

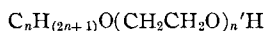
Solubilization of Benzoic Acid Derivatives by Polyoxyethylene Stearates

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A series of five hydrophilic surfactants, all polyoxyethylene stearates,¹ was used in aqueous solution to solubilize a group of solid benzoic acid derivatives. The concentration of solubilize rendered soluble was a linear function of surfactant concentration which is characteristic of solubilization of semipolar compounds. The critical micelle concentration of Myrj 59 was determined by two methods, and these data support the theory of micellar solubilization by nonionic surfactants. With a few exceptions, solubility was greater in the least hydrophilic surfactant solutions.

IN RECENT YEARS it has become quite common to employ nonionic surfactants as solubilizing agents for certain drugs. Although basic understanding regarding these phenomena is lacking, several reports have appeared regarding this type of solubilization. A nonalcoholic phenobarbital elixir has been prepared by using 2 to 5 per cent Tween 80 (1), and a parenteral solution of reserpine was stabilized using the same solubilizing agent (2). Numerous sources have pointed out the usefulness of nonionic surfactants for solubilizing vitamin A palmitate, vitamin A alcohol, vitamin D (3, 4), and volatile oils such as peppermint (5).

Correlation between the hydrophilicity of the nonionic surfactants and the chemical structure of solubilizates has not been investigated to any great extent. Cohen, using polyoxyethylene ethers of alkyl alcohols (6) as illustrated



found that if n was held constant, polar solubilizates dissolved better as n' increased (7). For a fixed n' , the solubility of hydrophobic substances increased as n increased (8, 9).

Moore and Bell (10) solubilized various perfumery compounds in a series of surfactants containing 10-60 units of ethylene oxide. They found the optimum amount of ethylene oxide content for maximum solubilization differed for the various solubilizates such as benzyl alcohol, phenylethyl alcohol, benzaldehyde, and others.

It can be seen from these studies that an optimum hydrophilic-lipophilic balance exists for solubilized compounds just as it does for emulsifiable oils. Therefore, this investigation was undertaken to relate the degree of solubilization of closely related solid solubilizates to the hydrophile-lipophile character of the surfactant.

A group of five polyoxyethylene stearates was chosen as the solubilizing agents. Since these surfactants were all of one chemical type differing only in ethylene oxide content, they served as an excellent series for comparing solubilization of related compounds as a function of hydrophile-lipophile balance.

EXPERIMENTAL

Materials and Reagents.—A series of five polyoxyethylene stearates (Myrj surfactants) listed in Table I; deionized-distilled water; hydrochloric acid, reagent grade; recrystallized benzoic, salicylic, *p*-aminobenzoic, and *p*-hydroxybenzoic acids; and recrystallized ethyl *p*-aminobenzoate, butyl *p*-aminobenzoate, methyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, and butyl *p*-hydroxybenzoate.

TABLE I.—SERIES OF POLYOXYETHYLENE STEARATES USED IN THE SOLUBILIZATION STUDIES

Surfactant	HLB
Myrj 49	15.0
Myrj 51	16.0
Myrj 52 ^a	16.9
Myrj 53	17.9
Myrj 59	18.8

^a Official in U. S. P. XVI as polyoxyl 40 stearate.

Instruments.—Beckman D U spectrophotometer, Cenco-du Nouy tensiometer, and a constant temperature shaking apparatus.

Solubilization Studies.—Since the presence of salts decreases the critical micelle concentration (cmc) (11) and, therefore, affects solubilization, the ionization of all solubilizates was suppressed by using hydrochloric acid solution, 0.005 *N*. This concentration of hydrochloric acid was found by experimentation over a range of concentration to be adequate. This acidic solution was used to prepare stock solutions of the Myrj surfactants and as a diluting agent for all spectrophotometric determinations.

The equilibration containers were one-half ounce screw-cap bottles. About 200 mg. of benzoic acid derivative was added to each of a series of bottles so as to provide an excess of solubilize in all samples. Various concentrations of Myrj stock solution and hydrochloric acid solution were pipetted into each bottle so that a range of surfactant concentrations was obtained. A blank containing

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¹ Myrj surfactants were supplied through the courtesy of Atlas Powder Co., Wilmington, Del.

only the solubilize and the hydrochloric acid solution was also prepared for each run. The samples were capped and sealed around the necks with a strip of water-resistant plastic tape. The samples were equilibrated in a shaking apparatus at a temperature of $25.0 \pm 0.1^\circ$ for a period of forty-six to fifty hours. This time was shown by preliminary experiments to be sufficient for equilibration. After equilibrium had been reached, aliquots were taken by means of a pipet fitted with a cotton filter. Sufficient dilutions were made so that the solutions could be read spectrophotometrically at the wavelength of maximum absorption for each solubilize. In all instances, the dilutions were large enough so that no absorption resulted from the presence of the Myrj compounds.

Determination of the cmc of Myrj 59.—Above a concentration of surface-active agent known as the critical micelle concentration (cmc), surfactant molecules form colloidal aggregates known as micelles. Two methods were employed to determine the cmc of Myrj 59 solutions. A solubility study was carried out in dilute Myrj 59 solutions. The method employed was the same as the solubility study previously discussed. A break in the solubility curve is indicative of micelle formation (12).

In order to corroborate the cmc determined by solubility equilibria, surface tensions of dilute Myrj 59 solutions were measured. The Cenco-du Nouy tensiometer was calibrated according to the conventional method (13), and the correction factor of Harkins and Jordan (14) was used to correct the observed readings. The cmc for Myrj 59 was found more precisely by saturating the surfactant solutions with benzoic acid. The sharp break occurring in the surface tension-concentration curve is again indicative of the cmc (12).

RESULTS AND DISCUSSION

Critical Micelle Concentration.—Figure 1 illustrates the solubility of benzoic acid in dilute Myrj 59 solutions. Up to a Myrj 59 concentration of about 0.1%, the solubility of benzoic acid is not increased. Above this concentration, benzoic acid is solubilized, presumably by the micellar aggregates of surfactant which form.

The surface tensions of Myrj 59 solutions are illustrated in Fig. 2A. The reduction in surface tension indicates the surfactant molecules are aggregating and forming micelles (12) until a practically constant limiting value is obtained. No cmc can be deduced from this curve. The curve representing the surface tensions of Myrj 59 saturated with benzoic acid (Fig. 2B), however, shows a sharp break at a surfactant concentration of 0.1%. The significance of this break is that the cmc has been reached and the solutions acquire new physical properties making them capable of solubilizing insoluble compounds (12). The agreement of a cmc of about 0.1% for Myrj 59 by both the solubility and surface tension measurements supports this fact.

Solubilization and Complexation.—It is a well established fact that carboxylic acids and phenols undergo complexation with surfactants of the polyether class (15, 16). Moreover, the present study indicates that micellar solubilization of benzoic

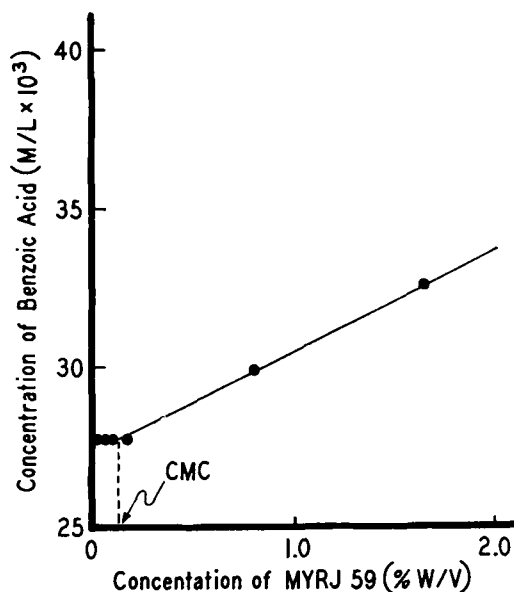


Fig. 1.—Solubility of benzoic acid at 25° illustrating one method of obtaining the critical micelle concentration (cmc).

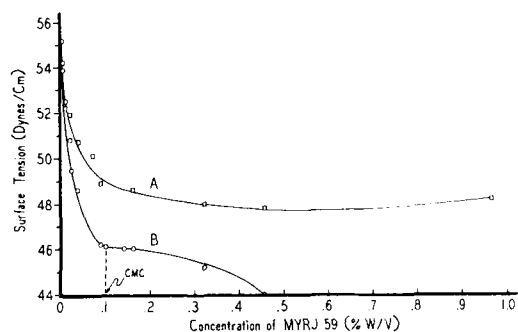


Fig. 2.—Surface tensions of Myrj 59 solutions at 23° illustrating cmc. A, In 0.005 *N* hydrochloric acid; B, in 0.005 *N* hydrochloric acid saturated with benzoic acid.

acid occurs in solutions of polyoxyethylene stearates above the cmc.

The colloid chemist has attributed increased solubility above the cmc to true or micellar solubilization. While Myrj surfactants do contain some free polyglycol (17), results obtained from measuring cmc indicate the principal mechanism of solubilization in this study is micellar solubilization. However, Patel and Kostenbauder (18) in their studies on the interaction of *p*-hydroxybenzoic acid esters with Tween 80 showed that a positive intercept on a Langmuir-type plot may be used to differentiate between complex formation and micellar solubilization.

Since complexation should be evident below the cmc where micellar solubilization is not a factor, and since no interaction was observed in this investigation by the solubilization method used, it is reasonable to conclude that complexation is insignificant in this study below the cmc. Whether

TABLE II.—MOLAR RATIOS OF SOLUBILIZATE TO SURFACTANT OBTAINED BY PLOTTING $(S - S_0)$ AGAINST ETHYLENE OXIDE CONCENTRATIONS (EQUIV./L.)^a

Solubilizate	Myrj 49	Myrj 51	Myrj 52	Myrj 53	Myrj 59
Benzoic acid	0.0670	0.0490	0.0440	0.0366	0.0259
<i>p</i> -Hydroxybenzoic acid	0.0669	0.0691	0.0655	0.0564	0.0512
<i>o</i> -Hydroxybenzoic acid	0.0643	0.0492	0.0397	0.0386	0.0223
<i>p</i> -Aminobenzoic acid	0.0484	0.0412	0.0450	0.0361	0.0264
Ethyl <i>p</i> -aminobenzoate	0.0395	0.0305	0.0277	0.0277	0.0135
Butyl <i>p</i> -aminobenzoate	0.0554	0.0386	0.0313	0.0249	0.0134
Methyl <i>p</i> -hydroxybenzoate	0.0495	0.0403	0.0359	0.0309	0.0183
Propyl <i>p</i> -hydroxybenzoate	0.0453	0.0318	0.0286	0.0228	0.0130

^a Percentages of ethylene oxide per surfactant molecules calculated from formula of Griffin (21). The percentages are: Myrj 49, 75.0% w/w; Myrj 51, 80.0% w/w; Myrj 52, 84.5% w/w; Myrj 53, 89.5% w/w; and Myrj 59, 94.0% w/w. Concentrations were corrected for water content.

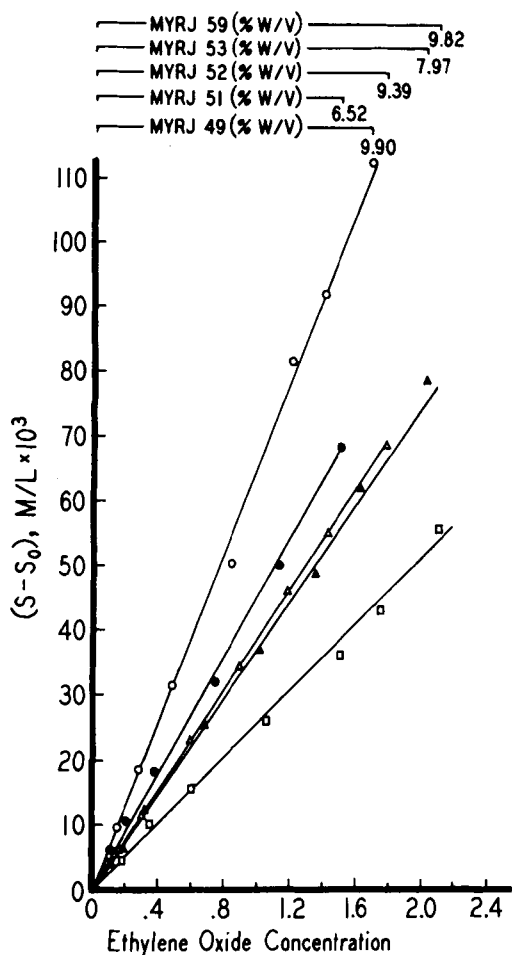


Fig. 3.—Solubilities of benzoic acid in Myrj solutions at 25°. O, Myrj 49; ●, Myrj 51; Δ, Myrj 52; ▲, Myrj 53; □ Myrj 59.

or not the two effects occur together above the cmc cannot be decided by the present experimental method.

Degree of Solubilization.—The quantity of solubilizate brought into solution by the surfactant was calculated by subtracting the solubility in the acidified water solution, S_0 , from the solubility, S , in the Myrj solutions. This quantity $(S - S_0)$ was plotted against the surfactant concentration in

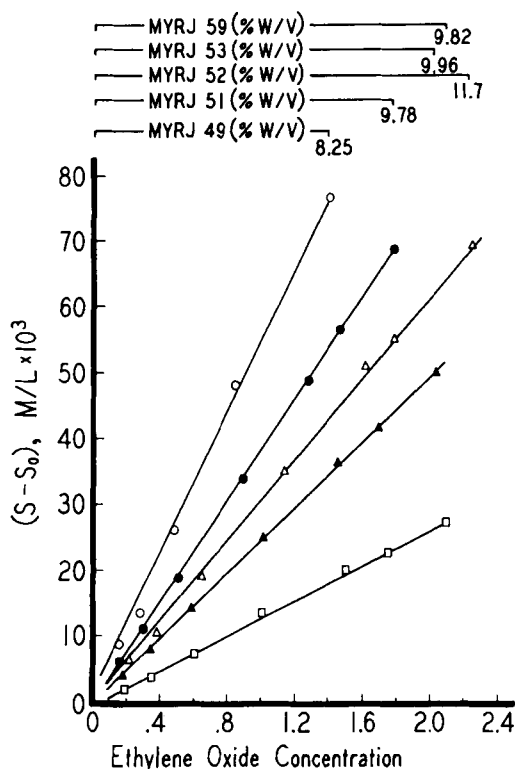


Fig. 4.—Solubilities of butyl *p*-aminobenzoate in Myrj solutions at 25°. O, Myrj 49; ●, Myrj 51; Δ, Myrj 52; ▲, Myrj 53; □, Myrj 59.

equivalents of ethylene oxide per L. on rectangular coordinate graph paper. Figures 3, 4, and 5 show the solubilization of benzoic acid, butyl *p*-aminobenzoate,² and propylparaben by the five surfactants studied. The results are typical of the solubilization curves obtained with all solubilizates. The linear relationships obtained with each of the five Myrj compounds correspond to results obtained by other workers using nonionic surfactants to solubilize semipolar molecules (18–20).

The moles of solubilizate per equivalent of ethylene oxide in the surfactant were obtained by calculating the slopes of the solubilization isotherms and are listed in Table II. From these data the

² Butesin is the trade name of Abbott Laboratories, North Chicago, Ill., for butyl *p*-aminobenzoate.

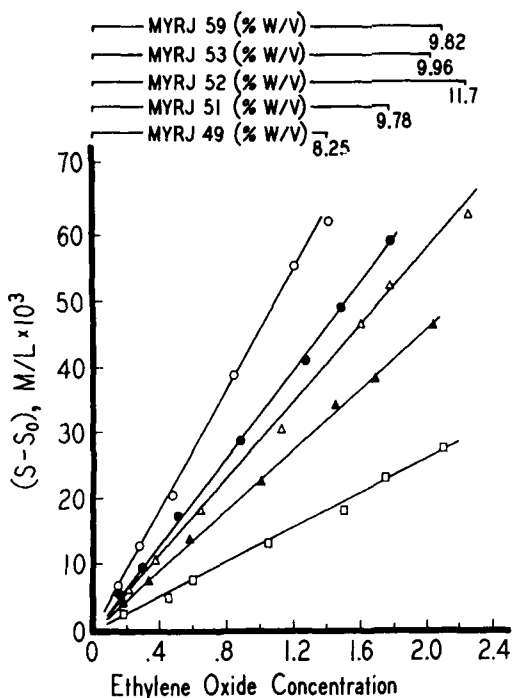


Fig. 5. —Solubilities of propylparaben in Myrj solutions at 25°. O, Myrj 49; ●, Myrj 51; △, Myrj 52; ▲, Myrj 53; □, Myrj 59.

quantity of solubilize brought into solution by a specific concentration of Myrj 49, 51, 52, 53, or 59 can be calculated. Since the solubility in the acidified water has been subtracted, the intercepts of these curves are zero.

If the moles of solubilize could be plotted against the moles per L. of surface-active agent, the slopes would be greatest for the most hydrophilic surfactant, i.e., the surfactant containing the longest polyoxyethylene chain. However, when molar solubilization is plotted against equivalents of ethylene oxide, the moles of solubilize taken into the micelle per individual ethylene oxide unit is measured. The slope of such a plot shows that the efficiency of solubilization in these terms decreases with increasing length of the polyoxyethylene chain, i.e., with increasing hydrophilicity or molecular weight.

Solubilization and Chemical Structure of the Solubilize.—The differences in the degree of solubilization for the various solubilizes can be compared on the basis of molar ratios. As shown in Table II, the molar ratios for benzoic, salicylic, and *p*-aminobenzoic acids were quite similar in all five surfactant solutions. However, *p*-hydroxybenzoic acid was solubilized to a significantly greater degree than these three acids. In general, the alkyl esters of *p*-hydroxybenzoic and *p*-aminobenzoic acids show a marked decrease in molar ratio when compared to the free acids. As a rule, all solubilizes have maximum solubilities in the least hydrophilic surfactant solutions and minimum solubilities in the most hydrophilic surfactant solutions when molar ethylene oxide concentrations are used as a criterion.

Solubilization Type.—Above the cmc, a solubilized compound is contained within the hydrocarbon layers of the surfactant or is adsorbed between the hydrophilic portions of the micelle known as the palisade layer (22). The solubilize may also be adsorbed on the surface of the micelle (23). Nonpolar compounds are solubilized in the hydrocarbon interior of the micelle as evidenced by an increase in long X-ray spacings, while polar solubilizes are solubilized in the palisade layers of the micelle and show no change or a decrease in X-ray spacings (24). Above the cmc, the molar ratio of a nonpolar solubilize to surfactant varies with the concentration of the solubilizing agent, while the molar ratio of a polar solubilize is constant (22, 23). Since the solubilizes employed in this work were partially polar and since constant molar ratios were obtained (Figs. 3, 4, and 5), it is reasonable to believe the principal interaction causing increased solubility is associated with the polyoxyethylene portion of the surfactant. A possible explanation is that of Beckett, *et al.* (16), which proposes some displacement of water molecules from the oxygen atoms in the glycol chain and the resultant attraction of phenol type compounds to the oxygen atoms.

Degree of Binding of *p*-Hydroxybenzoic Acid and Its Esters in Myrj Solutions.—Figure 6 illustrates the ratio of total to free methylparaben as a function of concentration of the five Myrj compounds studied. It has been pointed out that a plot of this type can be deduced from solubility data as well as dialysis studies (18). The inhibition of anti-

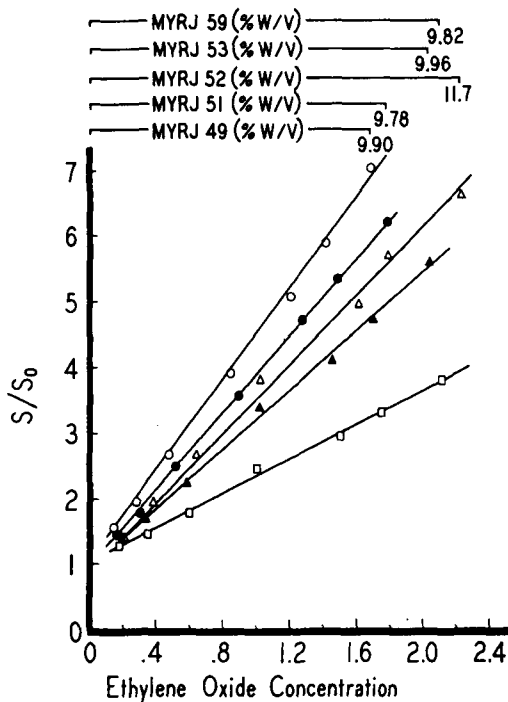


Fig. 6.—Binding of methylparaben in various Myrj solutions at 25° illustrating the ratio of bound to free paraben as a function of Myrj concentration. O, Myrj 49; ●, Myrj 51; △, Myrj 52; ▲, Myrj 53; □, Myrj 59.

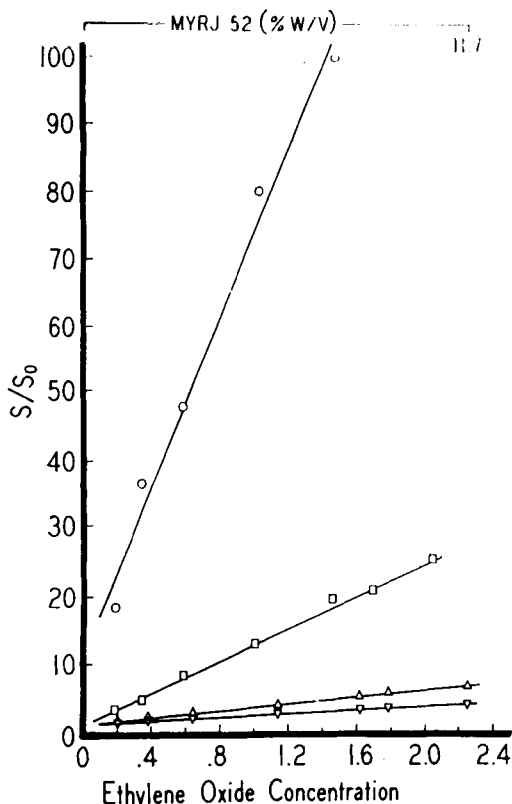


Fig. 7.—Binding of *p*-hydroxybenzoic acid and three of its alkyl esters in Myrj 52 solution at 25° illustrating the ratio of bound to free solubilize as a function of Myrj 52 concentration. ○, Butylparaben; □, propylparaben; △, methylparaben; ▽, *p*-hydroxybenzoic acid.

bacterial action by esters of *p*-hydroxybenzoic acid in the presence of nonionic surfactants has been well recognized by the pharmaceutical chemist (16). From graphs such as Fig. 6, the percentage of bound to free preservative can be calculated, thus giving the effective concentration of preservative employed (18, 25).

Figure 7 compares the binding of *p*-hydroxybenzoic acid and its butyl, propyl, and methyl esters in Myrj 52 solutions. It can be observed in Fig. 7 that an increase in the ester alkyl chain length enhances binding to Myrj 52. The binding is particularly pronounced for butylparaben which is 99% bound in a 7% Myrj 52 solution. Butylparaben, however, forms a milky white turbid

solution in high concentrations of Myrj 52. This phenomenon is not at all uncommon to solubilization by nonionic surfactants, but was not observed in any other system employed in this study.

SUMMARY

1. The relationship between the hydrophilicity of five polyoxyethylene stearates on the solubilization of a group of solid benzoic acid derivatives has been studied.

2. In general, the solubilities of the compounds studied were greatest in the least hydrophilic surfactant.

3. The linear solubility isotherms and the value of critical micelle concentration are characteristic of solubilization of semipolar compounds by nonionic surface-active agents.

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