to eliminate dissolution of crystalline material as the rate-limiting step to absorption (Pouton, 2000). For poorly aqueous-soluble drugs, the dissolution rate can be extremely low under physiological conditions, leading to poor oral bioavailability and nonlinear exposure with increasing dose (Hörter and Dressman, 1997). Many of these lipophilic drugs will also exhibit a strong food effect where the bioavailability increases due to the solubilizing effects of ingested food and concomitant excretion of bile (Charman et al., 1997; Fleisher et al., 1999). By introducing the drug in solubilized form, lipid-based formulations have the potential to increase bioavailability and eliminate the food effect.

When considering oral formulations, the term *LBDDS* encompasses a broad array of formulations based on blends of acylglycerides, fatty acids, fatty acid derivatives, and emulsifiers. The unifying concept behind these formulations is that poor aqueous-soluble drugs that would normally exhibit dissolution rate-limited absorption are presented in a solubilized form *in vivo*. A number of reviews provide discussion of their design and performance (Armstrong and James, 1980; Humberstone and Charman, 1997; Pouton, 1997; Charman, 2000; Porter and Charman, 2001; Wasan, 2001; Porter et al., 2008; Porter et al., 2013; Williams et al., 2013a). While lipid-based parenteral formulations are typically administered as emulsions, oral LBDDSs are generally administered as a liquid or semisolid with high lipid and low or no aqueous content. These oral formulations form emulsions only after ingestion and mixing with gastric or intestinal contents. In this chapter, we will review approaches to develop LBDDSs for oral applications. We begin with basic definitions and functions of the main components, and build on that understanding to describe approaches to solubilization and characterization of performance. Additional information regarding special considerations for stability and manufacturing is provided. In addition to solubilization applications, there are examples where suspensions of poorly soluble drugs are presented in lipid matrices (e.g., for controlled release applications) (Hamdani et al., 2003; Bummer, 2004; Galal et al., 2004, Mengesha et al., 2013) and for taste masking (Robson et al., 2000), but these are not considered in the discussion here.

DEFINITIONS AND CONCEPTS

In addition to the concepts such as emulsions, submicron emulsions, and microemulsions introduced in Chapter 10 (Part I: Parenteral Applications), the following concepts and background information are important for oral formulations.

Lipids

The primary solvent in LBDDSs is the lipid component, which may be either a single material or blend of several types of lipids. As discussed in Part I, the operational definition of lipids is those components of biological material (either occurring naturally or easily derived from those that do occur naturally) that are water-insoluble but soluble in organic solvents such as methylene chloride. Alternatively, lipids are fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds. These definitions include materials such as cholesterol and other sterols in the category of lipids; however, it is the aliphatic chain lipids (fatty acids and fatty acid derivatives) that are most important for oral formulations. The physical form at room temperature can be solid or liquid depending on the degree of unsaturation of the fatty acid chains, chain length, and homogeneity of the fatty acid profile.

Aliphatic chain lipids can be classified into several groups according to their relative polarity; examples are shown in Table 11.1. The differences in polarity are an important guide in selecting solubilizing lipids for formulation. Among the most hydrophobic lipids are neutral fats (triglycerides), which are triesters of glycerol with fatty acids. The component fatty acids can be either saturated or unsaturated (e.g., palmitic or stearic acid versus oleic or linoleic acid), and chain lengths can vary,