DRUG SOLUBILIZATION AND DELIVERY USING EMULSIONS

Rationale

Various formulation approaches can be used for solubilization and delivery of pharmaceutical compounds. If the compound has ionizable groups, salt formation is often the first strategy used to improve solubility. Otherwise, use of cosolvents is perhaps the most common alternative for solubilization of compounds, probably owing to the high efficiency and ease of use of cosolvents to solubilize drug. However, the use of cosolvents has the potential to cause problems like drug precipitation on dilution, and pain and/or tissue damage on parenteral administration. Emulsion formulations have the potential to avoid precipitation after injection. Other approaches include prodrugs, surfactant (micellar) systems, complexation, and liposomes. Combined approaches of emulsions with one of the other formulation strategies may also be used to advantage. As mentioned earlier, cosolvents are frequently used to incorporate drugs into an emulsion. Similarly, use of a lipophilic counterion to increase drug affinity to an emulsion may be considered an approach combining salt formation and emulsion strategies. There have been several reports of lipophilic prodrugs having higher affinity to and retention within the oil phase of an emulsion relative to the parent drug. Incorporation of palmitoyl rhizoxin into an emulsion protected the drug from degradation in plasma (Kurihara et al., 1996). Similar prodrug emulsion examples include a prostaglandin E1 prodrug (Matsuo, 1998), etoposide oleate (Azevedo et al., 2005), and paclitaxel oleate (Rodriguez et al., 2005).

Emulsions are an attractive alternative for drug solubilization. If the drug has moderate solubility in bioacceptable oils, emulsion systems could offer several benefits apart from drug solubilization that are rarely achievable with other formulation systems. Some of these include improvement in drug toxicity, sustained drug release *in vivo*, reduction in pain, irritation and tissue damage after parenteral delivery. For example, emulsion formulation of amphotericin B has been shown to cause significantly less damage to red blood cells (RBCs) than the commercial product, Fungizone (Forster et al., 1988). Emulsions have also been shown to reduce the toxicity of drug (e.g., miconazole) (Levy et al., 1995). Other examples of emulsions for reduction in adverse effects after parenteral dosing will be mentioned in subsequent sections.

Use of an emulsion formulation for pharmaceutical drug delivery generally mandates that the drug be present in the internal (i.e., dispersed) phase and/or at the interface. This means that the process meets one of the following criteria:

1. Drug has a high log *P* value, that is, the drug prefers to partition into lipophilic versus aqueous media. For example, an *O*-alkyl-*N*-aryl thiocarbamate has poor solubility in water or water containing cosolvents; however, its solubility is 2–3 orders of magnitude higher in oils, expediting emulsion preparation (Strickley and Anderson, 1993).
2. Drug is marginally soluble in oils; however, it can be improved with the aid of excipients. For example, the oil solubility of clarithromycin has been increased with the aid of counterions like hexanoic and oleic acid (Lovell et al., 1994).
3. Drug is soluble in neither oil nor water; however, it can be retained at the interface of an emulsion. Thus, if a liposomal preparation can be made in which the drug resides in the lipid bilayer, or if it can be solubilized into micelles by an appropriate detergent, an emulsion can probably be made wherein the drug resides at the interface.

Conformance to one or more of the above-mentioned criteria generally qualifies development of an emulsion formulation for drugs that otherwise cannot be successfully administered parenterally as a solution. Hence, emulsions have been explored for improved drug efficacy after oral, topical and parenteral administration, and for improved patient compliance (e.g., reduced pain or irritation after parenteral administration, and improved palatability after oral delivery).