Solvent Impact on the Product Quality of Pharmaceutical Formulations

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The production of polymer-based pharmaceutical formulations often involves solvent-based processing steps such as spray drying. In order to obtain homogeneous and stable formulations, any changes, like crystallization of the active pharmaceutical ingredient (API) or phase separation of the components involved must be avoided. The phase behavior during drying must be known for successfully drying the formulation from a solvent or solvent mixture. The proposed method for the first time enables identifying appropriate solvent candidates for the production of ASDs with significantly less experimental effort than before.

The aim of this work was to develop a thermodynamic approach that predicts the phase behavior of so-called amorphous solid dispersions (ASDs) and their drying curves using PC-SAFT to predict and to avoid unwanted ASD phase changes during drying. Identifying completely miscible polymer/solvent mixtures is the first important step towards a solvent-based ASD production, whereby in the second step it must be clarified whether the mixture remains homogeneous during the entire drying procedure. In cases where API and polymer are not soluble in one common solvent, solvent mixtures are used. Due to the different volatilities, the evaporation of the individual solvents varies. The ASD/solvent mixture therefore follows curves rather than straight lines across the phase diagram during drying, eventually reaching the solvent-free ASD.

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is a highly popular polymer for ASDs. It is one of those candidates, which needs to be spray dried from solvent mixtures, because it is not completely miscible with any of the solvents used in pharmaceutical production. To find a suitable solvent mixture for HPMCAS, first the phase diagram and the drying curves were calculated for HPMCAS ASDs and then validated experimentally via Raman spectroscopy. For an ASD consisting of naproxen (NAP) and HPMCAS, the predicted phase behavior and drying curves are shown for ethanol/water (Figure 1a) and acetone/water (Figure 1b) solvent mixtures. Starting from a homogeneous liquid phase in which both, API and polymer, are completely dissolved, the miscibility gaps and drying curves look quite different for the two solvent mixtures. The system with the ethanol/water mixture was predicted as being appropriate for the investigated ASD, since no phase separation occurred along the drying curve. In contrast, the use of an acetone/water mixture led to unwanted phase separation during drying. Furthermore, the solubility line was exceeded in both systems for ASD concentrations w_{ASD}>0.4, which led to NAP crystallization.

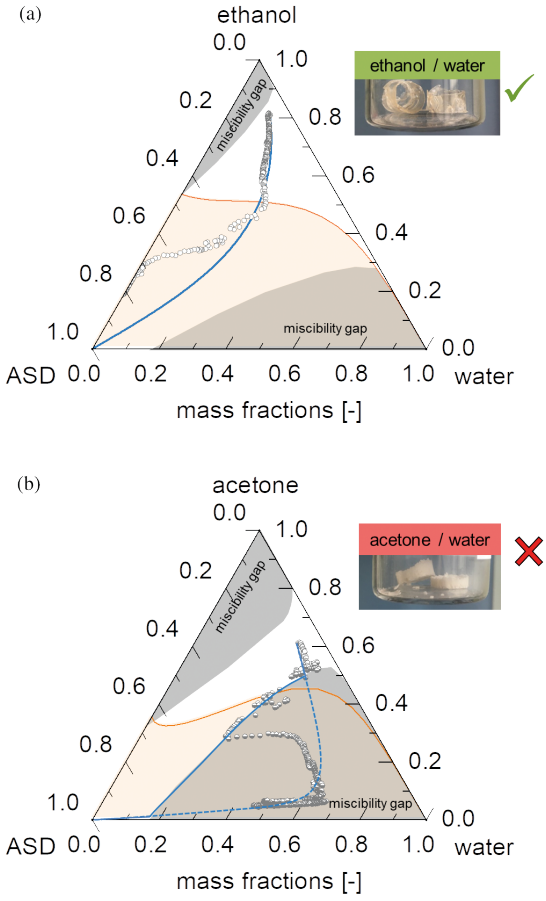

Figure 1: Drying of a NAP/HPMCAS ASD (wNAP = 0.15 in the ASD) from (a) an ethanol/water mixture and (b) an acetone/water mixture at 25°C. PC-SAFT calculated phase diagrams show miscibility gaps (gray regions), the solubility lines (orange lines), the predicted drying curves (blue lines) and the experimentally-observed liquid compositions (points) during drying.

The prediction of unwanted phase separation and NAP crystallization during ASD drying from solvent mixtures was in perfect agreement with the experiments. PC-SAFT thus allows for correctly identifying suitable solvent mixtures and even the best solvent-mixture ratios required for preparing and drying ASDs without any experimental effort.

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