Ravin, 1987; Forster et al., 1988; Collins-Gold et al., 1990; Lamb et al., 1991). These results imply an altering of the distribution of the drug away from sensitive membranes. The RES uptake of AmB emulsion has been suggested as a possible reason for its therapeutic advantage (Collins-Gold et al., 1990).

In cases where distribution of emulsion to the RES cells is undesirable, strategies similar to those used for extending the circulating half-lives of liposomes by incorporating PEG or sialic acids into the lipid bilayer could be used (Allen et al., 1989; Woodle and Lasic, 1992). *Long-circulating emulsions* have been described by Liu and Liu (1995), wherein a PEG-derivatized phospholipid has been incorporated into the outer layer of an emulsion. At 30 min after injection, only 30% of a conventional emulsion remained in the blood with 50% distributed to the liver, compared to 65% in blood and only 15% in liver at the same time point for the PEG-based emulsion. The apparent reason for this difference is the higher surface hydrophilicity, leading to reduced opsonization and phagocytosis by the RES cells (Liu and Liu, 1995). A similar approach has been used to deliver ibuprofen octyl ester in a poloxamer 338/oil emulsion. This emulsion reduced RES uptake compared to a PC/oil emulsion. The higher hydrophilicity of the poloxamer 338 was hypothesized to reduce the uptake of the emulsion by the RES cells (Lee et al., 1995). Use of more hydrophilic oils such as triacetin to increase dissolution has also been proposed as a strategy to decrease RES uptake of emulsions (Tarr et al., 1987). Incorporation of sphingomyelin into the surface of 100 nm emulsions prolonged their circulation (Takino et al., 1994).

There are fewer reports on other parenteral routes of administration of emulsions such as intramuscular, subcutaneous, and intraperitoneal. Water-in-oil and w/o/w emulsions of bleomycin, mytomycin C, and 5-fluorouracil have been administered by these routes, apparently resulting in increased regional lymphatic uptake, hence the term *lymphotropic emulsions* (Davis et al., 1987). Gasco et al. (1990) developed a w/o emulsion of an LHRH analog; measurements of testosterone levels after intramuscular administration to rats suggested that the formulation led to prolonged release of the drug.

EXAMPLES OF EMULSION FORMULATIONS OF WATER-INSOLUBLE DRUGS

Experimental Case Studies

Lipophilic properties of halothane have been utilized for its parenteral delivery through an emulsion formulation. In one study, 0.3 mL of a 5% halothane in fat emulsion (Intralipid), prepared *de novo* immediately before testing, was injected through the rat tail vein. The emulsion formulation allowed short-lasting (30–100 s), potent analgesia with reduced adverse effects. All major organs of the animals (e.g., lung, kidney, heart, brain, and liver) demonstrated normal histology over a 29-day test period after dosing. Although some animals died in this test after dosing the emulsion formulation (probably due to nonoptimized injection rates), this formulation was found to be superior to injections of regular halothane, which has been shown to cause serious damage to the lung tissue (Johannesson et al., 1984).

Cyclosporine A (CsA) is a potent immunosuppressant indicated for the prevention of transplanted organs. However, it is known to cause dose-dependent nephrotoxicity when administered in the conventional formulation containing Cremophor EL; this solubilizing agent itself is reported to be nephrotoxic and allergic to some patients. Hence, feasibility of parenteral delivery of CsA as an emulsion with reduced adverse effects has been assessed (Venkatraman et al., 1990). The test formulation was prepared extemporaneously by adding drug to 20% Intralipid and mixing the contents until the powder was dispersed. Its performance was tested in rabbits and compared with the marketed IV product, Sandimmune. Whereas the terminal half-life of drug delivered through emulsion formulation was comparable to that of Sandimmune, some distribution parameters changed as a result of reformulation. The area under the blood drug concentration versus time curve (AUC) was significantly lower with the emulsion formulation than that with Sandimmune (7397 ± 2223