TABLE 9.2
Examples of Solubilization Techniques and Limitations

Technique	Examples	Commercial Products (Radwan 1994)	Potential Drawbacks
Aqueous solution (physiological pH and osmolality)	Normal saline (0.9% NaCl)	pH 2–10 bolus	Precipitation
		pH 2–10 infusion (preferred pH range 4–9)	Pain
Cosolvent	Propylene glycol	≤68% bolus, ≤6% infusion	Precipitation
	Ethanol	≤20% bolus, ≤10% infusion	Pain/irritation
	PEG 300	≤50% bolus	Hemolysis
	PEG 400	≤9% bolus	Impact on PK properties
Surfactant	Cremophor EL	≤10% infusion	Precipitation
	Tween 80	≤4% bolus, ≤2% infusion	Pain/irritation
	Solutol HS 15	50%	Hemolysis
			Impact on PK properties
Complexing agent	HPBCD	20% Infusion	Precipitation
			Pain/irritation
			Hemolysis
Dispersed systems	Water + 10%–20% oil	(Lecithin + glycerol +	Impact on PK Profile
Emulsion/microemulsion (Darwish 1995, 1997)	Water + 5–20 mg/mL phospholipids	fatty acid) + buffer + isotonicifier + cholesterol	Sustained Release Instability
Liposome	Water with stabilizer	Not yet marketed (Oner 1995)	Slow dissolution
Nanosuspension			

are significant. Oner et al. (1995) determined that intravenous lorazepam formulations containing water miscible cosolvents were ten times more hemolytic than emulsion formulations. Al-Suwayeh et al. (1996) found that liposomal encapsulation of loxapine produced significantly less myotoxicity compared to the commercially available formulation containing propylene glycol and polysorbate 80. Stella et al. (1995a) determined that intramuscular injection of prednisolone in cosolvent mixtures produced significantly higher creatine kinase levels than when solubilized by SBE4-β-cyclodextrin, which was comparable to normal saline. Further work by this same team showed no change in pharmacokinetic parameters when methylprednisolone was injected intravenously as a cosolvent solution versus solubilized by SBE4-β-cyclodextrin, indicating that the drug was rapidly and quantitatively released from the cyclodextrin inclusion complex (Stella et al. 1995b). Table 9.2 shows the various techniques and the typical limitations one could potentially encounter.

COMMERCIAL INJECTABLE FORMULATIONS

When pH adjustment alone is not sufficient to achieve the desired level of solubility of a drug through parenteral route, a cosolvent approach using miscible organic solvent or a surfactant is the choice of method. Commonly used water miscible solvents and surfactants for parenteral formulations are propylene glycol 300 and 400, *N*-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), Solutol HS 15, and cremophors and polysorbates. Frequently, commercial formulations are formulated at much higher concentrations and diluted further at the point of care owing to various issues discussed previously. Table 9.3 lists the commercially available list of solubilized parenteral products in an alphabetical order (Strickley 2004).