

PHYSICAL ENTRAPMENT

Mechanical Dispersion Methods

In the mechanical dispersion methods, insoluble drugs and the copolymers can be dissolved in an organic solvent or a blend of solvents followed by evaporation of the solvent through a rotary evaporator for small-scale preparation, that is, thin-film method, or an explosion-proof spray dryer for larger-scale production. After drying, hydration, and micelle formation, the drug-copolymer complex can be carried out by addition of an aqueous solution with agitation. This method is most successful with block copolymers that have a relatively large hydrophilic fraction, and ultrasonification may assist formation of the micelles.

This process was used to prepare diblock copolymer micelle carriers of paclitaxel (Zhang, 1996b). In this case, the drug and the copolymer were dissolved in acetonitrile (ACN) followed by evaporation of the solvent under a stream of nitrogen at 60°C for about 2 h to obtain a solid paclitaxel/PDLLA-*b*-MePEG matrix. Residual ACN remaining in the taxol/copolymer matrix was determined by gas chromatographic analysis using flame ionization detection. Dissolution of the solid paclitaxel/copolymer matrix was carried out by preheating the matrix in a warm water bath (about 60°C) to obtain a transparent gel-like sample. This was followed by the addition of water at about 60°C and stirring by a vortex mixer or a glass rod to obtain a clear micellar solution.

Dialysis Method

The dialysis method consists of replacing a water-miscible solvent in which the drug and copolymer are both soluble (e.g., ethanol, *N,N*-dimethylformamide (DMF), ACN) with a solvent that is selective only for the hydrophilic part of the polymer (e.g., water). As the good solvent is replaced by the selective one, the hydrophobic portion of the polymer associates to form the micellar core incorporating the insoluble drug in the process. Extending the dialysis over several days helps ensure the complete removal of the organic solvent (Jones and Leroux, 1999).

The initial solvent used to prepare micelles by dialysis in water drastically affects the stability of the polymeric micelles. For example, PEO-*b*-PBLA micelles prepared by dialysis using DMF have a relatively large average diameter with a considerable amount of secondary aggregation (Kataoka et al., 1993). La et al. (1996) used the dialysis method to prepare PEO-*b*-PBLA micelles from several solvents. In their experiment, 100 mg of PEO-*b*-PBLA block copolymer was dissolved in 20 mL each of DMF, ACN, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), *N,N*-dimethylacetamide (DMAc), and ethyl alcohol, respectively, and stirred overnight at room temperature. Then, the block copolymer solution was dialyzed against distilled water using molecular porous dialysis tubing (molecular weight cutoff (MWCO) 12,000–14,000), followed by lyophilization. The yield of PEO-*b*-PBLA micelles from dialysis against water using the DMAc solution was 87% w/w. The average particle size, based on the number distribution of the micelles, was estimated to be ca. 19 nm. The secondary aggregates were less than 0.01% of the total amount and have a diameter of 115 nm. In addition, the PEO-*b*-PBLA micelles generated by using DMAc as an initial solvent had a narrow size distribution compared with other samples.

Cosolvent Evaporation Method

The cosolvent evaporation method consists of dissolving the drug and block copolymer in a volatile water-miscible organic solvent, for example, ACN, THF, acetone, or methanol. Water is added gradually pushing the self-assembly of the hydrophobic blocks into micelles (Figure 13.20). The organic cosolvent is then removed by evaporation (Jette et al., 2004; Shuai et al., 2004; Aliabadi et al., 2005b).

Jette et al. (2004) investigated the assembly of PEG-*b*-PCL micelles formed by addition of water to an ACN unimer solution, using DLS and ¹H-NMR. At the critical water content (CWC) between 10% and 30% water, depending on the PCL block size, micelle assembly was observed by DLS. Initial micelle structures were swollen having a diameter ranging from 200 to 800 nm, but when