

Comparison of the Solubilizing Capacities of Ionic and Nonionic Surfactants for Camphor

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The solubilizing capacities for camphor of one anionic, one cationic, and three nonionic surfactants have been investigated. The relative amounts of camphor solubilized were determined by measuring the areas under the ultraviolet absorption peaks. In solubilizing capacities the ionic agents, potassium laurate and dodecyltrimethylammonium chloride, were similar at low concentrations, but the anionic agent was superior at higher concentrations. The three nonionic agents, polysorbate 80, polysorbate 60, and polysorbate 40, were partially purified by ethyl acetate extraction before use. Their critical micelle concentrations were determined by a dye method to be 6.0×10^{-3} , 4.6×10^{-3} , and 5.5×10^{-3} Gm./100 ml., respectively. With increasing surfactant concentrations, the amount of camphor solubilized increased similarly but in differing degrees for each of the nonionic agents. Polysorbate 60 exhibited the greatest capacity and polysorbate 80 the least. Over the range of concentrations studied, the nonionic agents exhibited greater solubilizing capacities for camphor than the ionic agents when compared on a molar basis.

SURFACTANT solutions offer an attractive approach to problems involving the preparation of clear aqueous solutions of certain medicinal agents. Solubilized systems containing steroids (1), phenobarbital (2), iodine (3), and many other medicinals (4) have been investigated for pharmaceutical purposes. A formulator faced with a solubilizing problem is confronted with many choices regarding the nature and concentration of the surfactant, but his selection for a particular system remains largely empirical.

A number of reviews on the solubilization phenomenon have been published (5-8) and from these certain generalizations have been made. Above the critical micelle concentration (CMC) the amount of most substances solubilized appears to increase in direct proportion to the concentration of the surfactant. Among surfactants whose lipophilic character arises from the same fatty acid residue, cationic agents have been found more effective than anionic agents, and nonionic agents are the most effective. With nonionic surfactants, studies of related series can be conducted in which the lipophilic and hydrophilic portions of the molecule may be uniformly but independently varied. Within limits, higher solubilization capacities for polar solubilizates are thought to be favored by more hydrophilic surfactants, and higher solubilization capacities for solubilizates of low polarity by more lipophilic surfactants. Among nonionic agents of the same type and for the same solubilizate, solubilizing capacities have been found to vary directly with the ethylene oxide content of the surfactant polymer (9, 10).

This investigation reports an examination of the solubilizing capacities of various types of surfactants for a solubilizate which was of moderate molecular weight, slightly polar, and nonionizing. The solubilizate chosen was camphor, and the surfactants were potassium laurate, dodecyltrimethyl ammonium chloride (DTMAC), and polyoxyethylene 20 sorbitan monooleate, stearate, and palmitate (polysorbates).

EXPERIMENTAL

Solutions of potassium laurate were prepared by adding to a weighed amount of lauric acid (Eastman

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Organic Chemicals, white label). the equivalent amount of carbonate free 1.057 *N* potassium hydroxide plus 0.01 ml. in excess (11). The lauric acid contained less than 1% impurity, as estimated by gas chromatography. When recrystallized from ethanol, a sample of the potassium laurate melted at 274-276°. The CMC of potassium laurate has been reported as 2.34×10^{-2} *M* in aqueous solution (5, 8).

DTMAC was prepared by reacting *n*-dodecyltrimethylamine (K and K Laboratories) with methyl iodide and converting the quaternary iodide to the chloride by an ion exchange procedure with Amberlite IRA-400 anion exchange resin. The DTMAC was recrystallized from anhydrous acetone. Its molecular weight was determined by titration of the chloride ion in solution with standardized silver nitrate using fluorescein as an adsorption indicator (12) and was found to be 262.7 ± 3.7 (theoretical 263.9). The CMC of DTMAC has been reported as 2.28×10^{-2} *M* (13) and 2.16×10^{-2} *M* (14) in aqueous solution.

The nonionic surfactants chosen for study were a group of three commercial products of pharmaceutical interest: polysorbate 80,¹ polyoxyethylene 20 sorbitan monooleate; polysorbate 60,² polyoxyethylene 20 sorbitan monostearate; and polysorbate 40,³ polyoxyethylene 20 sorbitan monopalmitate. The commercial samples of the three nonionic agents were partially purified by partitioning between 5 *N* sodium chloride solution and ethyl acetate by the method of Weibull (15). Samples were dried over anhydrous sodium sulfate and stored in a desiccator until used. Removal of contaminating substances was followed by a modification of the technique of Nakagawa (16). Circular paper chromatography in a Petri dish revealed that the extraction procedure removed the pink spots of low *R_f* values (glycol impurities) and left only the yellowish orange spots of high *R_f* values (surfactants).

The CMC's were determined by measuring the differential absorbance of solutions containing varying concentrations of the surfactants in the presence of benzopurpurin 4B (17). The values for

¹ Marketed as Tween 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

² Marketed as Tween 60 by Atlas Chemical Industries, Inc., Wilmington, Del.

³ Marketed as Tween 40 by Atlas Chemical Industries, Inc., Wilmington, Del.

partially purified polysorbate 80, polysorbate 60, and polysorbate 40 were 6.0×10^{-3} , 4.6×10^{-3} , and 5.5×10^{-3} Gm./100 ml., respectively.

Saturated solutions of camphor were prepared by adding 80 mg. of camphor (purified by sublimation) to 10 ml. of the solvent in a 50-ml. conical flask. The flasks were shaken at room temperature for 24 to 36 hr. Preliminary experiments showed that saturation equilibrium was attained in 24 hr. Samples were then removed with a 10-ml. syringe and filtered into the absorption cell through a Swinney filter adapter containing a $0.45\text{-}\mu$ Millipore filter disk.

The ultraviolet absorption spectra of the solutions were determined with a Cary model 14 automatic recording spectrophotometer. Matched cylindrical silica absorption cells (10 and 1 mm. light path) were used, and the reference cell contained the appropriate surfactant solution. The base line for the reference was recorded for each measurement.

Due to the fact that the spectral maxima for the camphor solutions varied with the concentration of the surfactant, the measurements did not follow Beer's law. The area under the spectral curve, estimated by multiplying the height of the curve by its width at one-half the height, was found to give a direct relationship to the concentration of camphor. Camphor concentrations were expressed in arbitrary units of square centimeters. The observed solubility of each solution (S) was divided by the solubility in water (S_0) to give the relative solubility in the surfactant solutions.

RESULTS AND DISCUSSION

The relative solubility of camphor in potassium laurate and DTMAC solutions is shown in Fig. 1. The slopes of the solubilization *versus* surfactant concentration curves changed abruptly for both ionic surfactants. This type of discontinuity has been noted before in soap solutions and has been attributed to changes in micellar organization as the concentration increased. The surfactant has been said to achieve "full colloidal form" where the slope changes occur (5).

Comparison of the solubilizing capacities of the two types of surfactants does not bear out the generalization that cationic agents are better solubilizers than anionic (5, 8). At the lowest concentration examined, potassium laurate solution depressed the solubility of camphor slightly below that found for water. Above 0.075 M , potassium laurate solutions were better solubilizers of camphor than DTMAC solutions. Apparently a considerably different type of change in organization of the two micellar states occurred. An explanation of this unusual behavior must await more complete knowledge of micellar structure in the presence of a solubilize and the changes it undergoes with increasing surfactant concentration.

The relative solubility of camphor in the nonionic surfactant solutions up to 1% is shown in Fig. 2. Solubilization increased with increasing concentration of surfactant, as expected. Comparison of the capacities of the three nonionic agents, however, showed that polysorbate 80 was the least efficient as a solubilizer, polysorbate 40 next, and that polysorbate 60 was the most efficient.

This observation for polysorbates 40 and 60 agrees with the concept that larger micelles accom-

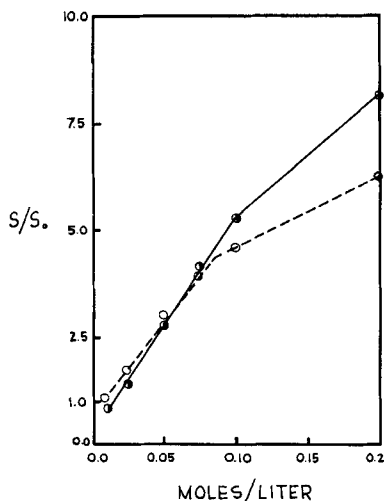


Fig. 1.—Relative solubility of camphor *vs.* the concentration of potassium laurate (●—●) and DTMAC (○—○) solutions.

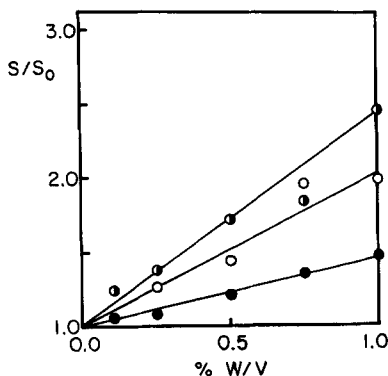


Fig. 2.—Relative solubility of camphor *vs.* the concentration of polysorbate 40 (○—○), polysorbate 60 (●—●), and polysorbate 80 (●—●).

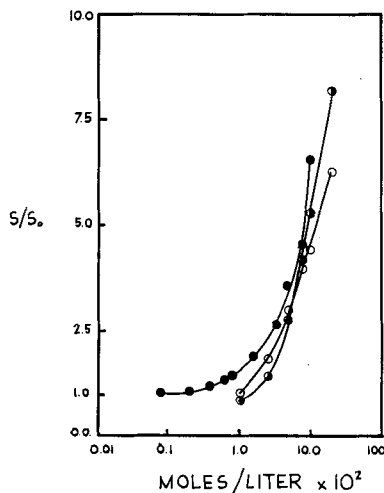


Fig. 3.—Relative solubility of camphor *vs.* the concentration of polysorbate 80 (●—●), potassium laurate (●—●), and DTMAC (○—○).

modate more solubilize (5), since the hydrophilic portions of the three nonionic agents are the same, and the micellar size is a function of the size of the lipophilic group (18). Polysorbate 80, as an oleate ester, is unique in the group. Its low solubilizing capacity may be related to its unsaturated lipophilic group (the oleate) which exists in the *cis* configuration and may have the steric effect of a much shorter alkyl chain.

The solubilization of camphor by the two ionic agents and polysorbate 80 is shown in Fig. 3. The surfactant concentrations were expressed on a logarithmic molar scale to allow comparison of the general surfactant types. The molar concentration of polysorbate 80 solutions was calculated from the theoretical molecular weight (1310) assuming 20 ethylene oxide units per molecule. Over the concentration range studied the solubilizing capacity of the nonionic agent (the least efficient of those used) was greater than for either ionic agent when the comparison was made on a molar basis. This observation agrees with prediction (5).

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Opium Alkaloids II. Isolation and Characterization of Codamine

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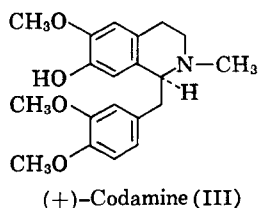
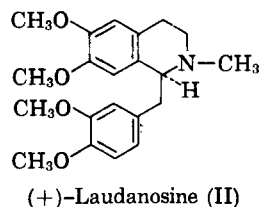
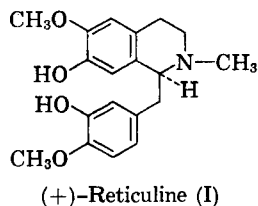
A minor phenolic alkaloid has been isolated from opium and characterized as (+)-codamine. Some of its physical and chemical properties are described. The alkaloid is of interest as a possible biogenetic intermediate between (+)-reticuline and (+)-laudanosine.

IN 1870, Hesse (1, 2) isolated a phenolic alkaloid from the opium mother liquors and named it codamine. He estimated that it constituted about 0.0033% of Turkish opium. Its structure was determined in 1926 by Späth and Epstein (3) on a sample from Hesse's collection. Racemic codamine has been synthesized by several investigators using different methods (4-6). However, all attempts to resolve this compound have been unsuccessful. Very little is known about the physical and chemical properties of naturally occurring codamine, and there is no evidence that it has ever been prepared since the work of Hesse almost 100 years ago. This alkaloid is of interest because of its structural relationship to (+)-reticuline (I) (7) and (+)-laudanosine (II), both of which are present in opium. In the course of studies of the minor phenolic opium alkaloids, the authors have isolated a base which has been characterized as (+)-codamine (III).

EXPERIMENTAL

Isolation.—The mother liquor from the purification of morphine¹ was extracted as described in previous communications (8, 9). After removal of

reticuline, the chloroform extract containing laudanine and other monophenolic and nonphenolic bases was subjected to preparative thin-layer chro-



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