

and Florence (1983) provide a comprehensive reference for the use of surfactants in drug formulation development. The treatment by Florence (1981) of drug solubilization in surfactant systems is more focused on the question at hand and provides a clear description of surfactant behavior and solubilization in conventional hydrocarbon-based surfactants, especially nonionic surfactants. This chapter will discuss the conventional surfactant micelles in general as well as update the reader on recent practical/commercial solubilization applications utilizing surfactants. Other uses of surfactants as wetting agents, emulsifiers, and surface modifiers, and for other pharmaceutical applications are not emphasized. Readers can refer to other chapters in this book for details on these uses of surfactants. Polymeric surfactant micelles will be discussed in [Chapter 13](#), “Micellization and Drug Solubility Enhancement Part II: Polymeric Micelles.”

## CLASSIFICATION OF TRADITIONAL SURFACTANTS

Traditional or conventional surfactants are made up of two discrete regions: a hydrophobic portion often referred to as the *tail* and a hydrophilic *head* group. The hydrophobic portion of these surfactants is commonly made up of straight- or branched-hydrocarbon chains, which may include cyclic or aromatic moieties. The hydrocarbon tails are normally flexible, and when aggregated, present a fluid hydrocarbon environment for the solubilization of hydrophobic materials (Tanford, 1980). Surfactant molecules with less than ten alkyl groups tend to be inefficient as solubilizing agents and those with more than eighteen alkyl groups are generally too insoluble to be effective. Tails consisting of fluorocarbons and hydrofluorocarbons are also available; however, their toxicity precludes them from use in pharmaceutical formulations (Kissa, 1994). Surfactant structures other than the traditional head/tail arrangement also exist. For instance, bile salts have a less common planar structure where the steroidal backbone presents a hydrophobic face and the reverse face is hydrophilic (Small et al., 1969). For traditional surfactants, the chemical nature of the hydrophilic portion (head group) provides the most useful way of characterizing or classifying surfactants. This allows the division of surfactants into four groups: nonionic, anionic, cationic, and zwitterionic.

### NONIONIC SURFACTANTS

The head groups of these surfactant molecules contain no charged moieties, with their hydrophilic properties due to the presence of hydroxyl groups. Nonionic surfactants are most frequently used in pharmaceutical systems because of their compatibility with other formulation excipients, stability, and low toxicity. They can be divided into those that are water soluble and those that are water insoluble. Some examples of water-insoluble nonionic surfactants include long-chain fatty acid analogs such as fatty alcohols, glyceryl esters, and fatty acid esters. Fatty alcohols act as coemulsifiers in the presence of more hydrophilic amphiphiles, while glyceryl esters are mostly used in topical preparations. Fatty acid esters of, for example, cholesterol, sucrose, and sorbitan, find a wide range of applicability in pharmaceutical systems. These compounds may include unsaturated groups or aromatic moieties. To increase the water solubility of these compounds, polyoxyethylene (POE) groups are added through an ether linkage with one of the alcohol groups. Among the most widely used water-soluble surfactants are POE sorbitan fatty acid esters, which are commonly found in oral, parenteral, and topical pharmaceutical formulations.

### ANIONIC SURFACTANTS

The head groups of these surfactant molecules are negatively charged. The most widely used anionic surfactants are those containing carboxylate groups, such as soaps, sulfonate, and sulfate ions. Soaps, which are salts of weak carboxylic acids, are formed by the hydrolysis of fats (triglycerides) by sodium hydroxide. Sulfonates, such as sodium docusate and decane sulfonate, have been widely used in pharmaceutical systems. The most popular alkyl sulfate is sodium lauryl sulfate, which is