Table 6-3 Dielectric Constants for Various Solvents

Solvent	Dielectric constant (ε) at 25°C
Water	78.5
Glycerol	42.5
Propylene glycol	32.0
Polyethylene glycol 400	13.6
Dimethyl sulfoxide	46.7
Dimethylacetamide	37.8
Ethanol	24.3
N-Octanol	10.3
Cottonseed oil	3.0

Solubilizing Agents

Solubilizing agents are either co-solvents (strictly speaking, part of the solvent system, not solutes, but still considered as solubilizing agents in this discussion) or amphiphilic compounds classified as either complexing agents or surface-active agents.

Co-solvents already have been covered along with examples given earlier in this chapter Table 6-1). A survey of injectable formulations containing co-solvents finds that ethanol and propylene glycol are the most commonly used co-solvents. Both have high solvent power for organic molecules because of a dielectric constant (measure of electric current conductance) in the 24 to 32 range (water is 78, cottonseed oil is 3). Both are relatively nontoxic in the ranges used in parenteral products (Table 6-1).

Table 6-3 gives dielectric constant (ε) values for several solvents. Dielectric constant is a measure of the electric current conductivity property of solvents. The higher the dielectric constant, the better electric current will travel through the solvent. Thus, water has the highest ε while oil has the lowest. Poorly soluble drugs will have greater solubility in solvents whose ε is not as high as water. Thus, mixtures of water and one or more water-miscible co-solvents will solubilize slightly polar drugs.

An example of the power of a co-solvent to increase solubility of a poorly water-soluble drug is given in Figure 6-1.

The primary problem in using co-solvents is the toxicity of these solvents. Table 6-4 shows the LD_{50} of the four major co-solvents and advantages and disadvantages of using them. In general, small amounts of co-solvents are acceptable, but if the drug dosage is large (i.e., greater than 5 mL), then the usage of co-solvents is limited.

Another disadvantage of using co-solvents is the concern for precipitation at the site of injection if the solution is administered too quickly and the blood stream does not have adequate

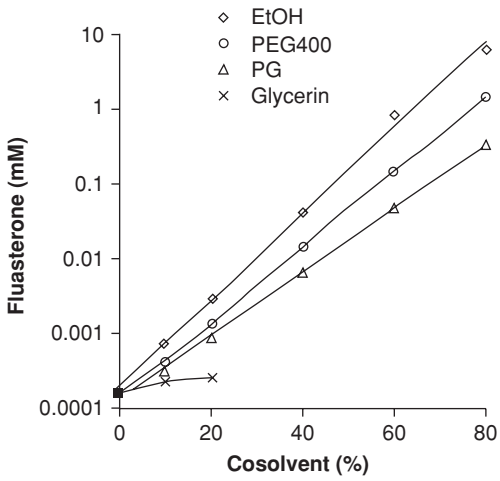

Figure 6-1 Example of co-solvent effect on drug solubility. *Source*: From Ref. 12.