DESIGN AND CHARACTERIZATION OF LIPID-BASED DRUG DELIVERY SYSTEMS

Although there is an understanding in principle of the factors influencing bioavailability from LBDDSs, there are no definitive *in vitro* tests that reliably and accurately predict *in vivo* performance. What happens on ingestion of the formulation depends on the components selected. In a manner analogous to tablet disintegration and dissolution, the dispersion of the lipid-based formulation has been shown to affect the plasma profile of a given drug. Much emphasis in the literature has been placed on the use of self-emulsifying or self-microemulsifying formulations with the notable success of Novartis Neoral formulation of cyclosporine (Trull et al., 1993; Mueller et al., 1994a, 1994b; Ritschel, 1996). Self-emulsifying formulations are designed to disperse readily in the presence of an aqueous medium and thus lessen the inherent variability caused by reliance on gut motility and digestive mechanisms. Nevertheless, several marketed products, such as Depakene® and Accutane®, present the drug in a triglyceride without additional emulsifiers (Physicians Desk Reference). The natural process of digestion, which involves breakdown of the triglycerides to mono- and diglycerides and fatty acids, will facilitate emulsification of these types of formulations, and their simplicity may enhance their desirability as a commercial product.

Importantly, development of LBDDSs should not focus solely on the *in vivo* behavior of the lipid fill, but must consider additional factors such as compatibility with encapsulation material and the physical and chemical stability of the product. An LBDDS can be encapsulated in hard- or soft-gelatin capsule shells and in hydroxypropyl methylcellulose (HPMC) capsules. In the case of gelatin shells, special attention must be paid to the formation of aldehydes, which can occur with unsaturated lipids and induce gelatin cross-linking (Chafetz et al., 1984), and to migration of solvents between the shell and fill (Tahibi and Gupta, 2000, from R. Liu, 2000), which can induce softening or brittleness (Kuentz and Röthlisberger, 2002). Furthermore, as these LBDDSs are typically liquid solutions, degradation kinetics are accelerated relative to solid systems. Other minor components of oral lipid-based formulations may include antioxidants (probably required if unsaturated lipids are used), viscosity modifying agents, pH modifiers, and other excipients with specific functional purposes.

PROCESSING *IN VIVO* AND CLASSIFICATION OF LBDDS

Lipid-based drug delivery systems are typically presented as encapsulated liquid formulations, though as discussed later, examples of semisolid or solid formulations exist (Serajuddin et al., 1988; Khoo et al., 2000). Regardless of form, after ingestion, LBDDSs undergo GI processing. This processing includes emulsification to form lipid droplets, hydrolysis of di- and triglycerides, solubilization of these digestion products by bile acids and transport through mixed micelles to the intestinal wall (Patton et al., 1985; Thomson et al., 1993; Embleton and Pouton, 1997). Figure 11.2 summarizes these processes that occur for an LBDDS in the GI tract. As a result of the GI processing, the solvent environment provided by the LBDDS is constantly changing after ingestion, and the mechanism for release of the drug is not completely understood. The possibilities include simple partitioning from the emulsion oil droplets; partitioning from the bile salt mixed micelles; or micelle delivery to the intestinal wall, with absorption facilitated by breakdown of mixed micelles due to protonation of the bile salts or uptake of the fatty acids and monoglycerides (Charman et al., 1997). Although the exact mechanism for release of the drug is not known, certain properties of the formulation do enhance bioavailability from these vehicles. For example, release from emulsions can result in higher bioavailability than release from neat oil (Humberstone and Charman, 1997); self-emulsifying systems tend to provide more reproducible blood levels than emulsions that require more energy to form (Holt and Johnston, 1997); and formulations that form viscous liquid crystals have shown delayed or reduced release of drug (Alfons and Engstrom, 1998; Trotta, 1999).

The *in vivo* processing step that dominates the ultimate bioavailability of the drug is dictated by the composition of the formulation. If a formulation is simply drug dissolved in a triglyceride,