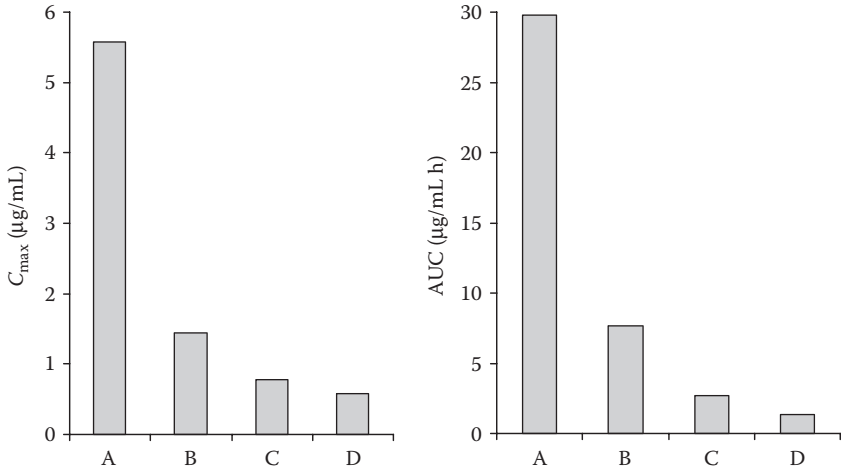

FIGURE 11.1 Comparison of the bioavailability for four formulations of a lipophilic drug, RO-15-0778, in dogs. (a) Lipid-based SEDDS; (b) PEG 400 solution; (c) capsule (powder); and (d) tablet. (Adapted from Gershanik, T. and Benita, S., *Eur. J. Pharm. Biopharm.*, 50, 179–188, 2000. With permission.)

bioavailability in dogs relative to a PEG 400 solution and over a 10-fold enhancement relative to a capsule or tablet (Gershanik and Benita, 2000). The amount of cosolvent used will be limited by the overall formulation compatibility with the encapsulation material. Certain cosolvents (e.g., propylene glycol) can migrate into gelatin capsule shells resulting in softening. Conversely, certain cosolvents may, by virtue of their hygroscopicity, induce water migration from the shell to the fill, resulting in brittle capsules. Compatibilities of various excipients with gelatin capsules have been summarized by Cole (1999).

Ideally, only excipients currently approved by the appropriate regulatory authorities should be used, in amounts established as safe, such as outlined in the approved inactive ingredients list of the US Food and Drug Administration (FDA) (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm). If novel excipients are required, regulatory hurdles will be encountered later in the development process, since safety of novel excipients is normally only evaluated in the context of a new drug application (NDA). However, pathways do exist for approval for novel excipients, requiring close cooperation between the pharmaceutical company and excipient manufacturers (Goldring, 2009). Tocopherol PEG succinate (tocophersolan) is a water-soluble (HLB ~13) Vitamin E derivative that can enhance solubilization and absorption of poorly water-soluble drugs (Wu and Hopkins, 1999). It was first used in the commercial formulation of the HIV protease inhibitor Amprenavir (Strickley, 2004).

Self-Emulsifying Drug Delivery Systems

Self-emulsifying drug delivery systems (SEDDSs) are oral dosage forms consisting of drug, oils, surfactants, and sometimes cosolvents (Constantinides, 1995; Pouton, 1997; Pouton, 2000). On addition to water (or on introduction to the gastrointestinal [GI] tract) and with gentle agitation, the system will easily form an emulsion or microemulsion (defined in the following). Self-emulsification may be driven by several mechanisms (López-Montilla et al., 2002). The mechanisms most likely involved in dispersion of pharmaceutical formulations are *diffusion and stranding*,