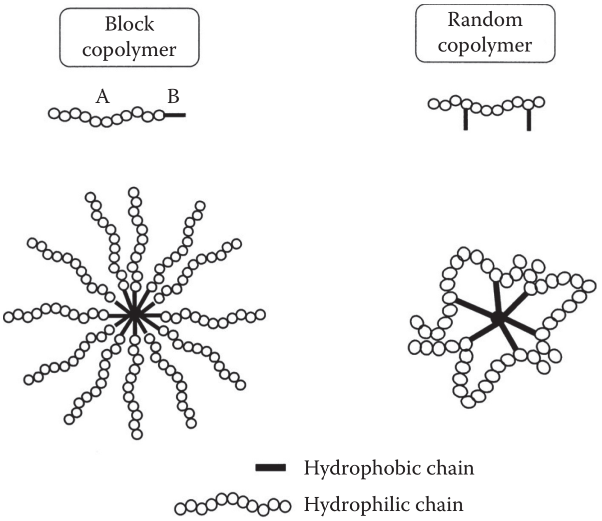

FIGURE 13.2 Schematic representation of block and random copolymer micelles. (Reprinted from *Eur. J. Pharm. Biopharm.*, 48, Jones, M.C. and Leroux, J.C., Polymeric micelles—A new generation of colloidal drug carries, 101–111, Copyright 1999, with permission from Elsevier.)

As summarized in Jones and Leroux's review article (1999), the use of non- or poorly biodegradable polymers such as polystyrene (PST) (Zhao et al., 1990; Zhang et al., 1995) or poly(methyl methacrylate) (PMMA) (Inoue et al., 1998) as constituents of the B block offer interesting properties such as a glassy state that confers remarkable stability to the micelle core. Though it must be pointed out that, to be considered clinically relevant drug carriers, nonbiodegradable polymers must be nontoxic and have a molecular weight sufficiently low to be excreted through the renal route (ca. less than 50,000 Da) (Seymour et al., 1987).

THERMODYNAMICS MICELLIZATION AND SOLUBILIZATION

Polymeric micelle formation occurs as a result of two forces. One is an attractive force that leads to the association of molecules, while the other one is a repulsive force, preventing unlimited growth of the micelles to a distinct macroscopic phase (Price, 1983; Astafieva et al., 1993; Jones and Leroux, 1999). Amphiphilic copolymers form micellar structures through self-association of the insoluble segments when placed in a solvent that is selective for the other monomer (Kataoka et al., 1993; Jones and Leroux, 1999). The process of micellization for amphiphilic copolymers is similar to the process described for conventional hydrocarbon chain-based surfactants as described in the first part of this chapter.

At very low concentrations, the polymers exist only as single chains. As the concentration increases to reach a critical value, called the critical micelle concentration (CMC), polymer chains start to associate to form micelles in such a way that the hydrophobic segment of the copolymer will avoid contact with the aqueous media in that the polymer is diluted. At the CMC, a significant amount of solvent may still be found inside the micellar core, and micelles are described as loose aggregates that exhibit larger size than micelles formed at higher concentrations (Gao and Eisenberg, 1993). At those higher concentrations, the equilibrium will favor tighter micelle formation; micelles will adopt their low-energy state configuration and the remaining solvent will gradually be released from the hydrophobic core resulting in a decrease in micellar size (Jones and Leroux, 1999). Two techniques for the formation of micelles, flash nanoprecipitation (Johnson and Prud'homme, 2003a, b) and azeotropic dialysis (Jette et al., 2004), replace a miscible organic solvent with water to derive micellization of amphiphilic block copolymers.