Solubilization of Salicylic Acid by Polysorbate 80 as Determined by Solubility Titration

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A solubility titration has been used to study the solubilization of salicylic acid in water by polysorbate 80 since a liquid phase separates from supersaturated solutions to give a distinct turbidity end point. The ratio of solubilizate to solubilizer necessary for complete water-miscibility was also determined. The method should be of general applicability in studying phenols solubilized by polyoxyethylene surface-active agents. The effect on the system of including a fixed weight fraction of certain additives in the polysorbate 80 was investigated. The additives included a series of monohydroxy alcohols of decreasing dielectric constants, a group of polyhydroxy alcohols, polyethylene glycol 400, and Tween 20. Added monohydroxy alcohols increased or decreased the solubilizing power of polysorbate 80 in order of their polarity. Added polyhydroxy alcohols and polyethylene glycol 400 showed little effect. Added Tween 20 decreased the solubilizing power of polysorbate 80 in a linear fashion.

In the preparation of solubilized systems the formulator is faced with the problem of selecting the proper amount of solubilizing substance to prepare stable isotropic liquids for a specific purpose. Studies on micellular solubilization conducted near the critical micelle concentration of the surface-active agent are valuable in elucidating mechanisms of solubilization, but because they deal with low concentrations of both solubilizer and solubilizate they are of limited utility in designing a suitable formula where relatively large amounts of each may be required.

For a rapid means of determining the amount of solubilizer needed for a given solubilizate, titration with water has been recommended as a simple procedure (1–3). Results can be tabulated or plotted as a phase diagram from which the relative quantities of solubilizer and solubilizate can be determined for each situation. Titrations where the solubilizate is a liquid, such as a volatile oil, give good end points easily detected by formation of an opaque emulsion. The end point is not always readily discernible if the solubilizate is a solid, however. Guttman and Higuchi (4) have reported complex formation between a number of phenols and macromolecules including polyethylene glycols. Complexes separated as oily liquids. Mulley and Metcalf (5) studied the complex form between chloroxylenol and cetomacrogol, a surface-active polyethylene glycol ether, and observed a similar separation of an oily liquid. These observations suggested that a solubility titration procedure could be used to examine solubilization in water of the salicylic acid complex by polysorbate 80, and preliminary experiments showed the system to give a suitable turbidity end point. Practically, the solubilization of the polyethylene glycol derivative-salicylic acid complex reflects the solubilization of salicylic acid by polysorbate 80. Pharmaceutically the use of polysorbate 80 could be criticized since its ester linkage is susceptible to hydrolysis in aqueous salicylic acid solutions, but it served to illustrate the general applicability of the method and presented no problems in the short term experiments of this study.

This investigation revealed that there was a critical ratio of solubilizate to surface-active agent which gave maximum complete solubilization, namely, a ratio which was miscible with water in all proportions. Coles (6) has shown that glycerol could be used to lower the amount of polysorbate 80 needed to produce a water-miscible solution of vitamin A palmitate, and has studied the glycerol:polysorbate 80:vitamin A:-water system in some detail (8). It was decided, therefore, to examine the effect of some added alcohols and Tween 20 upon critical miscibility ratios of salicylic acid and polysorbate 80.

EXPERIMENTAL

Materials.—Commercial samples of polysorbate 80 and Tween 20 (Honeywill-Atlas Ltd., London, England) were used without purification. The same samples were used in all experiments. Salicylic acid B.P. was recrystallized from 70% ethanol, dried under vacuum, and reduced to a fine powder in an agate mortar. All monohydric alcohols were dehydrated, redistilled, and stored under anhydrous conditions. Ethylene glycol, propylene glycol, and glycerin were dehydrated by heating to 180°, cooled and stored in a desiccator charged with sulfuric acid. Polyethylene glycol 400 U.S.P. was used as supplied by Government Medical Stores, Singapore. Mixtures of polysorbate 80 and added substances were prepared by weight. Dehydrated glycerin was not miscible with polysorbate 80; there-

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fore the mixture was shaken vigorously to assure homogeneity just prior to withdrawing the sample.

Solubility Titration.—The method was adapted from that of O'Malley, *et al.* (1). Five-gram samples of the solubilizer were weighed into 50-ml. beakers containing a weighed quantity of salicylic acid and a magnetic stirring bar. Beakers were placed in a shallow water bath on the platform of a magnetic stirrer and stirred until complete solution resulted. The titration was carried out in an air-conditioned room and the water bath was maintained at 25 ±1° by the application of heat at irregular intervals. A strong light was used to illuminate the beaker during the addition of purified water from a buret mounted so that the tip was just above the surface of the stirring liquid. Turbidity which remained for 2 minutes was taken as the end point. Titrations were accomplished with polysorbate 80 alone and containing various additives listed in Table I.

At the turbidity end point the ratio of salicylic acid to polysorbate 80 and the per cent water by weight was calculated for each sample. The ratio was based upon only the polysorbate 80 present without the additive; thus it expressed the weight of salicylic acid solubilized in the presence of 1 Gm. of polysorbate 80 in the system studied. The solubility of salicylic acid at the concentrations examined in the system excluding the surface-active agent was not large enough to significantly affect the results. Figure 1 shows several titration curves for polysorbate 80 alone and containing 20% by weight of various alcohols. The 20% concentration was selected as being a convenient concentration showing a well-defined behavior by preliminary experiments.

Determination of the Critical Miscibility Ratio (CMR).—The ratio (salicylic acid:polysorbate 80) at which complete miscibility with water was observed was termed the "Critical Miscibility Ratio" (*CMR*). Ratios of salicylic acid to polysorbate 80 above the *CMR* would not form an isotropic system with all proportions of water and any ratio below the *CMR* would. Systems containing low concentrations of salicylic acid where its solubility in the dispersion medium significantly affects the ratio must be excluded from the definition. For salicylic acid the *CMR* was found applicable to solutions containing 5% or more of polysorbate 80 (*ca.* 0.75% salicylic acid). An indication of the probable *CMR* was obtained from the titration curve.

A more exact determination of the *CMR* was made by adding to the weighed solubilizing mixture known weights of salicylic acid calculated to give the desired ratio to three figures. Each sample was quantitatively transferred to 50-ml. ground glass-

TABLE I.—EFFECT OF VARIOUS ALCOHOLS ON THE CRITICAL MISCIBILITY RATIO (*CMR*) OF SALICYLIC ACID AND POLYSORBATE 80

Polysorbate 80 Containing	*CMR*, Salicylic Acid/ Polysorbate 80
No Additive	0.150
Methanol [33][a], 20%	0.150
Ethanol [24], 20%	0.150
iso-Propanol [20], 20%	0.145
n-Propanol [18], 20%	0.145
n-Butanol [17], 20%	0.140
Cyclohexanol [15], 20%	0.110
n-Pentanol [14], 20%	0.095
n-Hexanol [13], 20%	0.075
Ethylene glycol, 20%	0.150
Propylene glycol, 20%	0.150
Glycerol, 20%	0.150
Polyethylene glycol 400, 20%	0.150

[a] Approximate dielectric constants for monohydroxy alcohols (7) are given in brackets.

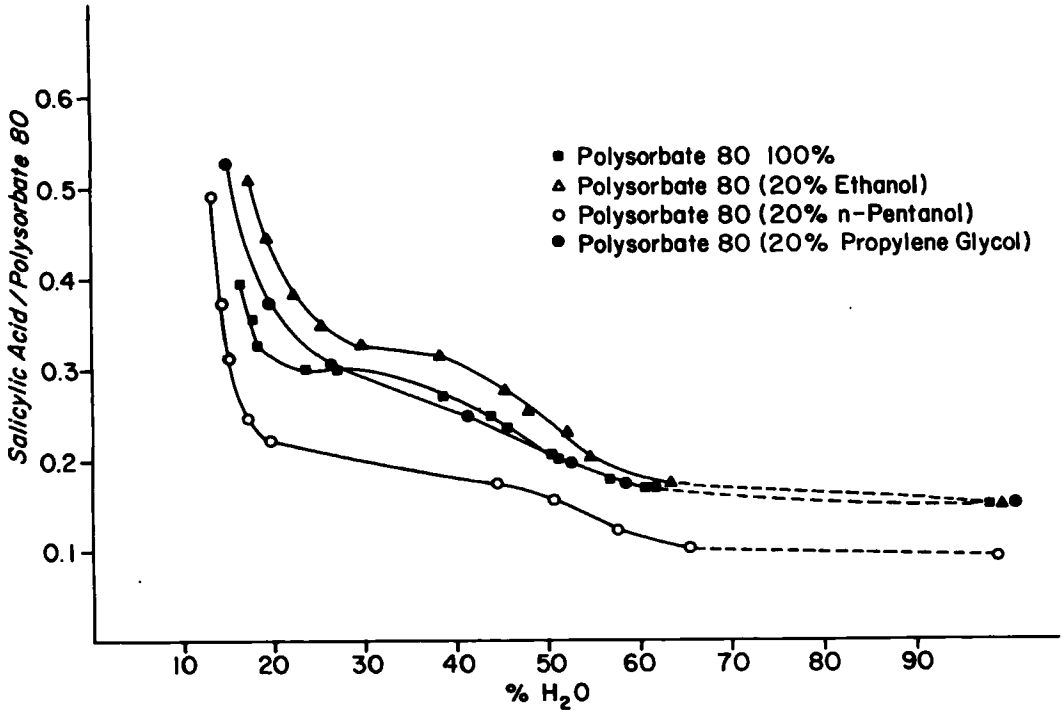

Fig. 1.—Titration curve for the system polysorbate 80 (with and without additives):salicylic acid:water.

TABLE II.—EFFECT OF TWEEN 20 ON THE CRITICAL MISCIBILITY RATIO (*CMR*) OF SALICYLIC ACID AND POLYSORBATE 80

Polysorbate 80 Containing	*CMR*, Salicylic Acid/ Polysorbate 80
No Additive	0.150
Tween 20, 20%	0.145
Tween 20, 40%	0.140
Tween 20, 60%	0.135
Tween 20, 80%	0.130
Tween 20, 100%	(0.130)

stoppered tubes with water and mixed. Each tube contained at least 90% water. The tubes containing the samples were suspended in a thermostatically controlled water bath at 25 ±0.1° for 24 hours. The tubes were then removed and turbidity was readily observable under a strong light. The highest ratio which showed no evidence of instability was taken as the *CMR*. Determinations were made in duplicate. Table I shows the effect on the *CMR* of various additives to polysorbate 80 and Table II shows the effect of mixtures of polysorbate 80 and Tween 20 on the *CMR*.

DISCUSSION

The titration curves of Fig. 1 are essentially phase diagrams. For systems containing percentages of water indicated, ratios of salicylic acid to polysorbate 80 above the line will not produce clear solutions; those below will. The titration curves can be used to calculate the amount of salicylic acid solubilized by a given weight of polysorbate 80 at known water concentrations and the reciprocal of the ratio can be used to calculate the amount of polysorbate 80 needed for a given weight of salicylic acid. The data may also be plotted as a three-component phase diagram if desired; however, as plotted for Fig. 1 the data are especially valuable to reflect comparative effects of added substances on solubilizing ability of polysorbate 80 for salicylic acid. Thus it is seen that ethanol assists considerably in the solubilization below 50% water but at high water concentrations it has little effect; propylene glycol has some power to increase solubilization at very low water concentrations but generally neither promotes nor inhibits the solubilization; *n*-pentanol generally depresses the solubilization.

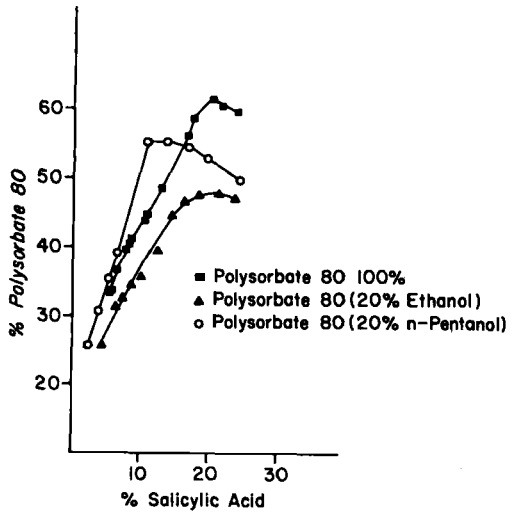

Fig. 2.—Titration data showing salicylic acid concentration at the turbidity end point as a function of polysorbate 80 concentration.

Another plot of the titration data in which the composition at the turbidity end point is used to determine the percentage of salicylic acid in the system as a function of the percentage of Tween 80 (all % by weight) is shown in Fig. 2. This shows in another fashion the solubilizing activity of polysorbate 80 and the maximum amount of salicylic acid which can be solubilized. The solubility of salicylic acid in the additives at the concentrations used does not significantly affect the plot. The solubilizing power of polysorbate 80 appears to follow increasing percentages until higher concentrations are reached. At higher concentrations the system becomes lipophilic in nature and the titration reflects the solubilization of water rather than salicylic acid. This explanation is borne out by the pronounced decrease in apparent solubilizing power shown with the less polar additives (*n*-pentanol curve, Fig. 2). These phenomena correlate well with Winsor's theory of intermicellular equilibria (9) which explains phase changes observed in proceeding from a lipophilic to a hydrophilic dispersion medium.

As the ratio of salicylic acid to polysorbate 80 is reduced, greater amounts of water can be tolerated by the system until a ratio is obtained which is completely water miscible. The highest ratio at which this occurs is termed the critical miscibility ratio (*CMR*). This ratio is not meaningful at very low salicylic acid concentrations approaching the limit of water solubility of salicylic acid; however it gives a good indication of the minimum amount of solubilizer needed for water-miscible combinations. Table I which records the *CMR* values for a series of added alcohols reveals that, although alcohols such as ethanol may assist in solubilization at the lower concentrations of water (Fig. 1), the effect disappears at the *CMR*. In the series of monohydric alcohols, the decrease in *CMR* follows their polarity, the decrease paralleling the decrease in dielectric constant. The constancy of the *CMR* for the polyhydric alcohols is remarkable in the light of the report by Coles (6) that glycerin markedly increases the solubilizing power of polysorbate 80 for vitamin A palmitate in the formulation of water-miscible vitamin A preparations. Possibly the different results observed in this study for salicylic acid could be due to its semipolar nature while vitamin A palmitate is of much lower polarity. For mixtures of polysorbate 80 and Tween 20 (Table II) the change in *CMR* parallels the relative concentration of the two micelle-forming agents.

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