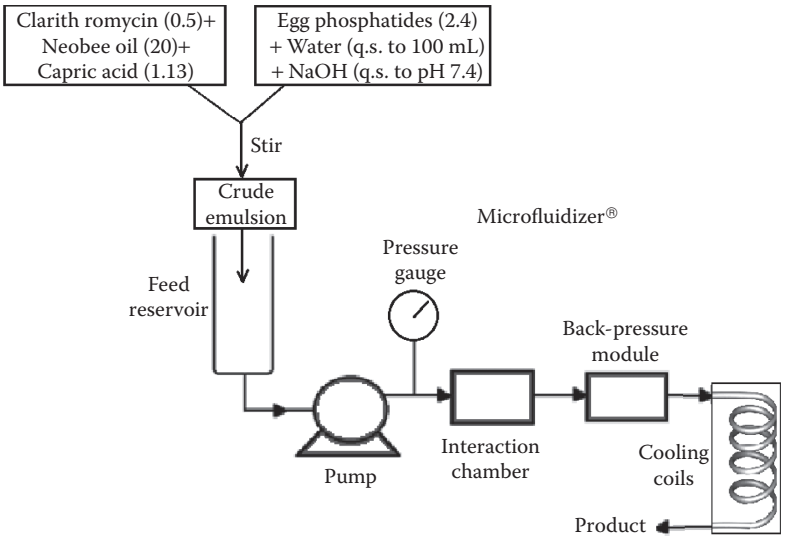

FIGURE 10.1 Flow diagram with composition for manufacture of a clarithromycin/capric acid/Neobee® MCT oil/egg phosphatide o/w emulsion using the Microfluidizer®. Amounts shown are in grams, to make 100 mL of emulsion. (From Lovell, M.W. et al., *Int. J. Pharm*., 109, 45–57, 1994.)

emulsion droplet (Caillot et al., 1992). However, the validity of this approach has been questioned, since undissolved amphotericin B has been detected in such preparations (Davis, 1995).

If phospholipid dispersions (liposomes) of the drug can be prepared, one can envision addition of the oil phase to the drug liposomes, followed by emulsification, to give a drug emulsion, as was done to prepare an amphotericin B emulsion (Davis et al., 1987; Forster et al., 1988). If the drug is present in the lipid bilayer of the original liposomes, it will probably remain at the interface of the resulting emulsion. A simpler approach was used to prepare an emulsion of Almitrine, whereby a drug-phospholipid solution in chloroform/methanol solution was rotary evaporated to form a drug-lipid film (the first step in the classical method for liposome preparation), which was then hydrated with 10% Intralipid to form an emulsion. However, it was reported that drug crystals formed within several weeks of the preparation of this emulsion (Van Bloois et al., 1987).

Recently a solvent-free approach (SolEmuls®) using high-pressure homogenization to incorporate poorly soluble drugs in parenteral emulsions has been reported by Muller et al. (2004). Powdered drug or finely milled drug suspension is added to a commercial emulsion (e.g., Lipofundin or Intralipid) by stirring. Alternatively, the drug can be admixed during the *de novo* production of emulsion. The obtained dispersion containing oil droplets and drug particles is then subjected to high-pressure homogenization. The high-streaming velocities lead to drug dissolution and partitioning into the interfacial layer. Stable emulsion formulations of several poorly soluble drugs including ketoconazole, itraconazole, carbamazepine, and amphotericin B have been prepared using these methods. A 1 mg/mL itraconazole emulsion with mean particle size of 255 nm has been shown to be stable at room temperature for 9 months and no drug crystal was observed under microscopic examination (Akkar et al., 2004). As the interfacial layer could only solubilize a certain amount of drug, exceeding the saturation concentration of the drug at the interfacial layer, hybrid dispersions consisting of drug-loaded oil droplets and drug nanocrystals could form. Tiny crystals were found in a 2 mg/mL amphotericin B emulsion using a polarized microscope (Müller et al., 2004).

In the case of parenteral emulsions, insuring the sterility of the product is crucial. The preferred method for sterilization is generally terminal autoclaving. The nutritional emulsions such as Intralipid and Liposyn can be sterilized by autoclaving without phase separation or other stability problems (Washington et al., 1993). However, autoclaving has been found to cause some