Moisture-induced amorphous amorphous phase separation can be predicted

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INTRODUCTION

Numerous recently-developed active pharmaceutical ingredients (APIs) have a low solubility in water leading to insufficient absorption and bioavailability. To overcome this solubility limitation, APIs are dissolved in hydrophilic polymers. The resulting formulations are denoted as amorphous solid dispersion (ASDs).

For the administration of new pharmaceutical formulations, long-term stability tests are imposed by regulatory authorities at defined conditions of temperature and humidity (25 °C, 60% relative humidity (RH) for 12 months long-term tests and 40 °C, 75% RH for accelerated six-months tests). Recrystallization of the amorphous API and/or moisture-induced amorphous amorphous phase separation (MIAPS) might occur during storage indicating the thermodynamic instability of ASDs. Long-term stable formulations are nowadays identified by trial-and-error principles. The aim of this work was to a-priory estimate the long-term stability of ASDs by applying advanced thermodynamic methods and thus to reduce the experimental effort for finding promising polymeric carriers suitable for formulation development.

METHODS

Raman spectroscopy

Confocal Raman spectroscopy is a powerful analytical method to non-invasively determine the composition of a multi-component mixture with a spatial resolution of 1 µm. An inverted microscope was used to focus the laser spot on solvent-casted films of poly (vinyl pyrrolidone) (PVP)/Ibuprofen (IBU) and PVP/Felodipine (FEL) ASDs. An equilibrium cell mounted on top of the films allowed for controlling RH and temperature of the ASDs. Using a motorized xy-stage, the local compositions in the ASDs were determined with a spatial resolution of 1 µm.

Indirect hard modeling1 (IHM) was applied to determine the concentrations of PVP, API and absorbed water at the same time. IHM accounts for shifted peak positions in mixtures and thus enables a highly-accurate determination of mixture compositions.

Long-term stability tests

For ASDs with different API/PVP composition, long-term stability tests were carried out at the conditions 25 °C and 0% RH, 25 °C and 60% RH as well as 40 °C and 75% RH. Recurring PXRD measurements were performed to detect recrystallization and the water content was monitored gravimetrically over time.

Modeling

To account for the influence of RH on the stability of an ASD, thermodynamic equilibrium calculations were performed. These equilibrium calculations accounted for the mutual influence of water sorption in the ASD and API crystallization and/or MIAPS in the water-containing formulation. The chemical potential of water and APIs required for the thermodynamic equilibrium calculations was estimated using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT)[2].

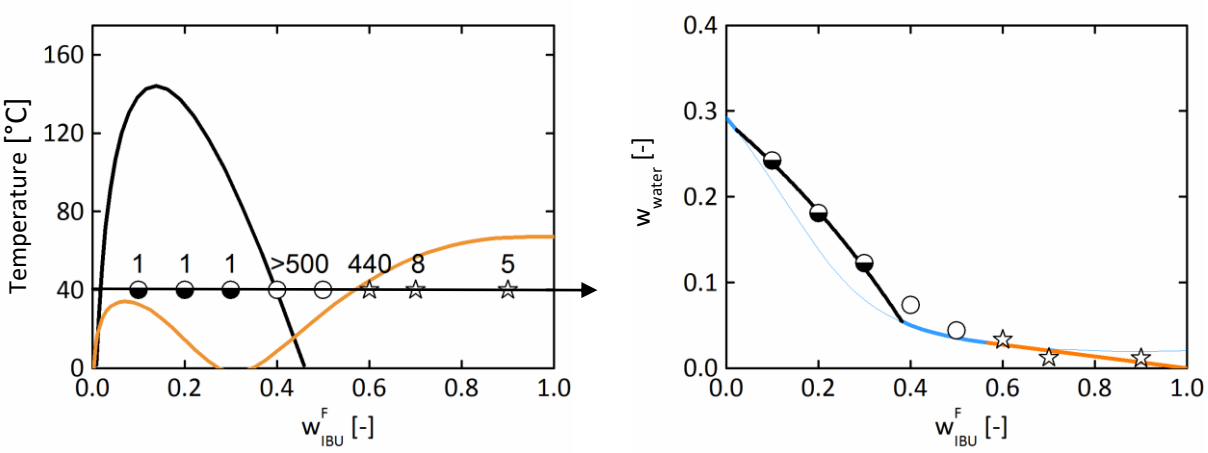

Figure 1: The left figure shows PC-SAFT predicted thermodynamic phase diagrams of PVP/IBU ASD at 75% RH as function of the API content in the water-free formulation w^F_{IBU} (orange line: solubility, black line: MIAPS). Numbers indicate the number of days after which recrystallization (stars), MIAPS (half-filled circles), or stable formulations (open circles) were observed. The right figure is the corresponding water-sorption diagram at 40°C. The blue line is the predicted water sorption in the amorphous formulation, the black line the water sorption after MIAAPS and orange line is the water sorption after complete recrystallization.

RESULTS

Raman spectroscopy

Raman-spectroscopy measurements revealed the composition of demixed formulations. As shown in Figure 2 for a PVP/IBU ASD, two amorphous phases can be clearly distinguished and the size as well as composition of the droplets can be easily obtained from this technique.

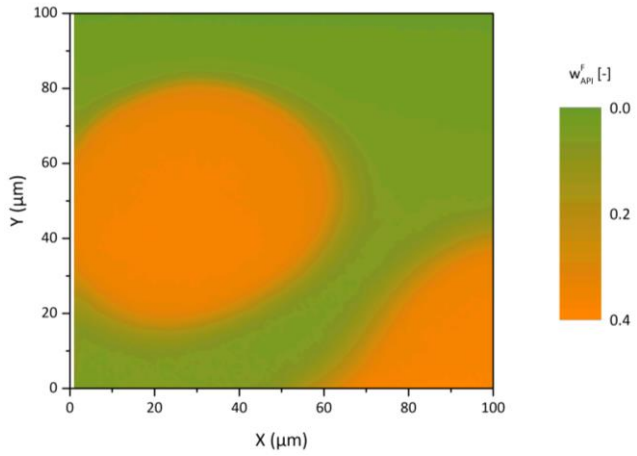

Figure 2: Raman map of a PVP/IBU ASD exhibiting MIAPS at 40 °C and 75% RH

The comparison of the results from Figure 2 with the predicted phase diagram in Figure 1 shows the excellent agreement of the Raman measurements and the predicted MIAAPS.

Long-term stability tests

As shown in Figure 1, MIAPS was observed for ASDs with w^F_{API}=0.1; 0.2 and 0.3 within one day. Recrystallization occurred in the correctly predicted composition range (0.56 < w^F_{API} < 1.00) within 5 and 440 days of storage. Moreover, also the water sorption experiments (Figure 1) revealed that sorption in PVP/IBU ASDs was influenced by MIAPS for API contents of 0.02 < w^F_{API} < 0.38 and influenced by

recrystallization for API contents above w_{API}^{F}=0.56. The sorption behavior for IBU formulations strongly differed from FEL ASDs where only recrystallization was found (not shown).

Conclusion

Confocal Raman mapping experiments elucidated heterogeneities in ASDs. Recrystallization events and MIAPS could be observed in situ during storage. Water sorption and thereby induced phase transitions (recrystallization or MIAPS) could be predicted in quantitative agreement with the experimental data. This study showed that results of long-term stability tests can be predicted correctly in early stages of drug development and that promising polymer candidates for long-term stable ASDs can be identified prior to long-term stability tests by thermodynamic modeling.

REFERENCES

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2. Gross, J., Sadowski, G., Perturbed-Chain SAFT: An Equation of State Based on a Perturbation Theory for Chain Molecules, Ind. Eng. Chem. Res., 40, 1244-1260 (2001).