PARENTAL USE OF COSOLVENTS

As discussed earlier, cosolvents can be an effective way to alter the solubility and stability of compounds. In formulating a parenteral product, often these two parameters can be exploited to produce a commercially acceptable, elegant product. Often cosolvents can be used to concentrate a formulation to allow production of a dosage form for presentation as an ampule or vial. The concentrated ampule or vial is then diluted before administration to the patient. Nema et al. (1997) has reviewed excipient use, including cosolvents, in commercially available injectable products.

Even though use of cosolvents has its advantages in parenteral formulation, their use also brings up some additional issues that need to be addressed by the formulator.

Compatibility of cosolvent formulations with packaging components, for example, vials, ampules, stoppers, and plastic administration devices, for example, IV infusion sets and syringes, is something that must be thoroughly investigated (Motola and Agharkar 1992). In addition, one should be also keenly aware that there is definite evidence of effect of formulation vehicles on metabolic enzymes, transporters, and distribution and hence unintentional alteration of drug pharmacokinetic properties. Very little is known about drug–excipient interactions in blood through parenteral route, specifically low dosed compounds, biomarkers, and microdoses. Hence, drug–excipient interactions are very important in the drug development process, especially those intended for parenteral route for *in vivo* animal pharmacokinetic studies, and a formulator must avoid the use of some excipients unless the interaction is well understood.

More than likely, if a cosolvent is required for your parenteral product, there is the potential for precipitation on injection. Cosolvents are a mixed blessing in this regard. On the one hand, cosolvents can afford order of magnitude that increases in solubility. However, once diluted, with even the smallest amount of water, solubility usually exponentially decreases. Formulating cosolvent systems to prevent precipitation on injection has been reported by Yalkowsky and Valvani (1997, 1983). The key to remember is to include not only enough cosolvent to be above equilibrium solubility in the formulation but also enough to help prevent precipitation on injection. Figure 9.4 illustrates this point for a fictitious compound.

The dashed lines in Figure 9.4 represent the formulation dilution profiles of Formulation A and Formulation B. Both Formulations A and B have the same concentration of drug and both are well below the equilibrium solubility of the drug in either formulation because they are well below the solid equilibrium solubility line. However, because Formula B has more cosolvent, it has less area above the solid solubility limit line and therefore, should be less prone to precipitation on injection. *In vitro* methods of assessing precipitation on injections include static methods

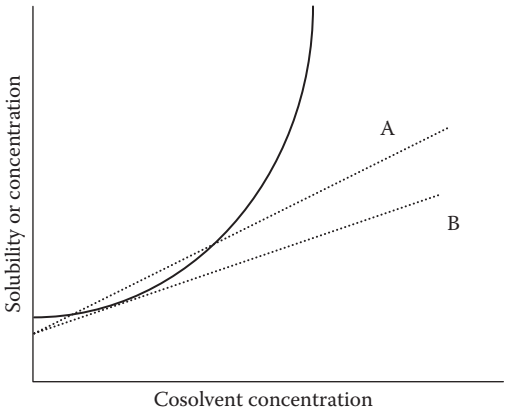

FIGURE 9.4 Dilution profile of two formulations containing same concentration of drug, but different concentration of cosolvent.