

Effect of Oil Chain Length and Electrolytes on Water Solubilization in Alcohol-Free Pharmaceutical Microemulsions

A major area of interest in the pharmaceutical sciences is the solubilization of drugs having low aqueous and lipid solubilities. Presently, these types of drugs are solubilized or dispersed in macroemulsions such as creams or gels. While these systems have the ability to solubilize or disperse drugs, they are turbid, viscous, and thermodynamically unstable.

Microemulsions are thermodynamically stable, isotropic, low-viscosity dispersions consisting of microdomains of oil and/or water stabilized by an interfacial film of surface-active molecules. Such microemulsions contain droplets with dimensions in the range of 10–100 nm and, hence, appear transparent like a single-phase liquid (1). Because they are *isotropic* and *thermodynamically stable* with a large amount of interfacial area, microemulsions may be superior to macroemulsions for solubilization of drugs. Jayakrishnan *et al.* (2) have shown that a microemulsion can solubilize hydrocortisone, a

drug with low aqueous and lipid solubilities (3), in an isotropic solution to a concentration of 8.51 mg/ml. This microemulsion required two pharmaceutical emulsifiers and a short chain alcohol to form an isotropic dispersion. Most microemulsions require a short chain alcohol in their formulation. This is a disadvantage to a pharmaceutical microemulsion because it prohibits the use of the solution in the eye and sometimes internally. Furthermore, the evaporation of alcohol can destabilize the system. Gillberg *et al.* have formulated alcohol-free, water-in-oil microemulsions (4). However, the surfactants used in these microemulsions are not acceptable for pharmaceutical preparations. The present paper reports the formulation and properties of an alcohol-free microemulsion formulated with a medicinal surfactant AOT (5) and a pharmaceutical emulsifier, sorbitan monolaurate (Arlacel 20 or Span 20) (6, 7).

While this microemulsion system has direct applications

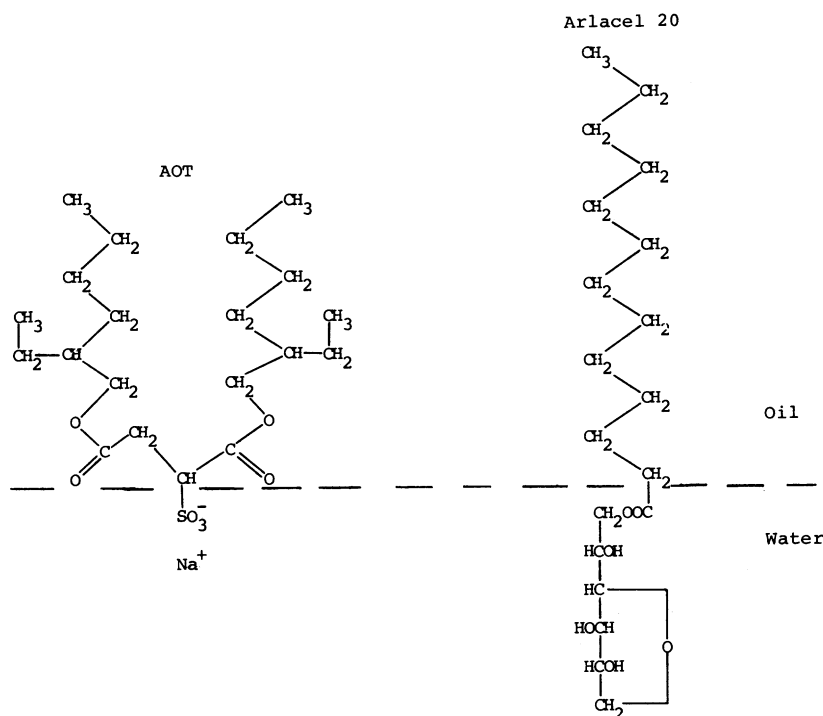


FIG. 1. Structures of AOT and Arlacel 20 and their assumed orientations at the oil/water interface of the microemulsion.

to the pharmaceutical sciences, the uses of alcohol-free microemulsions are quite diverse. For example, microemulsions can be used to simulate a cellular environment for enzymic reactions at interfaces. However, alcohol can denature proteins, so an alcohol-free microemulsion would be the ideal environment for studying such reactions. Furthermore, an alcohol-free microemulsion could be used for enhanced oil recovery processes where the use of volatile alcohols may be a fire hazard. It is important to note that such alcohol-free microemulsions may be useful in photochemical studies where the presence of short chain alcohols may be a disadvantage.

Microemulsions were prepared by mixing the surfactants in oil then titrating this solution with water or aqueous salt solution (brine) while stirring with a Teflon-coated magnetic bar. After each addition of water or brine, the solution was checked for clarity and then for birefringence by using crossed polarizing plates. The endpoint of the titration was the point where the solution became cloudy and/or birefringent. All oils were 99% pure. AOT was purchased from American Cyanamid, and Arlcel 20 was a gift from ICI Americas, Inc.

The structures of AOT and Arlcel 20 are shown in

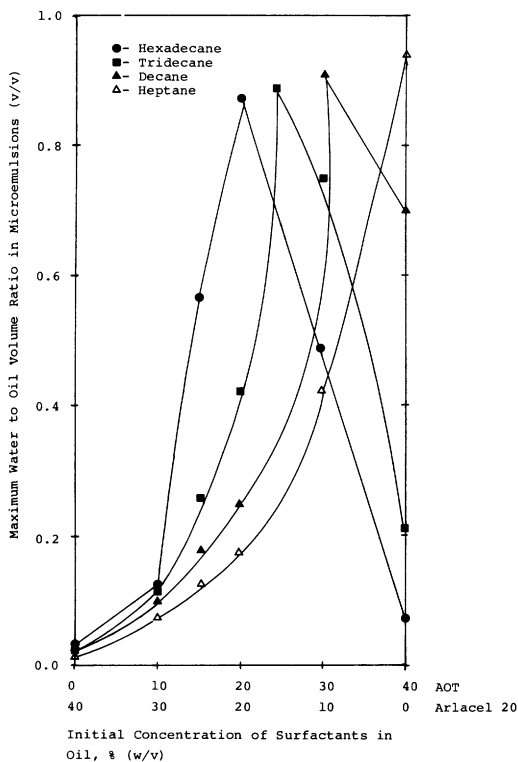


FIG. 2. Effect of oil chain length and surfactant weight ratio on the solubility of water in microemulsions. The system is clear and isotropic below the curve.

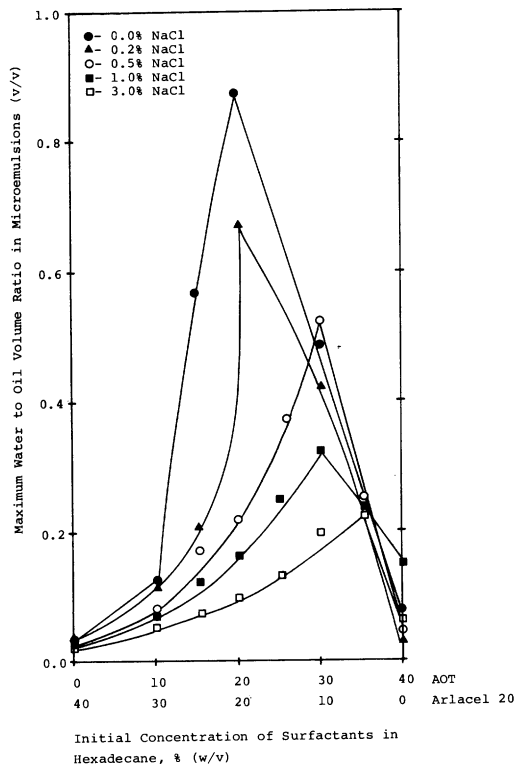


FIG. 3. Effect of sodium chloride concentration and surfactant weight ratio on the solubility of water in microemulsions. The system is clear and isotropic below the curve.

Fig. 1. It is evident that AOT has a highly branched lipophilic group while that of Arlcel 20 has a straight hydrocarbon chain. Also, the polar group of Arlcel 20 is a sugar while AOT has the sulfonate group.

Figure 2 shows the effect of oil chain length and surfactant weight ratio on the maximum solubilization of water in a clear, isotropic solution. With hexadecane as the oil, maximum water solubilization occurs when the surfactants are in a 1:1 weight ratio or 3:2 molar ratio of Arlcel 20 to AOT. At this composition, the molar ratio of water to surfactants is approximately 50. In contrast, the individual surfactants in hexadecane can only attain the maximum water to surfactant molar ratios of 2 and 5 for Arlcel 20 and AOT, respectively. Figure 2 also shows that the amount of anionic, branched chain surfactant (AOT) required to maximize the water solubilization reduces as the oil chain length increases. This behavior is presumably related to changes in the partitioning of the surfactants between the interface, the oil phase, and the aqueous phase of the microemulsion as the oil chain length is varied.

Many drugs are ionic in nature. Therefore, the effect

of salt on water solubilization was investigated. As the salinity of the water increases, the amount of water solubilized decreases as shown in Fig. 3. Also, the amount of AOT required to maximize the water-to-oil-volume ratio increases with increasing salinity. This observation can be explained by the salting out of the surfactants with increasing salt concentration (8).

In conclusion, it is possible to formulate an alcohol-free microemulsion using pharmaceutically acceptable, high molecular weight surfactants. Further work on the structural aspects as well as drug solubilization and delivery properties of such systems is in progress.

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