emulsions resemble chylomicrons, which are rapidly cleared by liver: 65% of exogenously injected chylomicrons are recovered in the liver within 30 minutes after injection (Van Berkel et al., 1991). Triglycerides are removed and digested by lipoprotein lipases present in capillary endothelium, and the remnant emulsion droplets are almost completely taken up by the liver within a few hours (Handa et al., 1994). Thus, these factors could have a significant impact on the pharmacokinetics and biodistribution of the drug. If the diffusion of drug from the emulsion is slow, then a high uptake of drug by the RES cells will be expected. This may be desirable in some cases where liver and spleen are the therapeutic targets, and where subsequent slow release of drug from these sites is desirable, and where toxicity of drug to sites of low emulsion uptake would otherwise be a problem. On the other hand, if diffusion of drug out of the emulsion is rapid compared to the metabolism and clearance of the emulsion droplets, then the pharmacokinetics and distribution of the drug will be little different from those of aqueous formulations. In studies using a rat liver perfusion system comparing emulsions with mean diameters of 252 and 85 nm containing [^{3}H] retinoic acid (log $P_{o/w} = 6.6$) and [^{14}C] cholesterol oleate (calculated log $P_{o/w} = 18$), the rates of RES uptake and plasma release were shown to depend on the emulsion size and drug partition coefficient (Takino et al., 1995). It has been suggested that drugs with a log $P_{o/w} > 9$ will be retained in the lipid phase regardless of the emulsion's composition and particle size (Kawakami et al., 2000).

On the basis of these considerations, formulation of a drug may or may not have a significant impact on the pharmacokinetic properties of the drug, and there have been a number of studies comparing emulsion and aqueous-based formulations with regard to this question. Cyclosporine (Sandimmune®), is normally formulated for IV use with Cremophor EL, a solubilizer, which is known to cause nephrotoxicity. When formulated as a 1.2% phospholipid/10% soybean oil emulsion incorporating 2–3 mg/mL drug, the nephrotoxicity in rats was decreased (Tibell et al., 1993) without changes in systemic clearance, volume of distribution, or elimination half-lives in rats and pigs. Hence the two formulations were considered bioequivalent (Tibell et al., 1995). Another study compared cyclosporine formulated as liposomes and as an emulsion (with 10 mg/mL cyclosporine in 20% Intralipid) with Sandimmune. All three formulations showed similar elimination half-lives, but Sandimmune showed significantly higher area-under-the-curve (AUC) values and lower volume of distribution than the other 2 formulations (Venkatraman et al., 1990). The binding of cyclosporine to lipoproteins was suggested as one reason for the differences in the *in vivo* behavior among the formulations. Similar contrasting results have been obtained with diazepam. Earlier reports indicated significantly lower plasma diazepam levels with Diazemuls emulsion than Valium injectable solution (5 mg/mL diazepam in 10% ethanol/40% propylene glycol) (Fee et al., 1984); however, later studies were unable to find a significant difference (Naylor and Burlingham, 1985).

An emulsion formulation of hexamethylmelamine in 20% Intralipid resulted in peak plasma drug concentrations and rates of elimination similar to those from a pH 2–3 aqueous formulation of the hydrochloride salt; however, the emulsion alleviated the vein irritation in rabbits (Ames and Kovach, 1982). This suggests that drug remains associated with the emulsion long enough to reduce local tissue irritation, but diffuses rapidly into serum at sites distal from the injection site. In the case of propofol emulsion (Diprivan), an anesthetic, the drug molecule distributes rapidly from blood to tissues, with a blood-brain equilibration time of only 2–3 min. No difference in pharmacokinetics has been observed between healthy patients and those with liver cirrhosis (Dundee and Clarke, 1989). These observations suggest that the emulsion has little effect on the distribution of propofol, which is not surprising, based on the low molecular weight of the drug.

The antifungal drug amphotericin B (AmB) is currently marketed for IV administration as a colloidal dispersion with sodium deoxycholate as a solubilizer (Fungizone). The formulation has hemolytic and nephrotoxic effects that are believed to arise from membrane damaging effects. Hence, alternate formulations (e.g., liposomes) (Lopez-Berestein, 1988; Gates and Pinney, 1993) and emulsions have been actively explored to alleviate these effects. *De novo* PC/oil AmB emulsions have shown reduced toxicity in cell culture and animal studies (Davis et al., 1987; Kirsch and