A simple method for drug release testing for ASD is performed by transferring a known mass of material into a known volume of biologically relevant dissolution medium (e.g., simulated gastric/intestinal fluid) under constant stirring. Solution concentrations are measured as a function of time to generate a concentration versus time release profile for the drug. Solution concentrations in significant excess of the equilibrium API solubility in the particular medium should be targeted to test the ability of the ASD to achieve and maintain supersaturation.

Accelerated stability studies on the ASDs should be conducted under stressed conditions (e.g., open dish at 40°C/75% RH, 60°C/75% RH, etc.) to understand both the physical stability of the ASD and any increased risk of chemical reactivity in the presence of excipients. Long-term stability of ASDs should be evaluated due to the increased risk of both physical and chemical instability associated with amorphous solids (Baghel et al., 2016).

PHASE APPROPRIATE FORMULATION CONSIDERATIONS

Formulation for Pharmacokinetics Screening *In Vivo*

When an *in vitro* hit is identified, the analogous compounds are synthesized to explore the structure–activity relationships (SARs) for the structural family of compounds in an effort to maximize the desired activity and overcome the pharmacokinetic liabilities (Lombardino and Lowe, 2004). As the compounds are filtered through *in vitro* screens, selected compounds must be tested for pharmacokinetic properties *in vivo* to assess how well the *in vitro* data predict *in vivo* performance.

It is desirable to have a thorough understanding of the physicochemical properties of the drug candidate for the duration of the study, the Biopharmaceutics Classification System (BCS) class of the drug candidate, and the desired route of administration. However, at hit to lead stage, the major challenges for formulation development are limited availability of drug, short turnaround time, lack of physicochemical characterization, and unfavorable drug properties (Shah and Agnihotri, 2011).

To be able to rank order a series of compounds from discovery, it is desirable to identify standard vehicles for a particular compound series. It is also preferable to use solution formulation for the PK screening studies at this early stage as the use of the solution formulation can avoid the variability in the PK results caused by differences in dissolution rates of different crystallinities and particle sizes and provide the best performance for each compound. The most commonly used approaches include pH adjustment, cosolvents, complexation, oils, and surfactants.

If suspension formulations of the compounds are used in *in vivo* PK screening studies, it is very important to understand the impact of solid state form on PK performance before rank ordering the compounds. If 100 mg API is available, it is recommended to keep at least 5 mg of drug substance aside for possible solid state form assessment while performing *in vivo* PK screening studies. If a compound in suspension formulation gives a promising PK result, the solid state form of the compound should be evaluated by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) to understand whether the high exposure of the compound is from a crystalline anhydrate, a solvate/hydrate, or an amorphous material. If the higher PK exposure of the molecule is the result of using more soluble amorphous material, a repeat PK study needs to be conducted using a crystalline material of the same compound. Only by doing this is the rank ordering of a series of compounds meaningful. At this early stage, most of the crystalline material can be obtained by simply slurrying amorphous material in different solvents. If the compounds in suspension formulations do not provide sufficient exposure, there is no need to conduct solid state characterization for those compounds.