when ionizable components are used. For example, the ease of dispersion of fatty acids increases when the environmental pH is above the pK_a of the carboxylic acid (e.g., 4.89 for caprylic acid) (Lide, 1993).

Constructing phase diagrams of the LBDDS as a function of aqueous content and condition (e.g., change of pH or addition of bile components) can help identify factors influencing dispersion. Combinations of low HLB and high HLB surfactants often lead to smaller emulsion droplet size than single surfactants; these more complex systems can be examined by pseudo-ternary phase diagrams. Although *in vivo* processing of the formulations is dynamic, equilibrium-phase behavior studies can provide a guide to the driving forces behind the transitions that occur. For example, phase diagrams can be used to compare the equilibrium state of the formulation in the acidic environment of the stomach versus the more neutral conditions of the intestinal tract. Addition of bile components can address the ability to solubilize the formulation. Formulations that self-emulsify should avoid formation of viscous liquid crystals. Thus, compositional regions where these occur would be mapped on the phase diagram allowing the formulator to alter the composition of the LBDDS to avoid the region. These phase diagrams can then be used to compare the effect of excipient substitution (e.g., using the emulsifier Tween® 80 in place of Cremophor® EL). Lipid/emulsifier combinations with similar phase diagrams are likely to behave similarly *in vivo* assuming that the surface-active components of the intestinal milieu do not interact differently with these combinations.

Visual observations of ease of dispersion are useful for formulation screening. An example is provided by Khoo et al. (1998) who constructed a visual rating system that described the ultimate state of the formulation after diluting 1 into 200 mL of aqueous solution (either 0.1 N HCl or water in the publication). Extension of this approach using simulated fed and fasted fluids, such as those described by Nicolaides et al. (1999), would provide guidance on the solubilizing effects of bile. Dispersion behavior can also be assessed by measuring the droplet size after addition of the formulation to an aqueous medium using dynamic light scattering (DLS) techniques described in Chapter 10 (Part I: Parenteral Applications). Gao et al. (2004) used a custom-built DLS probe to optimize an SEDDS formulations using a statistical mixture experimental design. Assessment of a formulation's dispersion behavior can be coupled with quantitative analysis of solubilized drug concentration to assess the extent to which the formulation loses solubilizing power under these conditions. With respect to solubilizing capacity, it is important to consider that precipitation from solution may not occur immediately, and an evaluation of the kinetics may prove useful for comparison of formulations (Bravo González et al., 2002).

Shahba et al. (2012) examined the dispersion behavior and precipitation tendency of optimized SEDDS formulations of cinnarizine by measuring the drug solubility upon aqueous dilution, and measuring particle size after dilution. Type II formulations containing medium-chain mixed glycerides (e.g., Miglyol 810/Imwitor 308/Tween85 25/25/50) yielded droplet sizes of ≤50 nm and transparent appearance upon aqueous dilution, with ~90% of drug remaining in solution after dilution.

The effects of dispersion are highlighted by the differences in the properties of the marketed cyclosporine oral formulations and the resulting influence on pharmacokinetics. The Sandimmune capsule formulation is based on a blend of corn oil and the low HLB emulsifier Labrafil® M 2125 CS (polyoxyethylated glycerides, corn oil PEG 6 esters). On dilution, the formulation forms a coarse emulsion. Under similar dilution conditions, the Neoral formulation, which is based on corn oil mono- and diglycerides and the high HLB surfactant polyoxyl 40 hydrogenated castor oil, readily forms a microemulsion. The microemulsion is characterized by the formation of small and uniform particles. In nonfasting renal transplant patients, Neoral gave a shorter tmax (1.2 versus 2.6 h), a higher C_{max} (892 versus 528 μg/L), and a higher AUC (3028 versus 2432 μg h/L) relative to Sandimmune. A clinical study comparing cyclosporine bioavailability in transplant patients found increases of 39% in C_{max} and 15% in AUC for the Neoral soft-gelatin capsule formulation when compared to the Sandimmune soft-gelatin capsule formulation (Mueller et al., 1994a). Greater differences were found in a study of healthy volunteers given higher doses where it was shown that