

Micelles are colloidal dispersions that form spontaneously, under certain concentrations, from amphiphilic or surface-active agents (surfactants), molecules of which consist of two distinct regions with opposite affinities toward a given solvent such as water (Torchilin, 2007). Micelles form when the concentration of these amphiphiles is above the critical micelle concentration (CMC). They consist of an inner core of assembled hydrophobic segments and an outer hydrophilic shell serving as a stabilizing interface between the hydrophobic core and the external aqueous environment. Micelles solubilize molecules of poorly soluble nonpolar pharmaceuticals within the micelle core, while polar molecules could be adsorbed on the micelle surface, and substances with intermediate polarity distributed along surfactant molecules in intermediate positions.

The total solubility of a drug in an aqueous surfactant solution can be described as

$$S_t = S_w + k(C_s - C_{cmc})$$

where k is the solubilizing capacity of micelles, C_s is the surfactant concentration, and C_{cmc} is the CMC of the surfactant. Usually, k increases with increase of the alkyl chain length, if the guest drugs are localized deep in the micelles (Kawakami et al., 2004).

Surfactant micelles form only above their CMC, and rapidly break apart on dilution, which can result in premature leakage of the drug and its precipitation *in situ*. Polymeric micelles are generally much more stable than surfactant micelles, exhibiting lower CMCs, slower rates of dissociation, and longer retention of loaded drugs (Kataoka et al., 1993; Francis et al., 2004; Gillies and Frechet, 2004).

Common surfactants used in micellar formulation are either amphoteric (e.g., Lecithin), nonionic (e.g., Tween-80, Cremophor EL, Solutol HS 15, TPGS), block copolymers (e.g., poloxamers), or ionic (e.g., sodium lauryl sulfate). The amphiphilic polyethoxylated castor oil derivative Cremophor EL is one of the most frequently used surface-active formulation ingredients in parenteral dosage forms. The surfactant is comparatively well tolerated on intravenous injection and has a high solubilizing potential for poorly water-soluble compounds. The plasma pharmacokinetics of Cremophor EL have been summarized by van Zuylen et al. (2001). Tween-80 (polyoxyethylene sorbitan monooleate) is another nonionic surfactant that is used as an ingredient in intravenous formulations of sparingly water-soluble compounds, such as lipophilic anticancer drugs. As with Cremophor EL, above its critical micelle concentration, Tween-80 exhibits micellar structures, potentially interacting with coadministered compounds (Shokri et al., 2001). In addition, Tween-80 modulates multidrug resistance *in vitro*, and is an even more potent *P*-glycoprotein (*P*-gp) inhibitor than Cremophor EL (Mountfield et al., 2000). An additional example of a surfactant that is tolerated intravenously at reasonably high concentration is Solutol HS 15, the main component of which is the PEG-660 ester of 12-hydroxystearate. Solutol HS 15 has a high solubilizing potential for a variety of different compounds (Bittner and Mountfield, 2002), but there is a lack of data on its pharmacokinetic profile in the literature. α -tocopherol polyethylene glycol 1000 succinate (TPGS) has been recognized as an effective oral absorption enhancer for improving the bioavailability of poorly absorbed drugs and as a vehicle for lipid-based drug delivery. TPGS is a potent inhibitor of an active efflux even at concentrations 10-fold below the CMC, suggesting that monomeric TPGS is capable of inhibiting the efflux mechanism. Therefore, TPGS improves *in vivo* performance not only by solubility-enhancing micelle formation but also by increasing the overall intestinal permeability via inhibiting an efflux mechanism (Wu and Hopkins, 1999). Overall, surface-active formulation ingredients may be suitable for preventing precipitation of coinjected, poorly water-soluble compounds.

The micelle formulation approach often possesses disadvantages such as its toxicity associated with surfactants even at relatively low concentrations. In general, nonionic surfactants have the least toxic effects. Cremophor EL produces hypersensitivity reactions in human and