penclomedine is soluble up to 100 mg/mL in soybean oil, allowing preparation of an emulsion with 10% soybean oil and 4.7 mg/mL final drug concentration (Prankerd and Stella, 1990). In some cases, an oil-soluble drug can be added directly to an already-prepared emulsion (e.g., Liposyn or Intralipid) and the drug preferentially partitions into the oil phase. In general, drugs that are liquid at room temperature are most amenable for these extemporaneously prepared emulsions, since the dissolution and required partitioning may be too slow for a solid drug. Anesthetics often meet this criteria. Examples are halothane and propofol: the latter is marketed as Diprivan®, an Intralipid/Liposyn–type emulsion containing 1% propofol and 10% soybean oil.

If a drug has sufficient water solubility, one can dissolve it into the aqueous component of the emulsion before formation of the premix for *de novo* emulsion preparation, or add the drug to a preformed emulsion for extemporaneous preparation. In these cases, knowledge of the oil–water partition coefficient is important to predict the final distribution of drug within the oil phases. Sila-On et al. (2008) examined the effect of incorporation method (*de novo* preparation vs. extemporaneous addition) into soybean-PC emulsions for four lipophilic drugs: alprazolam, clonazepam, diazepam, and lorazepam. The most lipophilic drug, diazepam, was readily incorporated into the oil phase regardless of preparation method. The other three, less lipophilic drugs, were preferentially localized in the phospholipid-rich region of the emulsion, and thus more efficiently solubilized in the *de novo* emulsions. If the drug is ionizable, one may be able to incorporate the drug by pH adjustment, that is, add the drug to the aqueous phase at a pH at which it is ionized and thus more water soluble, and then adjust the pH to a region in which it is nonionized and thus more hydrophobic, favoring partitioning into the oil phase.

Unfortunately, there are many drugs that have little or no solubility in either water or oil. In such a case, the final locale of drug would usually be the interface of the emulsion droplet, and emulsion preparation may be problematic. Nevertheless, several strategies have been devised for successful preparation of emulsions containing drugs in this category. Probably the most commonly used approach is the use of a cosolvent in which the drug is highly soluble; the drug solution can then be added extemporaneously to an emulsion, or to the oil phase before premix formation in a *de novo* preparation. Suitable pharmaceutically acceptable cosolvents include ethanol, propylene glycol (PEG), PEG 300, dimethylacetamide, triacetin, and mixtures of these solvents. However, the effect of cosolvent on chemical stability, emulsion droplet size, and drug partitioning must be carefully assessed. Diazemuls® is a diazepam (Valium®) emulsion marketed in Denmark; it contains 5% acetylated monoglycerides as the cosolvent along with 15% soybean oil, 1.2% egg phospholipids, and 2.25% glycerol (Collins-Gold et al., 1990). Amphotericin B emulsions have been prepared by a similar technique, wherein the drug is dissolved in dimethylacetamide to introduce the drug into the emulsion (Kirsch and Ravin, 1987). Similarly, triacetin allows preparation of a paclitaxel emulsion (Tarr et al., 1987), and addition of a solution of the chemotherapeutic agent Perilla ketone in 10% ethanol/40% propylene glycol/50% water to Intralipid results in a 1 mg/mL drug formulation (Collins-Gold et al., 1990). The same solvent mixture has been used to prepare an emulsion of Rhizoxin in 10% Intralipid (Prankerd and Stella, 1990). If the cosolvent is volatile, one can effect its removal following emulsion preparation. Such was the case for an amphotericin B emulsion, wherein methanol was used to introduce the drug and then allowed to evaporate from the formulation before emulsification with the oil (Forster et al., 1988). A similar approach involves the use of lipophilic counterions to increase the solubility of the drug in oil, allowing extemporaneous or *de novo* preparation of the emulsion. In this manner, clarithromycin was dissolved in a fatty acid/oil mixture (e.g., oleic acid/soybean oil or capric (decanoic) acid/Neobee® MCT oil) that was then formulated to obtain an o/w emulsion (Lovell et al., 1994). A flow diagram showing the composition and processing with the Microfluidizer for size reduction is shown in Figure 10.1. Another approach would be to solubilize the drug with an appropriate detergent and add this to an emulsion. For example, amphotericin B emulsions for clinical use have been prepared by dispersing lyophilized Fungizone into Intralipid 20% rather than into dextrose as is the standard practice; the presence of the deoxycholate in Fungizone apparently allows solubilization of the drug and partitioning into the