animals (Jonkman-de Vries et al., 1996). Tween-80 is also believed to cause acute hepatitis and renal failure (Uchegbu and Florence, 1996). On intravenous administration, owing to their surface activity, surfactant molecules have the potential to penetrate and disrupt biological membranes and can be hemolytic (Ten Tije et al., 2003). Often the absorption capacity of the micelle is too small and the extent of the solubilizing effect is too low. Therefore, frequently high surfactant concentrations are necessary, so that the liquid one-phase area is left under the formation of liquid-crystalline systems with high viscosity. Surfactants may also change the pharmacokinetic behaviors of coadministrated compounds, which is mainly due to the delayed drug release because of the thermodynamic stability of the associated micelles. However, the many advantages of micellar formulations uniquely positioned them as one of the most useful drug delivery systems.

The combination of micelle with either cosolvent or complexation in formulation has been studied on a number of occasions. In general, this combination did not provide significant synergetic effects on solubilizing water-insoluble compounds, and the effects were dependent on the type and concentration of surfactants, complexing agents, and individual cosolvents. A mathematical model was developed to provide the quantitative basis for the combined use of surfactants and CDs (Rao et al., 2006). The addition of cosolvent modified the interaction between surfactant molecules as well as solution properties. In their study on the effect of the combination of Gelucire 44/14 (a semi-solid waxy material with 20% mono-, di-, and triglycerides, 72% mono- and di-fatty acid esters of PED 1500 adn 8% free PEG 1500) and cosolvent on the solubilization of Indomethacin and Phenytoin, Kawakami et al. (2004) found that the combined use offered only little advantage on solubility. Similar results were also observed for the combination of sodium dodecyl sulfate (SDS), Tween-80, and cosolvents (Kawakami et al., 2006).

Emulsions and Microemulsions

Unlike micelles, an emulsion is a liquid system in which one liquid is dispersed in a second, immiscible liquid, usually in droplets, with emulsifiers added to stabilize the dispersed system. Conventional emulsions possess droplet diameters of more than 200 nm, and are therefore optically opaque or milky. Conventional emulsions are thermodynamically unstable, tending to reduce their total free energy by reducing the total area of the two-phase interface. In contrast, microemulsions with droplet diameters less than 100 nm are optically clear and thermodynamically stable. Unlike conventional emulsions that require the input of a substantial amount of energy, microemulsions are easy to prepare and form spontaneously on mixing, with little or no mechanical energy applied (Lawrence and Rees, 2000).

Emulsions are either oil phase dispersed in water phase, an oil-in-water (o/w) emulsion, or water phase dispersed in oil phase, a water-in-oil (w/o) emulsion. If a poorly water-soluble drug substance is soluble in oil, it can be solubilized in an emulsion where it partitions into the oil phase. The total solubility in an emulsion, S_t, is the summation of concentrations in the aqueous and oil phases (Strickley, 2004). The total solubility of the emulsion system is the sum of the drug concentration in the aqueous phase, S_w, and the concentration in the oil phase, which can be approximated by the product of the drug's solubility in the pure oil, S_{oil}, multiplied by the fraction of the oil in the emulsion, f_{oil}:

$$S_t = S_w + S_{oil} f_{oil}$$

Therefore, for compounds with good oil solubility, emulsion-based systems, especially lipid-based vehicles, can be used successfully.

Commercially available parenteral lipid emulsions, such as fat emulsion Intralipid®, usually contain 10%–20% oil phase, composed of long- or medium-chain fatty acids, lecithin, and glycerol.