surface-active agent.

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¹ Pluronic F-68, Wyandotte Chemical Corp., Wyandotte, Mich.

² Triton WR-1339, Winthrop Laboratories, New York, N. Y.

³ Marketed as Tween 80 by Atlas Chemical Industries, Wilmington, Del.

⁴ Marketed as Duponol C by E. I. du Pont de Nemours and Co., Wilmington, Del.

TABLE I—DISSOLUTION RATE AND SOLUBILITY OF BENZOIC ACID AT 25° IN VARIOUS CONCENTRATIONS OF AQUEOUS TYLOXAPOL

% Surfactant	Dissolution Rate, mg./cm. ² /hr.	C _s , Total Solubility (mg./ml.)	C _s - C ₀ , Micellar Solubility (mg./ml.)
0	42.80	3.23	...
0.01	41.79	3.31	...
0.03	42.96	3.11	...
0.07	44.18	3.35	0.12
1.00	50.88	4.35	1.12
2.00	53.40	5.62	2.39
5.00	59.38	10.22	6.99
6.00	59.25	11.60	8.37
8.00	55.80	14.85	11.62
10.00	53.55	17.48	14.25

The data for tyloxapol given in Table I and plotted in Fig. 1 are typical of the experimental results for the solubilization of benzoic acid at 25° in various concentrations of surface-active agent. The linear relationship between solubilization and concentration of surface-active agent was also found to exist in solutions of polysorbate 80, sodium lauryl sulfate, and poloxakol, as shown in Figs. 2 to 4.

Dissolution Rate in Concentrations of Surface-Active Agent Exceeding the CMC—When a single component, one phase solid of macroscopic size dissolves without disintegration and without chemical reaction in an agitated solvent, the dissolution rate (R) at a given temperature may be expressed by the Noyes and Whitney equation:

$$R = \frac{dw}{dt} \frac{1}{S} = k(C_s - C) \quad (\text{Eq. 1})$$

where dw/dt is the amount of solute dissolved per unit time, S is the surface area, C_s is the solubility, C is the concentration of the solute, and k is a constant.

When $C_s \gg C$ the dissolution rate will be:

$$R = k C_s \quad (\text{Eq. 2})$$

Numerous reports have substantiated this relationship which states that the dissolution rate is proportional to the solubility of a compound (8, 10-12).

Since any dissolution interaction may affect C_s and consequently alter the dissolution rate, it was thought that micellar solubilization, which increased the solubility of benzoic acid, would increase its dissolution rate. The experimentally determined dissolution rate and the corresponding quantity ($C_s - C_0$) for benzoic acid in various concentrations of tyloxapol are given in Table I and Fig. 1. With an increase in the concentration of tyloxapol, there is an increase in the solubility and an increase in the dissolution rate. The dissolution rate attains its maximum value at 5% tyloxapol, and the dissolution rate decreases upon further increases in the concentration of the surface-active agent.

Similarly, as shown in Fig. 2 an increase in the concentration of polysorbate 80 results in an increased solubility and an increased dissolution rate. A maximum dissolution rate is reached at 9% polysorbate 80.

Qualitatively the experimental results are in accordance with Eq. 2; however, with micellar

solubilization the micelle phase must be considered and according to the diffusion layer concept (3):

$$R = \frac{D}{h} C_0 + \frac{D'}{h} (C_s - C_0) \quad (\text{Eq. 3})$$

where h is the effective diffusion layer thickness, D is the diffusion coefficient, C_0 is the solubility of the solute molecule, and D' is the diffusion co-

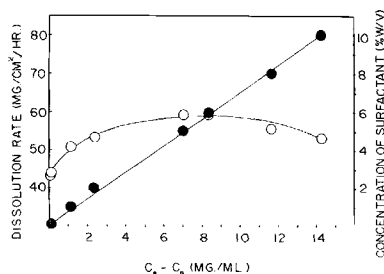


Fig. 1—The relationship of the solubility of benzoic acid at 25° to its dissolution rate and the concentration of tyloxapol. Key: O, rate; ●, concentration.

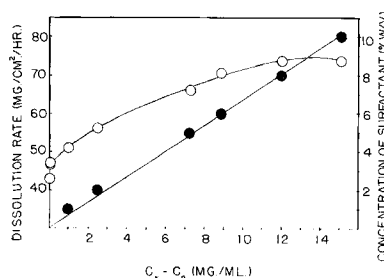


Fig. 2—The relationship of the solubility of benzoic acid at 25° to its dissolution rate and the concentration of polysorbate 80. Key: O, rate; ●, concentration.

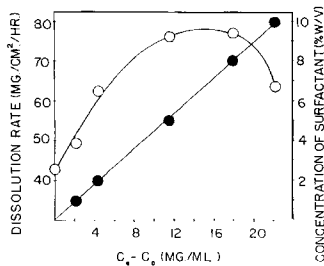


Fig. 3—The relationship of the solubility of benzoic acid at 25° to its dissolution rate and the concentration of sodium lauryl sulfate. Key: O, rate; ●, concentration.

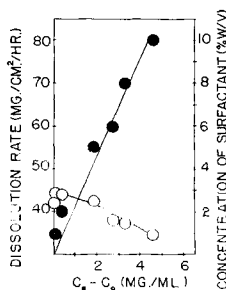


Fig. 4—The relationship of the solubility of benzoic acid at 25° to its dissolution rate and the concentration of poloxakol. Key: O, rate; ●, concentration.

efficient of the micelle-solubilized solute and ($C_s - C_0$) is the solubility increase due to solubilization.

As the concentration of tyloxapol and polysorbate 80 is increased, the increase in dissolution rate becomes progressively less, and at high concentrations the dissolution rate is decreased. If this effect were due to the influence of viscosity, it would be reflected in Eq. 3 in the diffusion coefficients which by the Stokes-Einstein equation are inversely proportional to the viscosity (13). If dissolution were an interfacially controlled process, viscosity should have little effect on the dissolution rate. If dissolution were a diffusion-controlled process, an increase in viscosity should decrease the dissolution rate (2). The fact that both tyloxapol and polysorbate 80 in high concentrations cause a decrease in dissolution rate suggests that the dissolution process is primarily diffusion controlled and would support the diffusion layer concept as the model of their dissolution behavior; however, a further study is necessary to substantiate this suggestion.

The effect of sodium lauryl sulfate on the dissolution rate of benzoic acid and prednisolone in the region of the CMC has been reported (14, 15). In this region the solubilities and dissolution rates of both compounds were increased. In the present study the effect on solubility and dissolution rate was determined in concentrations greatly in excess of the CMC. The system was buffered to pH 3 with McIvaine's buffer in order to suppress ionization and minimize salt formation which would contribute to the solubility of benzoic acid by a mechanism other than micellar solubilization.

As shown in Fig. 3, the dissolution rate of benzoic acid is increased with increased concentrations of sodium lauryl sulfate; however, a maximum dissolution rate is reached at 9% sodium lauryl sulfate. Further increases in the concentration of sodium lauryl sulfate result in a decrease in dissolution rate.

The dissolution rate may be considered to be determined by 2 consecutive reaction rates: the rate of reaction at the interface and the rate of diffusion from the interface. If the reaction at the interface is infinitely fast, the Nernst and Brunner concept of dissolution by diffusion from a saturated film existing at the interface is acceptable. This appears to be the dissolution model of benzoic acid in solutions of sodium lauryl sulfate. If the surface reaction is the rate-limiting step, the dissolution kinetics would be different from that expressed by Noyes and Whitney.

The solubility of benzoic acid is a linear function of the concentration of poloxakol. It might be postulated that poloxakol is too hydrophilic to form micelles, but that it increases the solubility through association or hydrogen bonding of the benzoic acid to its polyoxyethylene groups. As shown in Fig. 4 the dissolution rate of benzoic acid

in poloxakol is not proportional to the concentration of the surface-active agent. This suggests that the dissolution process occurs by a mechanism other than a primarily diffusion-controlled process.

Dissolution Rate in Concentrations of Surface-Active Agent Less Than the CMC—As shown in Table I, in concentrations of tyloxapol less than the CMC, the dissolution rate of benzoic acid is not significantly increased by the addition of the surface-active agent. Since no solubilization was shown to occur in this region, any increase in dissolution rate may be attributed to a lowered interfacial tension which improved the wetting of the surface and increased the effective surface area (13). Similar results were found with poloxakol.

The greatest effect of wetting the surface was shown with polysorbate 80. Although the solubility was not increased, at 0.001, 0.002, and 0.003% polysorbate 80, the dissolution rates were 45.9, 46.8, and 47.5 mg./cm.²/hr., respectively.

SUMMARY

A linear relationship between solubilization of benzoic acid and concentration of a surface-active agent was found to exist in solutions of polysorbate 80, sodium lauryl sulfate, tyloxapol, and poloxakol. At concentrations of these surface-active agents less than the CMC, the dissolution rate was only slightly increased due to improved wetting of the surface. At concentrations exceeding the CMC, the dissolution rate was increased to a maximal rate by an increase in concentration of tyloxapol, polysorbate 80, and sodium lauryl sulfate. This behavior agrees with the diffusion layer theory. At higher concentrations the dissolution rate decreased; however, this may be rationalized by the diffusion layer theory when the micelle phase and its diffusional coefficient are considered. The dissolution rate of benzoic acid was retarded by poloxakol.

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