

studies was that the pH dependency of the tetracycline–PLE micelle interactions did not correlate with the octanol–water partition data. Octanol–water partition coefficients of a particular drug in model solvents/membranes are, in general, a useful predictor of mucosal absorption but cannot be used in a reliable manner to replace *in vivo* studies owing to other complex physicochemical and physiological factors that are involved during drug absorption (Nook et al., 1988; Alcorn et al., 1991, 1993).

Sheng et al. (2006) investigated the combined effect of pH and surfactant on the solubility and dissolution of ketoprofen. The solubility and dissolution rate enhancement were determined in buffers with pH range from 4.0 to 6.8 and sodium lauryl sulfate (SLS) concentration from 0% to 2.0%. It was found that the maximum solubility enhancement was approximately 232-fold whereas maximum dissolution amplification is only 54-fold because of the smaller diffusivity of micellar species. The authors further propose that the absorption of ketoprofen would be predominantly controlled by gastric emptying owing to the dramatic enhancement of solubility and rapid dissolution under *in vivo* condition similar to that of small intestine. This behavior is very similar to BCS I drugs, thus ketoprofen may be considered for possible waivers of bioequivalence. Similar results were reported in the literature (Granero et al., 2005; Joshi et al., 2006; Park et al., 2006).

### Electrolytes and Ionic Strength

For ionic surfactant micelles, electrolyte addition results in an increase in micellar size (aggregation number) and a decrease in the CMC. Decrease in the CMC value is due to a decrease of the electrical double layer, reducing the charge interactions, which favors micellization. Therefore, the addition of electrolytes or increasing the ionic strength in a solution can increase the micellar solubilization capacity when using ionic surfactants as solubilizers. In the case of nonionic surfactants, it is important to consider the location of the solute within the micelle when determining the effect of electrolyte addition on the solubilization of a particular drug by surfactant micelles. Thus, for solutes that are located deep within the micelle core, solubilization may be increased owing to the increase in micellar volume following electrolyte addition. On the other hand, reduction in repulsion between head groups on electrolyte addition can lead to a closer packing of surfactant molecules and potentially result in a decrease in the solubilization of polar compounds that are located in this region. For example, several alkylparabens in the presence of increasing amounts of sodium chloride show a decrease in the partition coefficient between SDS micelles and water (Goto et al., 1980). The reduction in the alkylparabens solubility was also attributed to changes in the shape of the micelles from spherical to ellipsoid, leading to a concomitant decrease in surface area and thus limited penetration of the solute. Electrolyte addition also leads to an increase in aggregation number or micellar weight as well as an increase in the solubilization capacity for nonpolar compounds. This increase in solubilization parallels the depression in the cloud point temperature. Although the solubilization of polar compounds by nonionic surfactants in the presence of electrolytes follows no clear pattern, increase in the micelle/water partition coefficients has been reported in the case of sodium 2-naphthalene sulfonate and polysorbate 80 micelles.

Shihab et al. (1979) determined the effects of electrolytes on the solubility of furosemide in 5% polysorbate 80 solutions. It was found that the CMC of the surfactant decreased and the micellar volume increased in the presence of electrolytes (Table 12.6). All the electrolytes used increased the solubilizing power of the surfactant at the concentrations employed.

Some carboxylate surfactants, such as long-chain fatty acids or their anionic esters with Coenzyme A, are precipitated in the presence of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  (Constantinides and Steim, 1986). Measurements of CMC in the presence of divalent ions should be avoided since the insoluble surfactant could introduce serious artifacts. Traces of transition-metal ions can catalyze autooxidation of some polyoxyethylene surfactants. In a recent article by Xiao (Xiao et al., 2006), interactions