To fully explore the potential of spray dried ASDs from co-solvent drug-polymer solutions, a fundamental understanding of the solvent chemistry, droplet composition throughout drying and its impact on the drug-polymer interaction, stability and phase behavior are required. These mechanisms are, in turn, strongly influenced by the process conditions, such as thermodynamic layout, atomizing characteristics and spray drier geometry. The focus of the present work lies on the evaporative dynamics of binary solvent droplets and how they impact the onset of supersaturation/precipitation and phase separation during the droplet drying history. These dynamics are investigated numerically with (1) a model of co-solvent evaporation coupled to (2) a model for phase separation applied to film casting.

1. Co-solvent evaporation model:
Unlike the single component counterpart modelling the evaporation of binary mixtures depends not only on the process parameters, but also on the mass, heat and momentum transfer within the droplet since the different evaporation rates lead to a relative diffusion between the two solvents. Due to the droplet’s spherical symmetry the 1D diffusion problem is solved. The importance of the relative diffusion between the solvents is demonstrated in Figure 2 by considering the two limiting cases of infinitely slow or infinitely fast relative diffusion [1].

2. Phase separation model - TKE model based on Flory-Huggins [2]:
The co-solvent evaporation model is also implemented on the previously developed platform for phase separation prediction of drug-polymer-solvent systems to systems with binary solvent blends in an effort to generalize a screening methodology for ASDs (Figure 3). The TKE model is a system of partial differential equations based on diffuse interface theories (i.e., Cahn-Hilliard and Allen-Cahn) to describe drug-polymer microstructure evolution.

Case Study
The model system consists of 50:50 %w/w Itraconazole:PV/PVA 64 obtained from feed solutions with a mixture of DCM:EtOH (varying ratios). The drying temperature is set to 41°C and the initial film height to 50µm.

Combination of the co-solvent evaporation and the phase separation models: Model predictions of the film drying history. The co-solvents and solids fraction as well as the onset of supersaturation/precipitation are obtained for various film heights as well as the time lag between (super)saturation and the drying end point. This time lag relates to the crystallization tendency when no polymer is present.

Comparison with the experimental data of contact angles of Xiu et al. (poster M1259): The wetting contact angle is a good surrogate of the fraction of polymer/drug at the surface. Lower contact angles generally correspond to a larger fraction of polymer at the surface which correlates well with the lower time of exposure to a supersaturated state during drying.

Predicting the droplet drying history allows a preliminary estimate on whether the drug becomes supersaturated in advance of the polymer gelification or the opposite occurs. The 1D model further allows taking into account heterogeneity in the solvents composition and phase separation. Both effects have a strong impact on the ASD stability and crystallization risk as shown experimentally (see poster M1259).