INTRODUCTION

Over the past several decades, emulsion formulations have been explored for resolving a variety of drug delivery challenges. Unlike solutions for oral or parenteral administrations, which are usually homogeneous one-phase systems or molecular dispersions, emulsions are colloidal dispersions of at least two immiscible phases stabilized with the aid of a third component generally referred to as the emulsifying agent. Most of the advantages of emulsion systems over conventional dosage forms such as oral solutions and liquid injectables can be attributed to this stable heterogeneity, and their ability to deliver immiscible phases in a reliable and reproducible manner. This chapter focuses on demonstrating the usefulness of emulsion systems for the delivery of water-insoluble compounds for parenteral administration. Following some basic definitions and general properties of emulsions, their potential utility for parenteral delivery of lipophilic compounds is rationalized. Wherever possible, examples of experimental and clinical use of emulsion formulations for parenteral delivery of water-insoluble compounds are provided. The challenges encountered in development of these formulations are also discussed. Finally, the utility of this approach is compared with other pharmaceutical techniques of drug solubilization.

EMULSIONS AS PHARMACEUTICAL DOSAGE FORMS

Definitions

An emulsion can be defined as a mixture of two immiscible phases (namely, water and oil) with an emulsifier added to stabilize the dispersed droplets (Davis et al., 1987). As conventionally defined, emulsions will have droplet diameters of more than 100 nm (up to 50 μm), and thus are opaque or milky in appearance. In addition, they are thermodynamically unstable by nature, that is, on standing they will eventually separate into two phases. However, proper choice of emulsifier (generally 1%–5%) and preparation conditions can delay this separation and thus lead to nominal shelf lives of more than 2 years, as typically required for pharmaceutical products. An emulsion can be characterized as oil-in-water (o/w) (containing up to 40% oil) or water-in-oil (w/o), depending on the identity of the dispersed and continuous phases. Multiple (e.g., w/o/w) emulsions can also be prepared, but these are less widely used in pharmaceutical applications.

In contrast to the conventional emulsions or macroemulsions described earlier are the disperse systems currently termed microemulsions. The term was first introduced by Schulman in 1959 to describe a visually transparent or translucent thermodynamically stable system, with much smaller droplet diameter (6–80 nm) than conventional emulsions. In addition to the aqueous phase, oily phase, and surfactant, they have a high proportion of a *cosurfactant*, such as an alkanol of 4–8 carbons or a nonionic surfactant. Whereas microemulsions have found applications in oral use (as described in the next chapter), parenteral use of microemulsions has been less common owing to toxicity concerns (e.g., hemolysis) arising from the high surfactant and cosolvent levels. In one example, microemulsions composed of polyethylene glycol (PEG)/ethanol/water/medium-chain triglycerides/Solutol® HS15/soy phosphatidylcholine have been safely infused into rats at up to 0.5 mL/kg. On dilution into water, the microemulsion forms a o/w emulsion of 60–190 nm droplet size (Von Corswant et al., 1998).

Typically, emulsions for parenteral use should have droplet size less than 1 μm (generally 100–1000 nm), and hence are often called *submicron emulsions*, or (less properly) *nanoemulsions*. Use of the latter term is unfortunate and can lead to confusion, since their droplet size is actually larger than the microemulsion systems described earlier. The term *nanoemulsion* has been proposed to include metastable emulsions ≤100 nm as well as thermodynamically stable microemulsions (Sarker, 2005). Manufacture of submicron emulsions require special homogenization equipment will be described later.