Influence of Viscosity and Solubilization on Dissolution Rate

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Abstract □ The dissolution rate of benzoic acid in aqueous sucrose and methylcellulose solutions is inversely proportional to the viscosity of the dissolution medium. The total solubility of benzoic acid in aqueous solutions of polysorbate 80 increases linearly as the concentration of the surfactant is increased. As the concentration of polysorbate 80 is increased with a limited increase in viscosity of the micellar solution, the dissolution rate of benzoic acid is increased to a maximum rate and is related to the total solubility as depicted by the Noyes–Whitney relation. At concentrations of polysorbate 80 exceeding the concentration corresponding to the maximum dissolution rate, the dissolution rate is decreased as the concentration of the surfactant is increased. Because the dissolution rate is inversely proportional to the viscosity, high concentrations of polysorbate 80 increase the viscosity of the micellar solutions to the extent that the dissolution rate is slowed although the total solubility is greatly increased. In micellar solutions maintained at a constant viscosity, the total solubility of benzoic acid increases linearly as the concentration of the surfactant is increased. The dissolution rate of benzoic acid in micellar solutions with a constant viscosity increases progressively without a maximum rate as the concentration of the surfactant is increased.

Keyphrases □ Benzoic acid dissolution rates—in sucrose, in methylcellulose, and in polysorbate 80 aqueous solutions □ Micellar solutions—dissolution rate, effect of viscosity and solubilization □ Dissolution rate—effect of total solubility and viscosity □ Viscosity—effect on dissolution rate in micellar solutions

The physicochemical factors that influence dissolution rate of a solid were reviewed by Wurster and Taylor (1). These factors may be concerned with the total system, the solute particle, or the dissolution medium. In recent years, the effect of surfactants in the dissolution medium on dissolution kinetics has been the subject of considerable research in terms of wetting (2–5) and solubilization (6–8). The effect on dissolution rate of unreactive additives (9) and reactive additives (10, 11) has been studied. Although viscosity-imparting substances are present in many pharmaceuticals, little research has been reported on the influence of viscosity on dissolution rate.

The influence of viscosity on the rate of heterogeneous reactions was investigated (12, 13). If the interaction at the interface of the solid and the dissolution medium occurs much faster than the rate of transport of the reactants to and the products from the interface, the rate is determined by the transport process. Thus, diffusion-controlled interactions would be expected to decrease in rate with an increase in viscosity. In an early report, it was demonstrated that the rates of dissolution of zinc in hydrochloric acid solutions containing various concentrations of sucrose were inversely proportional to the viscosity (14).

Numerous equations have been proposed which show the dissolution rate to be a function of the viscosity raised to a power, where the exponent ranged from −0.25 to −0.8 (15–17). Over a range of 1–260
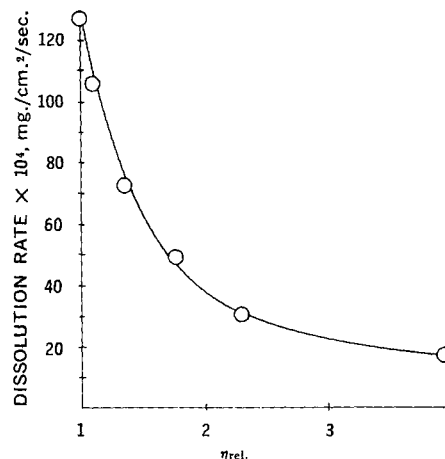

Figure 1—*Relationship of viscosity to dissolution rate of benzoic acid in aqueous sucrose solutions at 25°.*

cps. the dissolution rate of benzoic acid in methylcellulose solutions was found to be a function of the viscosity raised to the −0.5 power for 96% of the viscosity range studied (18).

In their study of the effect of high concentrations of surfactants on the dissolution of benzoic acid, Parrott and Sharma (19) found that (in concentrations exceeding the CMC) as the concentration of the surfactant was increased, the increase in dissolution rate became progressively less until a maximal dissolution rate was obtained; at higher concentrations, the dissolution rate was progressively decreased as the concentration of the surfactant was increased. Elworthy and Lipscomb (20) substantiated these results by reporting that at high concentrations of surfactants the viscosities of the dissolution medium were increased
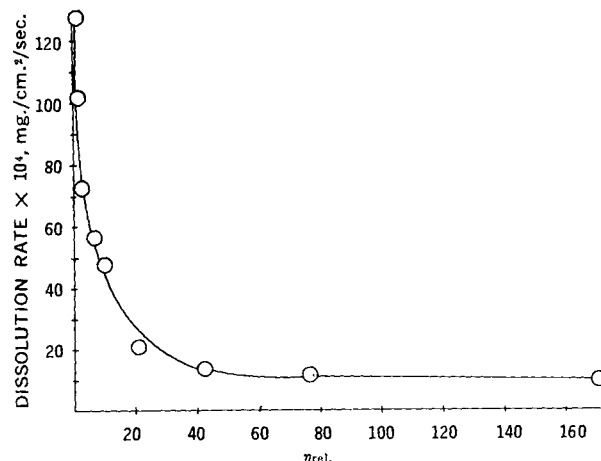

Figure 2—*Relationship of viscosity to dissolution rate of benzoic acid in aqueous methylcellulose solutions at 25°.*

Table I—Dissolution Rate (R) and Total Solubility (C_s) of Benzoic Acid in Aqueous Sucrose Solutions and Properties of the Solutions at 25°

Concentration, % w/v	Density, g./cm.^{3}	Relative Viscosity	C_s, mg./ml.	$10^4 R$, mg./cm.^{2}/sec.
0	0.997	1.00	3.42	127.16
10	1.033	1.10	3.33	105.80
20	1.075	1.35	3.27	72.62
30	1.112	1.77	3.28	49.82
40	1.150	2.29	3.18	30.77
50	1.186	3.95	3.10	17.18

Properties of Solution

markedly and slowed the dissolution rate of griseofulvin. In the mechanistic study of the influence of micelle solubilization on dissolution rate, Singh et al. (21) suggested that deviations from theory may be due to changes of viscosity as the concentration of polysorbate 80 is increased.

The Noyes–Whitney relation expresses the concept that an increase in solubility leads to an increase in dissolution rate. This study was undertaken to explore the relationship of dissolution rate to total solubility and viscosity. Another purpose of this study was to maintain the viscosity constant over a large range of surfactant concentration in order to determine if the Noyes–Whitney concept is valid when the factor of viscosity is considered.

EXPERIMENTAL

Dissolution Rate Determinations—The procedure for tablet production and the dissolution apparatus were similar to those previously described (9). Spherical 0.953-cm. diameter tablets of pure benzoic acid were used. All determinations were made at 25 ± 0.1° and at a stirrer speed of 324 r.p.m. The 2 l. of dissolution medium was changed at appropriate intervals, ranging from 30 to 120 min., so that the concentration of the dissolved benzoic acid was not permitted to exceed 3% of its solubility in the dissolution medium. With each change of dissolution medium, the tablet or sphere was weighed and its diameter was measured with a micrometer. Distilled water, aqueous 0.10–1.50% methylcellulose (1500 cps.) solutions, and aqueous 10.0–50.0% sucrose solutions were used as dissolution media. The dissolution rates were determined in these dissolution media which contained from 0 to 20% polysorbate 80. At each concentration of polysorbate 80, the dissolution rate was determined in triplicate, with the rates being within a 2% range.

Other Parameters—All determinations were made at 25°. Solubility measurements were made as reported earlier (19). The densities of the solutions were measured using a pycnometer. The vis-

Table II—Dissolution Rate (R) and Total Solubility (C_s) of Benzoic Acid in Aqueous Methylcellulose[a] Solutions and Properties of the Solutions at 25°

Concentration, % w/v	Density, g./cm.^{3}	Relative Viscosity	C_s, mg./ml.	$10^4 R$, mg./cm.^{2}/sec.
0	0.997	1.00	3.42	127.16
0.1	0.997	1.35	3.65	101.80
0.3	0.997	2.58	3.68	72.57
0.5	0.998	6.72	3.70	56.59
0.6	0.998	10.00	3.84	47.81
0.8	0.999	21.16	3.85	20.72
1.0	0.999	42.30	3.84	13.30
1.2	1.000	76.20	3.90	11.44
1.5	1.001	171.00	4.08	10.10

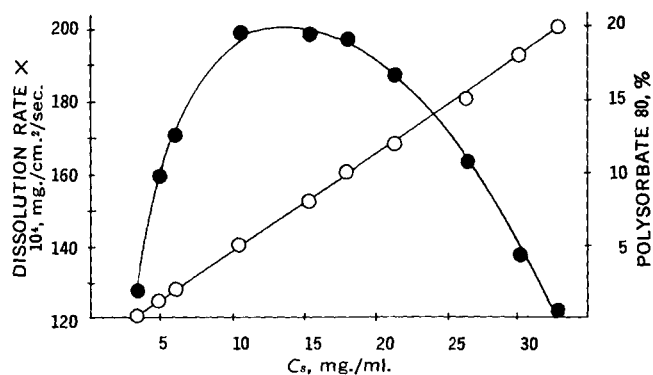*Properties of Solution*

[a] 1500 cps.

Figure 3—*Relationship of total solubility (C_s) of benzoic acid at 25° to dissolution rate and concentration of polysorbate 80. Key:* ●, *rate; and* ○, *concentration.*

cosities of the solutions were measured using an Ostwald-Fenske viscometer. Since dissolution rate and solubility in various dissolution media were studied in relation to their values in distilled water, relative viscosity is reported. The values of the relative viscosities were reproducible to within ±2%. The dissolution rates of benzoic acid were determined in various concentrations of polysorbate 80 at relative viscosities of 3.95 and 6.72, as adjusted by a trial-and-error method with sucrose and methylcellulose, respectively.

RESULTS AND DISCUSSION

Dissolution Rate and Viscosity—In the preliminary stage of this investigation, simple systems, in which various concentrations of sucrose and methylcellulose were used to obtain various viscosities, were used to demonstrate the influence of viscosity on dissolution rate of benzoic acid. The dissolution rate is inversely proportional to the viscosity, as shown in Figs. 1 and 2 for aqueous solutions to which sucrose and methylcellulose, respectively, were added to vary the viscosity. As shown in Table I, there is a slight decrease in the solubility of benzoic acid as the concentration of the sucrose is increased, because the quantity of water in a given volume of solution is decreased. The results of Wurster and Polli (18) are substantiated by the data in Table II and Fig. 2 for solutions of methylcellulose.

The addition of high concentrations of a surfactant increases the solubility of a poorly water-soluble compound and tends to increase the dissolution rate as a result of solubilization; however, in high concentrations, the surfactant increases the viscosity to the extent that the dissolution rate is slowed (19). Such a complex system was used to investigate the concomitant and individual effects of solubilization and viscosity on the dissolution rate of benzoic acid.

Dissolution Rates in Micellar Solutions—The total solubilities and dissolution rates of benzoic acid at 25° were determined in aqueous polysorbate 80 solutions ranging in concentration from 0 to 20%. As shown in Fig. 3, the total solubility of benzoic acid in aqueous polysorbate 80 solutions increases linearly with increasing concentration of the surfactant. According to the Noyes–Whitney equation, the dissolution rate is directly proportional to the total solubility. As shown in Fig. 3, as the total solubility is increased by the addition of polysorbate 80, the dissolution rate of benzoic acid
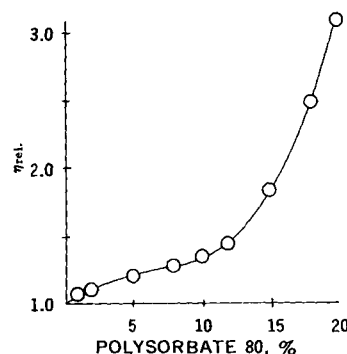

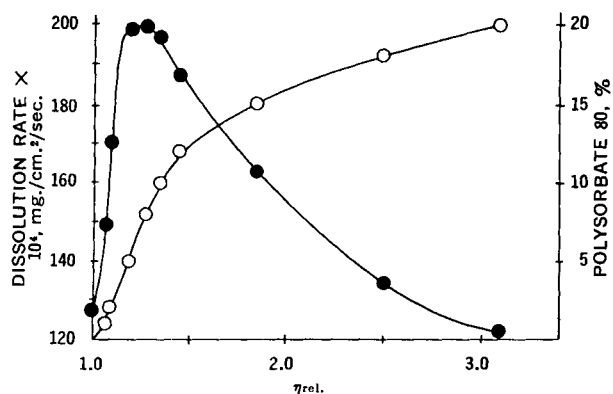**Figure 4**—*Relative viscosities of various solutions of polysorbate 80 at 25°.*

Figure 5—*Relationship of viscosity at 25° to the concentration of polysorbate 80 and the dissolution rate of benzoic acid. Key:* ●*, rate; and* ○*, concentration.*

is increased to a maximum dissolution rate, which is attained at a solubility corresponding to approximately 8% polysorbate 80. Although the addition of more than 8% polysorbate 80 increases the total solubility of benzoic acid, there is a decrease in the dissolution rate. For example, 20% polysorbate 80 produces a total solubility approximately 10 times as great as the solubility of benzoic acid in distilled water, but the dissolution rate is slightly less than the rate in distilled water.

Prior to this report, the effect of high concentrations of a surfactant on dissolution rate had not been reported in terms of factors other than solubility. As the concentration of the surfactant is increased, the viscosity of the liquid is increased and the dissolution rate is affected. As shown in Fig. 4, the viscosities of polysorbate 80 solutions increase gradually until a concentration of approximately 8% is reached. As the concentration of polysorbate 80 is increased more than 8%, there is a marked increase in viscosity. Thus, any influence on dissolution rate exerted by viscosity would be most pronounced in concentrations exceeding 8% polysorbate 80.

The relationship of relative viscosity (η_{rel}) to concentration of polysorbate 80 and to dissolution rate of benzoic acid is shown in Fig. 5. As the concentration of polysorbate 80 is increased initially, the dissolution rate is rapidly increased to a maximum value in approximately 8% polysorbate 80. Since the solubility of benzoic acid was demonstrated to be directly proportional to the concentration of surfactant, and the viscosity of the dissolution medium was not greatly increased by the addition of less than 8% polysorbate 80, the dissolution rate in solutions containing less than 8% polysorbate 80 is described by the Noyes–Whitney concept. In solutions containing more than 8% polysorbate 80, the viscosity increases greatly and decreases the mass transport in the solution, as demonstrated in Fig. 5 by a progressively diminishing dissolution rate as the concentration of polysorbate 80 is increased to 20%.

The relationship of the product of dissolution rate (R) and relative viscosity to the total solubility of benzoic acid in aqueous polysorbate 80 solutions is shown in Fig. 6. The sigmoidal shape of the curve may be rationalized on the basis of the rate of change of
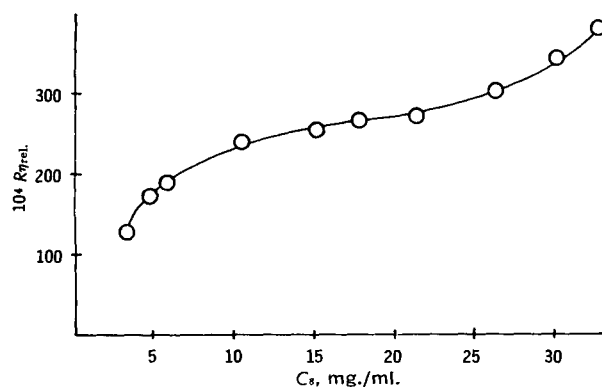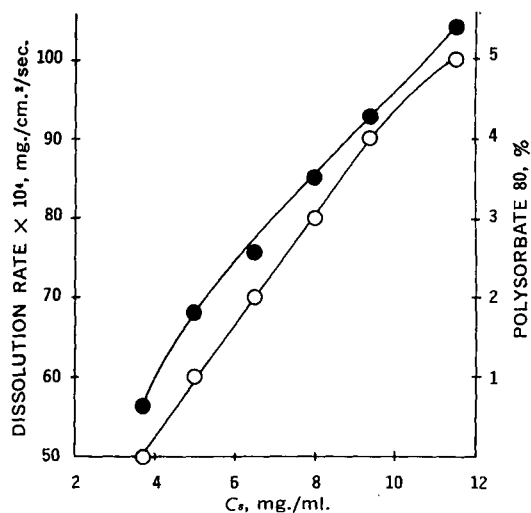

Figure 7—*Relationship of total solubility of benzoic acid at 25° to dissolution rate and the concentration of polysorbate 80 in aqueous solutions adjusted with methylcellulose to a relative viscosity of 6.72. Key:* ●*, rate; and* ○*, concentration.*

viscosity and solubility with the changing concentration of polysorbate 80. For a total solubility of 3.42–15.25 mg./ml., corresponding to 0–8% polysorbate 80, $R\eta_{rel}$ increases rapidly, because the rate of change of viscosity with changing concentration of polysorbate 80 is small and the change in total solubility primarily influences the dissolution rate.

In the solubility range of 15.25–21.35 mg./ml., corresponding to 8–12% polysorbate 80, the rate of change of solubility with changing concentration of polysorbate 80 remains constant (Fig. 3) and the rate of change of viscosity is not great. Consequently, $R\eta_{rel}$ is increased only slightly.

The dissolution rate decreases rapidly if the rate of change of viscosity with changing concentration of polysorbate 80 is great. At concentrations of polysorbate 80 greater than 12%, the rate of change of viscosity with changing concentration is much larger than at lower concentrations. As a result, the influence of viscosity
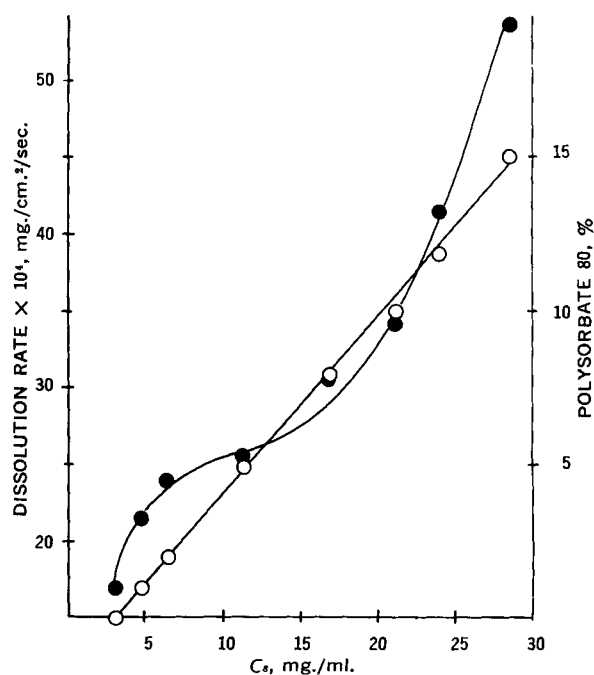

Figure 6—*Relationship of dissolution rate* (R)*, relative viscosity, and total solubility of benzoic acid at 25° in aqueous polysorbate 80 solutions.*

Figure 8—*Relationship of total solubility of benzoic acid at 25° 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.*
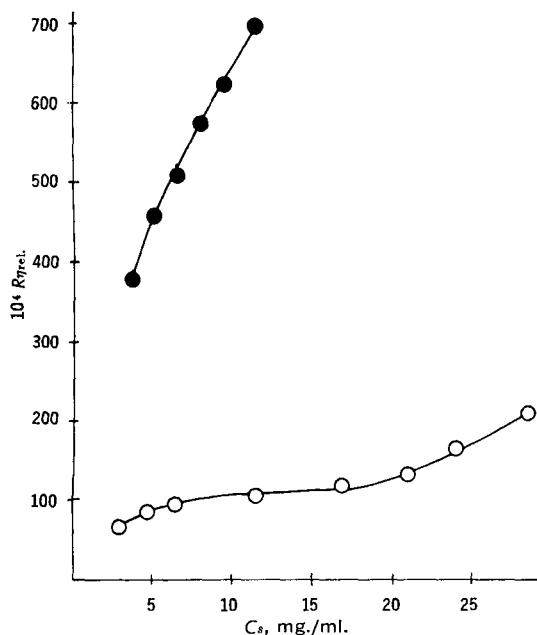
Figure 9—*Relationship of dissolution rate, relative viscosity, and total solubility of benzoic acid at 25° in aqueous polysorbate 80 solutions adjusted with sucrose and methylcellulose to a relative viscosity of 3.95 and 6.72, respectively. Key: $\bigcirc$, $\eta_{rel.}$ = 3.95; and $\bullet$, $\eta_{rel.}$ = 6.72.*

on dissolution rate is great compared to the effect of increased solubility, and the dissolution rate is decreased as shown in Fig. 3. As indicated by the greater slope of the curve in Fig. 6, viscosity is the dominant factor; the net result is an increase in $R\eta_{rel.}$ when the solubility exceeds 21.35 mg./ml., corresponding to 12% polysorbate 80.

Dissolution Rates in Micellar Solutions at Constant Viscosity— To characterize further the relationship of dissolution rate to solubility, dissolution rates were determined in various concentrations of polysorbate 80 solutions in which the factor of viscosity was constant. Methylcellulose was selected to adjust the viscosity to a constant value, because it is a nonionic and neutral substance which shows no interaction with benzoic acid (22). Since the relative viscosity of an aqueous 20% polysorbate 80 solution was 3.10, a series of aqueous solutions of polysorbate 80 was adjusted with methylcellulose to a relative viscosity of 6.72. The solubilities and dissolution rates of benzoic acid in this series are shown in Fig. 7. The dissolution rate of benzoic acid increases as the solubility is increased to 11.5 mg./ml. For the dissolution medium adjusted to a constant viscosity, the deviation from linearity is less than that shown in Fig. 3 for aqueous polysorbate 80 solutions with uncontrolled viscosity.

To confirm these results over a greater range of total solubility and concentration of polysorbate 80 and at another constant viscosity, the viscosity of the dissolution medium was adjusted by means of sucrose to a constant relative viscosity of 3.95. The solubilities and dissolution rates of benzoic acid in various concentrations of aqueous polysorbate 80 solutions maintained at relative viscosity of 3.95 are shown in Fig. 8. The relationship of dissolution rate to solubility is sigmoidal. The segments of the rate-solubility curves having a solubility less than 11.5 mg./ml. are similar for dissolution media maintained at constant viscosity with methylcellulose and sucrose. With solubilities of 11.5-28.5 mg./ml., corresponding to 5-15% polysorbate 80, the dissolution rate has an increase in its rate of change with changing solubility.

A comparison of Figs. 3 and 8 shows that the attainment of a maximum dissolution rate and the subsequent decrease in dissolution rate upon the further addition of a surfactant is caused by viscosity. When the viscosity is constant, the relation of the dis-

solution rate to total solubility is approximated by the Noyes–Whitney relation (Fig. 8). Thus, the Noyes–Whitney concept appears to be valid if additional factors influencing dissolution are properly considered.

In solutions adjusted to a constant viscosity by methylcellulose and sucrose and in solutions with uncontrolled viscosity, the solubility is increased linearly as the concentration of the surfactant is increased. Thus, the effect of polysorbate 80 on total solubility is independent of the viscosity.

The relationship between $R\eta_{rel.}$ and total solubility in aqueous polysorbate 80 solutions adjusted with methylcellulose to a relative viscosity of 6.72 is shown in Fig. 9. This plot is less curvilinear than the corresponding plot in Fig. 6 for solutions in which the viscosity is uncontrolled. A similar relationship is shown for solutions adjusted with sucrose to a relative viscosity of 3.95. The curve is sigmoidal, but the curvature is less than that observed in aqueous polysorbate 80 solutions of uncontrolled viscosity. The changes in curvature occur at approximately the same solubilities for dissolution media with constant and uncontrolled viscosity.

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