Table 6-4 LD_{50} and Advantages and Disadvantages of the Major Injectable Co-Solvents Used in Commercial Sterile Product Formulations

Co-Solvent	LD_{50} (IV dose in mice)	Advantages and uses	Disadvantages
Ethanol	1.97 g/kg	High solvent power	Can be painful
Glycerin	4/25 g/kg	Popular with insulin and other protein products	Low solvent power compared to others
Polyethylene glycol 400	8.6 g/kg	Stable, low irritation	Viscous, can contain peroxide impurities
Propylene glycol	6.63 g/kg	Stable, wide usage	Moderate solvent power compared to ethanol

Source: From Ref. 6.

time to dilute the drug. Also, all co-solvents have hemolytic effects on red blood cells that can be minimized simply by minimizing the amount of co-solvent administered.

If the co-solvent approach either is unsuccessful or not preferable, then the next formulation approach to increase drug solubility is the use of solubilizing solute additives such as complexing agents or surface-active agents. Some drugs will interact with certain additives to form more soluble complexes. Such additives typically are polymeric amphiphilic molecules, a listing of which is given in Table 6-5. The most commonly used surface-active agents from a safety standpoint for injectables are the nonionic polyoxyethylene fatty acids (Polysorbates or Tweens). The most commonly used complexing agent in recent years has been Captisol®. The chemical structures of Captisol® and Polysorbate 80 are shown in Figures 6-2 and 6-3, respectively, where the amphiphilic nature of both solubilizing agents can be seen.

Complexing agents increase the solubility of drugs anywhere from 2- to 10-fold, but they are not as powerful as co-solvents. In Figure 6-4 it can be seen that nonionic hydroxypropyl beta cyclodextrin (α form contains six glucopyranose rings, β form contains seven rings, and the γ form contains eight rings) and anionic sulfobutylether beta cyclodextrin (Captisol) increases the solubility of the same steroid as was shown in Figure 6-1 for co-solvent solubilization. However, comparison of the ordinates of the two figures shows that the solubilization effect of the cyclodextrins on the drug is linear while the solubilization effect of the co-solvents was logarithmic.

Examples of marketed injectable products containing cyclodextrins as solubilizing agents include Sporanox® (hydroxypropyl-beta-cyclodextrin) and Vfend®, Geodon®, and Zeldox® (sulfobutylether-beta-cyclodextrin). Hydroxypropyl-beta-cyclodextrins suffer from potential renal toxicity problems while sulfobutylether beta cyclodextrin does not accumulate and is more easily eliminated by the renal system.

Surface-active agents will solubilize drugs via micellar solubilization where the drug molecule is "encapsulated" with the hydrophobic core of the agent. A primary use of surface-active agents in the biopharmaceutical product development arena is to help stabilize large molecules from aggregating due to hydrophobic interactions at liquid–air and liquid–solid

Table 6-5 Examples of Added Solute Substances Used In Commercial Sterile Dosage Forms To Increase Injectable Drug Solubility

Hydroxypropyl-beta-cyclodextrin
Sulfobutylether-beta-cyclodextrin (Captisol®)
Polyvinylpyrrolidone (PVP)
Polyethylene glycol 3350
Ethyl lactate
Niacinamide
Desoxycholate sodium
Gelatin
Sodium lauryl sulfate