Development and validation of a platform to determine amorphous solubility and characterize liquid-liquid phase separation behavior

Michaela McNiff[1], Brittney Mills[2], Jeffrey Hall[2], Philip Zocharski[2], David Lindley[2], Thomas Borchardt[2]

[1]Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS
[2]Formulation Sciences – Pharmaceutics, AbbVie Inc., North Chicago, IL

Formulation of poorly water-soluble drugs to achieve maximum oral bioavailability is a consistent challenge in the pharmaceutical industry. Excipients can be added to the crystalline API to enhance solubility, but in many instances, the increase in solubility results in a permeability tradeoff that may impede overall flux and result in a reduction in bioavailability. Compared to the crystalline form of the drug, the high energy amorphous form offers significant advantages through formulation such as enhanced solubility and dissolution. Amorphous solid dispersions (ASDs) consist of the amorphous drug stabilized with the addition of polymers and may represent an opportunity to maximize exposure by inhibition of crystallization upon dilution with water. Once exposed to this aqueous environment, a supersaturated solution of hydrophobic drug is formed and the drug begins partitioning from the aqueous solvent phase into hydrophobic drug-rich pockets; a phenomenon often described as liquid-liquid phase separation (LLPS). LLPS forms at a concentration above the amorphous solubility and therefore is an indication of the concentration at which you can achieve the maximum driving force for flux through the intestinal epithelium and provide formulation scientists with reasonable concentrations to target in dissolution experiments. A method to investigate the LLPS onset concentration is necessary to determine the amorphous solubility and potential extent of supersaturation under various conditions (e.g. various polymers or intestinal fluids). The LLPS onset concentration is determined from an increase in light scattering at non-absorbing wavelengths. A manual benchtop apparatus was compared to the automated Sirius Analytical Inform to provide alternative methods to determine LLPS onset concentrations for both model and AbbVie compounds. To further explore the environment and extent of LLPS, a 96-well plate formatted fluorescent probe assay was developed. The benchtop and fluorescent probe assays provide methods to rapidly determine amorphous solubility and screen different formulations of ASDs.