Interaction of Substituted Benzoic Acids with Polysorbate 20 Micelles

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Abstract □ Equilibrium solubilities of a series of substituted benzoic acids in different concentrations of polysorbate 20 at controlled pH were measured. The maintenance of pH was achieved using a pH-stat assembly. A linear relationship was found between the amount of benzoic acid solubilized and surfactant concentration. As solubilizate polarity increased, the amount solubilized also increased. Solubility data were analyzed, and the interaction between solubilizate molecules and micelles was calculated in terms of partition coefficients of ionized and unionized molecules between aqueous and micellar phases. A linear relationship between π values (log partition coefficients) of functional groups and aqueous–micellar partition coefficient was found.

Keyphrases □ Benzoic acid and derivatives—solubilization in polysorbate 20 at controlled pH, partition coefficients between aqueous and micellar phases □ Polysorbate 20—effect on solubilization of benzoic acid and derivatives at controlled pH, partition coefficients between aqueous and micellar phases □ Micellar–aqueous partition coefficients—benzoic acid and derivatives in polysorbate 20 □ Solubilization, benzoic acid and derivatives—effect of various polysorbate 20 concentrations at controlled pH

There are various methods of studying solubilization including equilibrium dialysis, molecular sieving, potentiometry, and solubility measurement. Although they all have limitations (1), they have been used to provide useful data of micellar solubilization of benzoic acid derivatives (2–5) and barbiturates (6) by micelles of nonionic surfactants. None of the reports has given information of the interactions of the ionized and unionized solubilizate moieties with the surfactant. Such information can be obtained for weakly ionizing compounds from analysis of equilibrium solubility data in surfactant solutions at different pH values (7).

This report describes the solubilization of a series of substituted benzoic acids in polysorbate 20. Partition ratios of ionized and unionized molecules between aqueous and micellar phases were calculated, and correlations between these values and substituent parameters of the solubilizate were examined.

EXPERIMENTAL

Materials—Polysorbate 20 (polyoxyethylene 20 sorbitan monolaurate) was used as received. It was characterized by its mass spectrum and proton magnetic resonance spectrum (8) and found to contain 21 oxyethylene units/molecule.

Benzoic acid and its 2-hydroxy, 3-hydroxy, 4-hydroxy, 4-chloro, 4-bromo, 4-iodo, 4-nitro, and 4-methoxy derivatives[1] were used as solubilizates. They were chosen because they represent typical weak acids with low aqueous solubility and are capable of being absorbed from the stomach in an unionized form.

Assay—Benzoic acids were assayed by UV absorption spectroscopy. The presence of polysorbate 20 at the concentration in the diluted solutions did not interfere with the assay either by absorption at the wavelengths used or by shifting the absorption peak.

Solubility—An excess of benzoic acid or its derivatives was
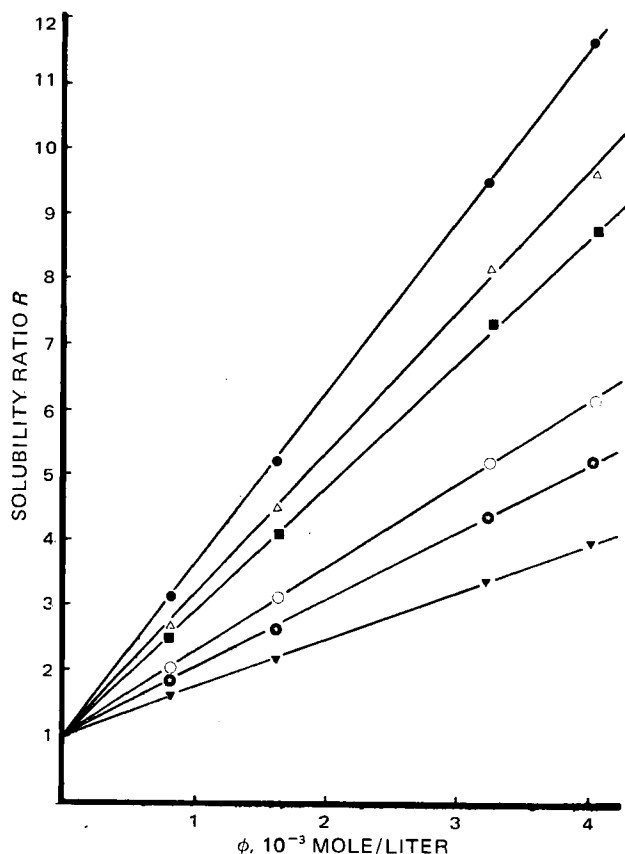

Figure 1—*Solubility of 4-chlorobenzoic acid in different concentrations of polysorbate 20 at different pH's. Key:* ●, 3.00; △, 3.40; ■, 3.62; ○, 4.00; ◐, 4.15; and ▼, 4.40.

added to 30-ml volumes of aqueous solutions containing different concentrations of polysorbate 20. The pH of the solution was adjusted by the addition of sufficient hydrochloric acid or sodium hydroxide. The volume of adjusting solution added was known, thereby permitting correction of polysorbate concentrations due to dilution. The pH was maintained by the addition of acid or alkali by the automatic control of a pH-stat assembly[2]. Solutions were stirred in a water-jacketed vessel at 25° during the initial pH adjustment.

After pH adjustment, the solutions were placed in 50-ml erlenmeyer flasks[3] and then shaken for 48 hr in a water bath at 25°; the pH was checked periodically. In the presence of surfactant, the addition of electrolytes not exceeding an ionic strength of 0.2 mole/liter had no effect on the solubility of the benzoic acids. This ionic strength is greater than that produced by the addition of hydrochloric acid or sodium hydroxide to control pH. After equilibration, aliquot samples were filtered through 0.45-μm filters[4] and assayed for benzoic acid content.

Density—Apparent densities of polysorbate 20 in 1, 2, 4, and 5% (w/v) aqueous solutions were determined at 25° using 50-ml density bottles.

Table I—Molar Ratios and Solubility Ratios of Benzoic Acid Derivatives to Polysorbate 20 Concentration at Various pH Values

Compound	(a)[a]	(b)[b]	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
Benzoic acid	pH 3.20		pH 3.60		pH 3.85		pH 4.20		pH 4.35		pH 4.55	
	0.120	0.397	0.121	0.342	0.124	0.282	0.126	0.205	0.124	0.160	0.131	0.118
2-Hydroxy-benzoic acid	pH 2.30		2.80		3.00		3.15		3.40		3.65	
	0.110	0.728	0.112	0.470	0.115	0.378	0.120	0.298	0.105	0.177	0.134	0.144
3-Hydroxy-benzoic acid	pH 3.10		3.45		3.70		4.00		4.25		4.45	
	0.164	0.163	0.162	0.221	0.175	0.208	0.172	0.150	0.209	0.130	0.190	0.084
4-Hydroxy-benzoic acid	pH 3.50		3.85		4.10		4.40		4.65			
	0.141	0.286	0.137	0.247	0.135	0.211	0.151	0.179	0.165	0.128		
4-Chloro-benzoic acid	pH 3.00		3.40		3.62		4.00		4.15		4.40	
	0.00918	2.568	0.00914	2.095	0.00945	1.880	0.00962	1.243	0.00996	1.029	0.01024	0.722
4-Bromo-benzoic acid	pH 3.00		3.40		3.60		3.90		4.20		4.40	
	0.00655	4.047	0.00647	3.480	0.00673	3.130	0.00672	2.327	0.00701	1.601	0.00711	1.101
4-Iodo-benzoic acid	pH 3.00		3.30		3.60		3.90		4.20		4.40	
	0.00568	6.291	0.00534	5.074	0.00650	4.656	0.00602	3.316	0.00583	2.444	0.00500	1.418
4-Nitro-benzoic acid	pH 2.45		2.80		3.05		3.40		3.60		3.80	
	0.00904	0.819	0.00943	0.749	0.00967	0.648	0.01038	0.531	0.00994	0.353	0.01062	0.257
4-Methoxy-benzoic acid	pH 3.50		3.80		4.10		4.40		4.70		5.00	
	0.113	0.601	0.111	0.542	0.115	0.474	0.123	0.366	0.122	0.225	0.118	0.160

[a] Column (a) represents the slope of solubility curves expressed in terms of molar ratios of solubilizate to polysorbate 20 concentration.
[b] Column (b) represents the slope of solubility ratios obtained from plots of R against ϕ.

RESULTS AND DISCUSSION

Solubilities of the substituted benzoic acids in solutions containing graded concentrations of polysorbate 20 were measured at different pH values between 0.5 pH unit above and 1.0 pH unit below the pKa of the substituted benzoic acids. Typical solubility curves of 4-chlorobenzoic acid in solutions of different concentrations of polysorbate 20 at different pH values are shown in Fig. 1. At any one pH, solubility increased linearly with surfactant concentration. This observation is in agreement with other reports (1–4) and is attributed to solubilization of the acid by micelles of the surfactants.

The slopes of solubility curves for substituted benzoic acids at different pH values in graded concentrations of surfactant are shown in Table I. In each case, a linear relationship was observed, as would be expected for the solubilization of polar solubilizates. For each compound, the slope of molar ratio of solubilizate to polysorbate 20 concentration was similar at all pH values. The slope of the curves for each compound increased with decreasing polarity. A similar observation, that the amount of substituted benzoic acid solubilized by a surfactant increased as the polarity of the drug increased, has been reported (6).

Increased solubilization may have resulted from the smaller size of the benzoic acids. Although the polarity of solubilizate molecules is usually the most important factor determining their degree of solubilization, the molar volume of solubilizate has also been considered to be a significant factor. The volume of various hydrocarbons solubilized by potassium laurate was found to be inversely related to the molar volume of hydrocarbons (9). Alternatively, there may be some solubilization within the polyoxyethylene chains, and increased solubilizate polarity will result in an increased amount of solubilization at this site.

A treatment of solubility data (7, 10) based on the pseudophase model of surfactant solutions permits the individual quantification of the interactions of both ionized and unionized solubilizate mole-

Table II—Partition Coefficient of Unionized Species and π (13) Values of the Respective Functional Group of Benzoic Acid Derivatives

Compound	Partition Coefficient of Unionized Moiety	π
Benzoic acid	43.5	0
2-Hydroxybenzoic acid	83.0	—
3-Hydroxybenzoic acid	28.5	−0.38
4-Hydroxybenzoic acid	30.8	−0.30
4-Chlorobenzoic acid	277.0	0.87
4-Bromobenzoic acid	445.0	0.98
4-Iodobenzoic acid	678.0	1.14
4-Nitrobenzoic acid	92.7	0.02
4-Methoxybenzoic acid	66.5	0.08

cules with surfactant. The concentration of solubilizate in the micellar phase is related to its concentration in the aqueous phase by:

$$P = \frac{(C_m)}{(C_a)} \tag{Eq. 1}$$

where C denotes concentration; subscripts a and m refer to aqueous and micellar phases, respectively; and P is the micellar–aqueous partition coefficient. If concentrations are expressed in terms of the total volume of the system rather than the volumes of individual phases, then:

$$P = \frac{(C_m)}{(C_a)}\left(\frac{1}{\phi}\right) \tag{Eq. 2}$$

where ϕ, the volume fraction of surfactant, is small (ϕ is the volume of the surfactant as a fraction of the total volume of the solution containing the surfactant).

The ratio, R, of solubility in surfactant to solubility in water is given by:

$$R = \frac{(C_m^-) + (C_m^0)}{(C_a^-) + (C_a^0)} + 1 \tag{Eq. 3}$$

where superscripts 0 and − denote unionized and ionized solubilizate, respectively. A plot of R against volume fraction, ϕ, of surfactant has an intercept on the R axis of unity. The slope, S, of the plot is:

$$S = \frac{(C_m^-) + (C_m^0)}{(C_a^-) + (C_a^0)}\left(\frac{1}{\phi}\right) \tag{Eq. 4}$$

Table I gives values of S obtained from plots of R against ϕ at several pH values. The slope, S, for any one compound decreases with an increase in pH. The higher solubilizing capacity of polysorbate 20 at pH values where the solute is predominantly unionized indicates that this form of the acid is solubilized to a greater extent than the ionized form.

Values of S at different pH's can be plotted against the fraction, fi, of ionized solubilizate present. At $fi = 1.0$, Eq. 4 becomes:

$$S = \frac{(C_m^-)}{(C_a^-)}\left(\frac{1}{\phi}\right) \tag{Eq. 5}$$

and the value of S at $fi = 1.0$ is the partition coefficient of ionized molecules between surfactant micelles and water.

The micellar–aqueous partition coefficients of unionized benzoic acid derivatives and their respective lipophilicity expressed in terms of the hydrophobic–lipophilic constant, π (13), of the functional groups are presented in Table II (π is defined as $\pi = \log P_X - \log P_H$, where P_X is the partition coefficient of a derivative and P_H is the partition coefficient of the parent compound).
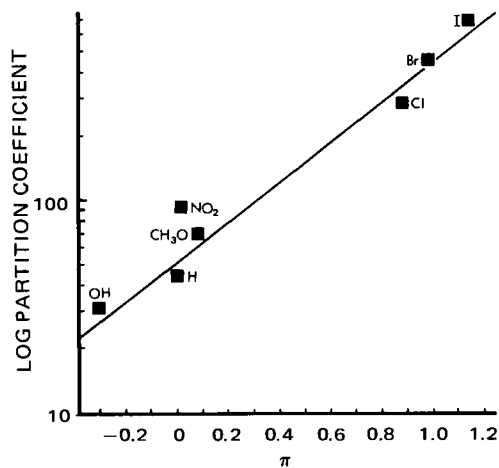
Figure 2—*Micellar–aqueous partition coefficients of substituted benzoic acids and π values of the functional groups.*

It can be seen in Fig. 2 that as the lipophilicity of the benzoic acid derivatives increases, the partition coefficient of the corresponding unionized molecules increases. 2-Hydroxybenzoic acid and 3-hydroxybenzoic acid are excluded from the plot because the hydroxy group is at positions other than the *para*-position; factors such as steric and electronic effects may contribute to the variations in their partition coefficient. The relationship between log partition coefficient and π is linear, with a slope of 0.885 and a correlation of 0.981.

The partition coefficient of 4-nitrobenzoic acid indicates a higher degree of solubilization than expected due to the negative inductive effect of the functional group, nitro, as compared with the positive effect of other groups (11), resulting in a greater interaction between the solubilizer and the solubilizate. When 4-nitrobenzoic acid is excluded, a better relationship can be obtained, with a slope value of 0.929 and a correlation of 0.994, indicative of a direct relationship between the micellar–aqueous partition coefficient of the unionized species and the π value of the substituent group. This relationship suggests that the unionized species is solubilized in a lipophilic region of the micelles.

Ismail *et al.* (6) reported an increase in the amount of substituted barbituric acids solubilized by polyoxyethylene stearates as solubilizate polarity decreased. The amount of each barbituric acid solubilized showed a rank-order correlation with their partition coefficients between 1-octanol and water. However, their work and that of Kakemi *et al.* (12) were limited to systems at pH 1.0.

The present data are particularly useful since, with a knowledge of micellar–aqueous partition coefficients of unionized parent compounds and of substituent π values, it is possible to calculate the amount of free drug present in micellar solution for other substituted derivatives. These calculations may find application in the interpretation of results from drug stability studies with micellar solutions and in drug absorption studies with micellar solutions.

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