

solubility (Cao et al., 2004). The authors developed a model using six model solutes for which the Abraham descriptors had been established. They adjusted the solvency using mixtures of MCT with squalane. After demonstrating accurate prediction of partitioning in squalane, they developed a log-linear correction to partitioning with the added hydrogen-bond acidity, basicity, and polarizability contributions of the ester portions of the MCT. The study also attempted to model the effects of water typically resident in acylglycerides. The authors demonstrated experimentally that water modulated the solubility of the solutes studied (benzamide and *N*-methylbenzamide), but concluded that the current solute descriptors for water used in the modeling would require revision. More recently, Persson et al. (2013) measured the solubility of 30 structurally diverse lipophilic drug molecules in LCT, MCT, polysorbate, and PEG400. The experimental results were then used to develop a partial least squares model to predict drug solubility based on molecular descriptors such as melting point, octanol–water partition coefficient, polar surface area, and nitrogen content. The models could predict the solubility in LCT and MCT with r^2 values of 0.81 and 0.84, respectively. The use of computational models may be more appropriate for comparing partitioning of solutes into simple lipid solvents rather than actual solubility. This should be sufficient to use as a guide in selecting primary solvent systems versus modeling of more complex systems that include cosolvents and emulsifiers.

CHARACTERIZING DISPERSIBILITY AND DISSOLUTION/DISPERSION BEHAVIOR OF LBDDS

Much of the published literature on the design and performance of LBDDSs describes characterization of the dispersion properties. Attention has been focused on the resulting particle size, the concept being that smaller particle size increases the surface area for partitioning of drug or diffusion rate of the carrier droplets to the enterocyte. For particle size to be an important criterion there needs to be some assessment of the stability of the emulsion formed within the time period for measurement to allow the measurement to be meaningful. In addition, careful selection of the medium in which the measurement is carried out is required. Depending on the composition of the LBDDS, the medium pH, osmotic strength, and presence of bile can all affect the ultimate particle size formed after dispersion. In addition, the force of mechanical agitation can alter the particle size distribution.

While still sensitive to the medium environment, the ease of dispersion rather than particle size may be a better measure of the performance *in vivo*. Ease of dispersion refers to the facility for the formulation to mix with the aqueous phase and is typically represented by low interfacial tensions. It is this property that drives the process of self-emulsification. Mechanisms for promoting self-emulsification are a topic of current study (Pouton, 1997; Buchanan et al., 2000; Nishimi and Miller, 2000; Shahidzadeh et al., 2000; López-Montilla et al., 2002). The mechanisms most likely involved in dispersion of pharmaceutical formulations are *diffusion and stranding*, those driven by osmotic pressure imbalances (Greiner and Evans, 1990), phase transformations, and changes due to alteration of environmental conditions (e.g., pH). Given the number of components found in pharmaceutical formulations, it is not unexpected for several mechanisms to operate in parallel.

Diffusion and stranding is a mechanism of emulsion formation that relies on the presence of a solute in one phase that is in fact soluble in both phases and couples those phases within a limited composition range. Addition of a hydrophilic cosolvent can induce diffusion and stranding emulsification (Miller, 1988; Zourab and Miller, 1995; Pouton, 1997; Rang and Miller, 1999). The cosolvent may initially improve the miscibility of the lipid formulation with the aqueous medium, but as it continues to be diluted into the aqueous phase, the more lipophilic material is *stranded* as droplets. An osmotic mechanism is possible in the case of water-in-oil droplets where a solute is dissolved into the internal aqueous phase and the continuous oil phase presents a semipermeable barrier. The solute can be an additive such as a hydrophilic polymer or salt. Change in pH can trigger dispersion