the increase in the aqueous solubility of benzoic acid (Humphreys and Rhodes, 1968). The increase in K_m with increasing temperature was attributed to an increase in micellar size, as the cloud point temperature of the surfactant is approached (Humphreys and Rhodes, 1968).

pH

Many water-insoluble drugs are either weak bases or weak acids. There exists an equilibrium of ionized and unionized species for a weak base or a weak acid in an aqueous solution. The pH can affect the equilibrium between ionized and nonionized solute species, and consequently can have an effect on the capacity of micellar solubility. An example of this is the decreased uptake of 4-chlorobenzoic acid by polysorbate 80 micelles observed when the pH is changed from 3 to 4.4 (Collette and Koo, 1975). Another example regarding the effect of SDS micelles on the pK_a of atenolol, nadolol, midazolam, and nitrazepam is provided by Castro et al. (1998). Apparent acidity constants (pK_{app}) of the drugs were determined potentiometrically or spectrophotometrically in aqueous and SDS solutions at 25°C with 0.1 M NaCl. The concentration of SDS ranged from 5.0×10^{-4} to 2.0×10^{-2} M. The pK_{app} of a given compound is independent of the SDS concentration up to the CMC ($\sim 1.0 \times 10^{-3}$ M), but starts to decrease above this value. This behavior has been observed for many indicators, for which at least one form is cationic that interact with anionic micelles (Khaledi et al., 1990; Pal and Jana, 1996). In another case, for a pH-dependent drug cefpodoxime proxetil, a self-emulsifying system with <40% of surfactant was developed (Date and Nagarsenker, 2007), where the mean droplet size was not affected by the pH of the dilution medium. In general, stronger interactions with micelles cause larger shifts in the pK_a values (Khaledi et al., 1990). The pK_a of the β-blockers shifts approximately 0.5 log units and that of benzodiazepines changes approximately 1 log unit. As strong interactions of cationic species with anionic micelles drive the equilibrium from the protonated forms to the neutral forms of these substances, the values of pK_{app} thus increase. The results also suggest that the interactions of anionic micelles with protonated benzodiazepines are stronger than that with β-blockers.

An anionic surfactant is soluble only at a pH greater than the pK_a of its ionizable group, whereas a cationic surfactant (e.g., primary, secondary, or tertiary amines) is soluble only at a pH less than its pK_a. However, quaternary ammonium surfactants remain soluble at all pH values. Zwitterionic surfactants, for example, sulfobetaine surfactants, are neutral from pH 2 to 12, whereas some nonionic surfactants, for example, alkyldimethylamine oxides, are converted to cationic surfactants by protonation at acidic pH.

Shahjahan and Enever (1992) have determined the solubilization of nitrofurazone, uvinul D-50 (2,2′,4,4′-tetrahydroxy benzophenone), and uvinul N-35 (ethyl-2-cyano-3,3-diphenyl acrylate) in aqueous solutions of nonionic surfactants at various temperatures and pH values. They found that uvinul D-50 exhibits minimum solubility at pH 4, as shown by Figure 12.10, while nitrofurazone showed a decrease in solubility with increasing pH of the buffer solution (Figure 12.11). These results were interpreted in terms of a partition coefficient between the micellar and aqueous phases (K_m), which followed the order of uvinul N-35 > uvinul D-50 > nitrofurazone. In addition, K_m values increased with increasing oxyethylene chain length. The work by Ikeda et al. (1977) nicely illustrated the interactions between tetracycline antibiotics and anionic, cationic and nonionic surfactants as a function of pH. They studied the micellar interactions of drugs including tetracycline, oxytetracycline, chlortetracycline, and minocycline, and surfactants polyoxyethylene lauryl ether (PLE), sodium lauryl sulfate (SLS), and dodecyltrimethylammonium chloride (DTAC) at various pH values (2.1–5.6) using equilibrium dialysis. The tetracycline derivatives used in these studies existed in solution as zwitterions, positively charged and/or negatively charged species as a function of pH and therefore were expected to exhibit differences in their micellar interaction/binding in a given surfactant solution. The extent of these interactions was quantified by the corresponding partition coefficients (K_m) of the ionized and zwitterionic species. Table 12.5 shows the dependence of K_m on pH. K_m values for tetracycline, oxytetracycline, and chlortetracycline decreased as pH increased, while minocycline showed the opposite behavior. This indicates that