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Biochemical and Chemical Engineering

Crystallization kinetics in amorphous solid dispersions can be quantified by water sorption measurements

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Introduction

- Amorphous solid dispersions (ASDs) increase solubility and dissolution rate of poorly water-soluble active pharmaceutical ingredients (APIs)
- Amorphous API dissolved in a suitable polymer
- Long-term stability tests imposed by regulatory authorities (FDA) for newly developed ASDs at defined temperature and relative humidity (RH)
- Most marketed ASDs might crystallize during storage
- Information on crystallization kinetics required to predict shelf life of metastable ASDs
- ⇨ Investigating the effect of relative humidity (RH) and API loading on crystallization velocity

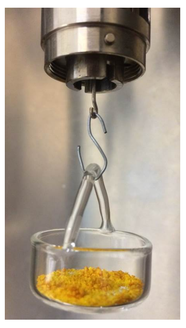
METHODS

Preparing ASDs

- spray drying
- API: Nifedipine (NIF)
- Polymer: poly (vinyl acetate) (PVAC)

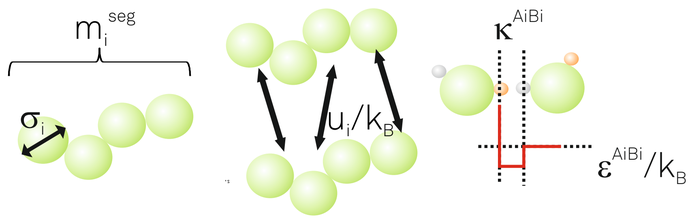
Water sorption

- Magnetic suspension balance



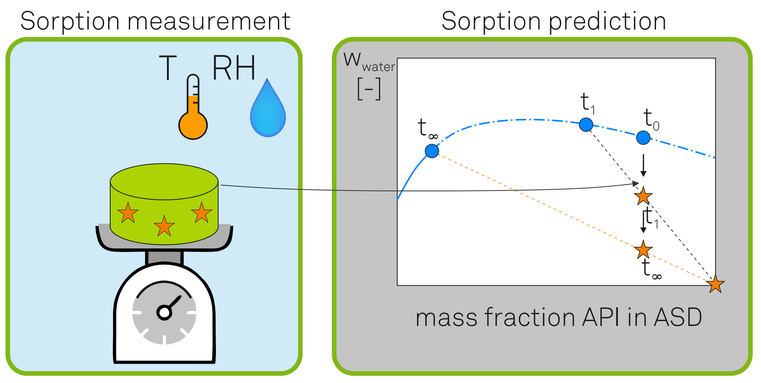
Thermodynamic predictions using PC-SAFT[1]

- Model for residual Helmholtz energy a^{res}
- Five pure-component parameters
- Molecules considered as segmented chains
- Used for predicting mutual impact: Water sorption in ASDs and NIF crystallization[2]



$$a^{res} = a^{hc} + a^{disp} + a^{assoc}$$

Crystal content



Water content in an ASD depends on the degree of crystallinity and vice versa[2]

RESULTS

Sorption measurements → **Thermodynamic prediction** → **Crystallization kinetics** → **Shelf life estimations**

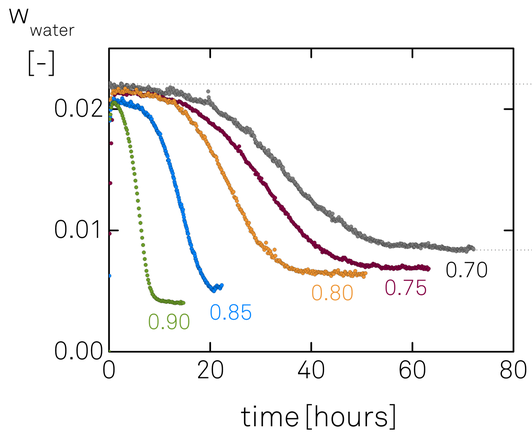


Fig. 1: Experimental time-dependent water sorption of NIF/PVAC formulations with different NIF contents stored at 40°C/ 75% RH.

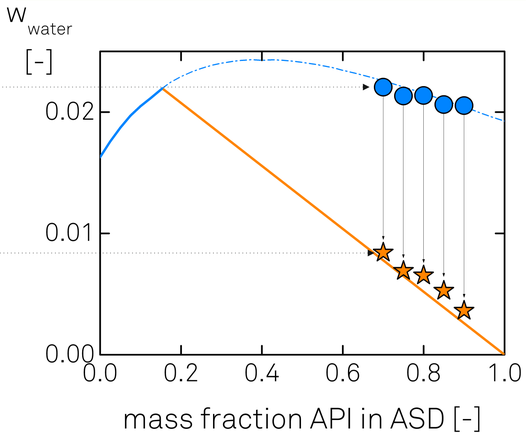


Fig. 2: PC-SAFT predicted water sorption in amorphous (blue) and crystallized (orange) NIF/PVAC ASDs stored at 40 °C / 75% RH. Stable states are indicated by thick lines and metastable states by dash-dotted lines. The first and last value of the sorption measurement (Fig. 1) is indicated by circles (amorphous) and stars (crystallized ASD).

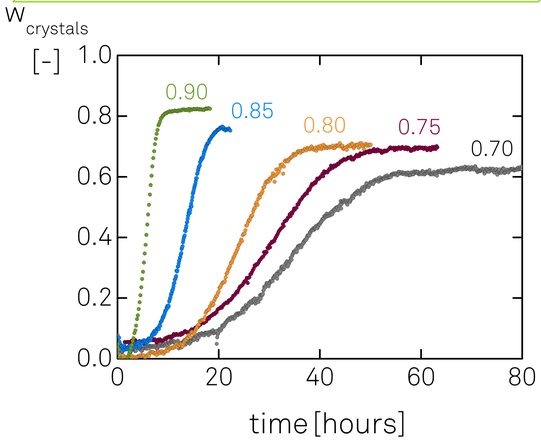


Fig. 3: Amount of NIF crystals in the ASD calculated using PC-SAFT water sorption prediction, the water sorption measurements and a mass balance.

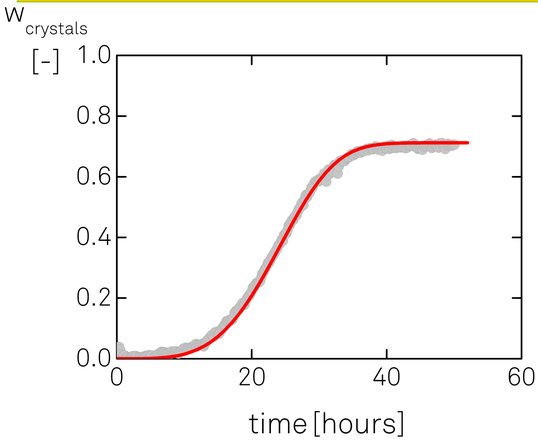


Fig. 4: Avrami-modeled crystallization kinetics of a NIF/PVAC ASD with w_{NIF}=0.80 stored at 40 °C/ 75% RH. Light-gray symbols are crystallization data points (Fig. 3) and the red line is the resulting Avrami modeling.

- Storage at constant conditions (temperature and RH)
- Decrease of water sorption over time
- Initially amorphous samples confirmed to be crystalline after storage via X-ray diffraction

- Mutual impact of water sorption/ crystallization[2] considered
- <u>Quantitative</u> agreement of the PC-SAFT predicted water sorption in amorphous and crystallized NIF/PVAC ASDs and the measurements

- Amount of crystals estimated by coupling
  - Sorption measurements (Fig. 1)
  - PC-SAFT prediction (Fig. 2)
  - Mass balance
- Crystal content increases sigmoidally from zero to the final equilibrium value

- Avrami-Equation[3] used for modeling
- Avrami constants determined
- Estimating crystallization velocity at other storage conditions and API loadings

Conclusion

- Crystallization kinetics was investigated via water sorption measurements
- Degree of crystallinity obtained by coupling with sorption predictions and mass balance
- Calibration-free and easy method to estimate amount of crystals as function of time

Crystallization promoted by
- High API content in ASD
- High storage RH
- High storage temperature

References:
[1] Gross J, Sadowski G, Ind. Eng. Chem. Res., **2001**, 40(4), 1244-1260
[2] Luebbert C, Wessner M, Sadowski G, Mol. Pharm., **2018**, 15(2), 669-678
[3] Avrami M., J. Chem. Phys., **1939**, 7, 1103-1112

DFG Deutsche Forschungsgemeinschaft

For further information:
Luebbert C, Sadowski G: In-situ determination of crystallization kinetics in ASDs via water sorption experiments. Eur. J. Pharm. Biopharm., **2018**, 127, 183-193.