Cosolvents can increase the solubility of a nonpolar drug up to several orders of magnitude compared to its aqueous solubility. This is significant for a formulation where it may be necessary to increase substantially the solubility of a drug. Other methods such as complexation or micellization may not achieve the desired solubility for a necessary therapeutic dosage. Techniques such as complexation could suffer because identification of a suitable substance that will form a soluble complex with the drug may not be possible unless the drug conforms to certain structural requirements (Higuchi and Kristiansen 1970). The use of surface-active agents in drug formulations may result in toxicity problems, especially when given by the parental route (Attwood and Florence 1980). Even though methods such as prodrug and salt formation can result in an increase in solubility, it requires synthesis of new drug entities that results in additional animal studies to confirm their efficacy and toxicity. Thus, the advantages of using cosolvents are not only the dramatic increase in drug solubility but also its simplicity.

Another aspect of using cosolvents is that a change in solvent property can considerably change the rate and order of a reaction. In 1890, Menschutkin demonstrated the effect of various solvent media on the rate of reaction between triethylamine and iodoethane in 23 solvents (Menschutkin 1900). For drugs that may undergo hydrolytic degradation, an advantage of using a cosolvent is to reduce the degradation of the drug by reducing the concentration of water in the formulation and hence, increasing the chemical stability of the drug in its liquid state. Alternatively, a cosolvent may enhance the stability of a drug by providing a less suitable environment for the transition state of the reactants. This is provided the transition state is more polar than the reactants (Connors et al. 1979; Soni et al. 2014; Chen et al. 2015; Thakkar et al. 2016; Verma et al. 2016; Jouyban et al. 2017).

When delivered parentally or orally, a drug in solution is more rapidly bioavailable compared to a solid dosage form. The cosolvent approach also has some limitations as pointed out for other solubilization techniques. When solubilization of a drug is achieved by use of cosolvent, it must meet certain requirements, such as nontoxicity, compatibility with blood, nonsensitizing, nonirritating, and above all physically and chemically stable and inert. There is also some concern about whether cosolvents alter the affinity of a hydrophobic drug to its target (Senac et al. 2017). The biggest disadvantage of using a cosolvent is the toxicity of most of the water-miscible solvents that have a high potential for increasing drug solubility. The toxicological property of a solvent that may limit or eliminate its use in a formulation is its general toxicity, target organ toxicity, tissue irritation, or tonicity with respect to biologic membranes. Poor taste of a formulation is always a major consideration for a selection of a cosolvent intended for oral dosage formulation. There have been major efforts to mask a poorly tasted formulation with certain excipients such as corn syrup, citric acid, and fructose. The discussion on flavoring and taste masking of an oral formulation is outside the scope of this chapter, but those readers interested in that area may want to refer to review articles by Roy as a starting point (Roy 1990, 1992, 1994).

Under extreme time constraint for early phase animal studies, and availability of drug quantities to conduct appropriate solubility studies, it is very tempting to utilize various *exotic* excipients to solubilize the drug. However, one should be 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 intended for parenteral route for *in vivo* animal pharmacokinetic studies or later for commercial dosage form. A formulator must avoid the use of some excipients unless the interaction is well understood.

In this chapter, the uses of cosolvents are discussed with some specific limitations. The discussion is limited to the cosolvent effects on solubility and stability, and their use in parenteral products. For information on the use of cosolvents in other dosage forms such as soft gelatin capsules, the reader is referred to the specific chapter in this book on the topic.