



FIGURE 13.9 Formation of core-cross-linked micelles by chemical reactions (a) and core-surface cross-linked micelles (SCNs) from amphiphilic brush polymers (b). (Reprinted with permission from Xu, P. et al., *Biomacromolecules*, 5, 1736–1744, 2004. Copyright 2004 American Chemical Society.)

forming short series of unimers linked at the junction of the amphiphilic blocks (Figure 13.9). The unimers were sufficiently short to be excluded renally, yet the CMC of the micelles decreased 10-fold over the unlinked micelles. This approach may avoid long-term accumulation of carrier and prevent the use of cross-linking agents in the presence of drug, reducing the likelihood of cross-linking agents and side products in the final formulation.

Effects of Solubilizes and Additives on Solubilization

As with traditional surfactants, additives may influence the onset of micellization of polymeric surfactants and thus affect solubilization. These additives can include inorganic salts and sugars used to adjust isotonicity and even the solubilize drug itself. In addition to micellization, these additives can influence the LCST or CP and even the structure of micelles formed.

Several factors affecting solubilization of aromatic solutes in triblock oxyalkylene copolymers (PEOn-*b*-PPOm-*b*-PEOn or PPOm-*b*-PEOn-*b*-PPOm) known to form micelles have been investigated (Gadelle et al., 1995). Solubilization isotherms of toluene, benzene, chlorobenzene, and *p*-xylene in various aqueous polymeric solutions were determined using headspace gas chromatography. The solute partition coefficient in the polymer was shown to have a strong dependence on the solute concentration for all polymers. The amount solubilized was at its highest for the high molecular weight hydrophobic polymers. For the less hydrophobic or lower molecular weight polymers, it was determined that solubilization capacity was a function of the polymer concentration. Comparisons between the different solute solubilization isotherms indicate that PPO-PEO, polymer–water, and polymer–solute interactions have a strong influence on aggregation and solubilization.

The effect of the medium composition or the loaded drug on the CMC may be difficult to predict. Zhang et al. (1996a) found that the incorporation of 10% paclitaxel into MePEO-*b*-PDLLA micelles did not cause the CMC to change significantly. Those authors also showed that the CMC of methoxy (Me) PEO-*b*-PDLLA (poly[*dl*-lactic acid]) micelles remained the same in water, 0.9% saline solution, and 5% dextrose solutions. This is not surprising considering the nonionic nature of the polymer.