The nanosuspension technique usually does not work well for basic compounds with high pH-dependent solubility. When administered orally, nanoparticles of a basic drug may dissolve rapidly in stomach, but only to precipitate out in the small intestine as uncontrolled particles, thus defeating the purpose of nanosizing (Peagram et al., 2005). Some tend to agglomerate or increase in particle size owing to crystal growth (Neervannan, 2006). Another disadvantage is that not all compounds can form nanosuspensions.

Amorphous Solid Dispersions

The amorphous state of drugs lacks an ordered structure and possesses higher free energy, the thermodynamic driving force that leads to higher apparent aqueous solubility and dissolution rate, which could eventually lead to improved oral absorption. The high free energy form frequently came with such disadvantages as poor physical and chemical stability. As a result, pure amorphous drugs are rarely used in formulation development. To take advantages of enhanced solubility and dissolution rate of the amorphous drugs, many amorphous solid dispersions (ASDs) have been developed. ASDs are dispersions of amorphous drug in a polymer matrix. Upon dosing, supersaturated solutions are formed, thus the flux across the intestinal membrane is greatly increased. The duration of supersaturation can last for as long as several hours, thus providing much-enhanced drug absorption. ASD technology has not only been used to drive high plasma exposures in toxicology studies with reduced variability, and to deliver challenging molecules in clinical studies (Verreck and Six, 2003; Vandecruys et al., 2007; Bikiaris, 2011), but it also has led to many successful commercial products as well (Baghel et al., 2016).

Polymers are critical components in ASDs because they act as carriers for the drug and inhibit crystallization in both the dosage form and *in vivo*. By remaining in an amorphous state during dissolution, the drug can achieve supersaturation and potentially greater absorption, when solubility is the limiting factor for absorption. In addition to *in vivo* performance considerations, polymer properties such as the glass transition temperature (Tg), solubility in organic solvents, and hygroscopicity are the key considerations in order to make the ASD stable and manufacturable. Polymers that are commonly used in ASD applications include hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinylpyrrolidone (PVP), and methacylate-methacrylic acid copolymers (Eudragits). In addition to polymers, surfactants are often used as solubilizers or emulsifying agents in ASDs. The primary purpose of surfactants is to increase the apparent aqueous solubility and bioavailability of the drug. Common surfactants used in ASDs include Vitamin E-TPGS, polysorbate 20, polysorbate 80, sorbitan monostearate 60/80 (span 60/80), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), and so on.

Amorphous solid dispersions present a greater level of complexity, and require greater resources for formulation development and preparation of supplies for *in vivo* studies, when compared to the other formulation approaches that have been described in discovery support. Various amorphous solid dispersion techniques were reported in the literature. In discovery support to early phase preclinical studies, the methods of preparation typically include solvent cast, rotary evaporation, fusion, hot-melt extrusion, and spray drying.

Solvent Cast/Rotary Evaporation

Solvent-based ASD preparations enable molecular level mixing which is preferred to increase the solubility and stability of the product. Solid load is generally dictated by API/polymer/surfactant solubility in the solvent, and typically is 5%–25% by weight. This technique starts with dissolving the API and formulation components (polymers, surfactants) in a pharmaceutically acceptable solvent, followed by subsequent solvent removal. For solvent cast, the solution mixture is spread onto a mold, a scintillation vial, or a simple glass slide, and allowed to dry in a fume hood. Once dried, the film will then be collected for subsequent characterization. Preparation of ASDs by rotary