

# Moisture-induced amorphous-amorphous phase separation can be predicted

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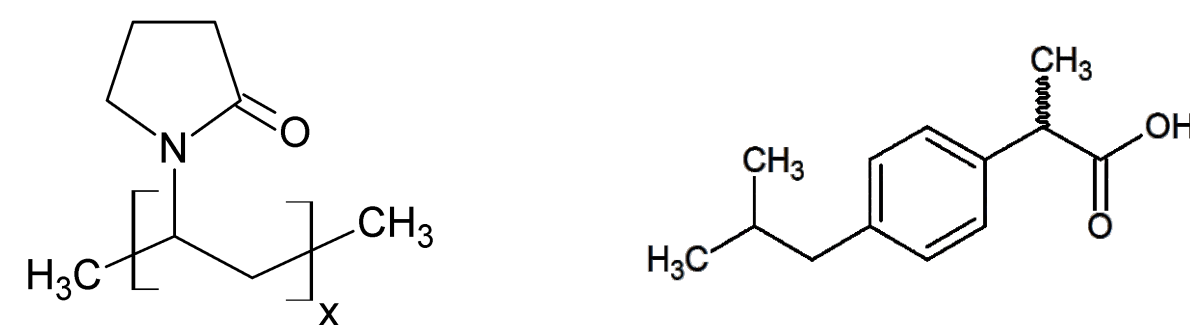


## Introduction

- Amorphous solid dispersions (ASDs) increase solubility and dissolution rate of poorly water-soluble active pharmaceutical ingredients (APIs)
- Amorphous API dissolved in suitable polymer
- Long-term stability tests imposed by regulatory authorities (FDA) for newly developed formulations at defined temperature and RH
- Stable ASDs: No (re)crystallized API neither moisture-induced amorphous-amorphous phase separation (miAPS)
- Long-term stability predicted via phase diagrams considering recrystallization (solubility) and miAPS (liquid-liquid equilibrium)
- ⇒ Predicting the effect of relative humidity (RH) on solubility as well as on APS

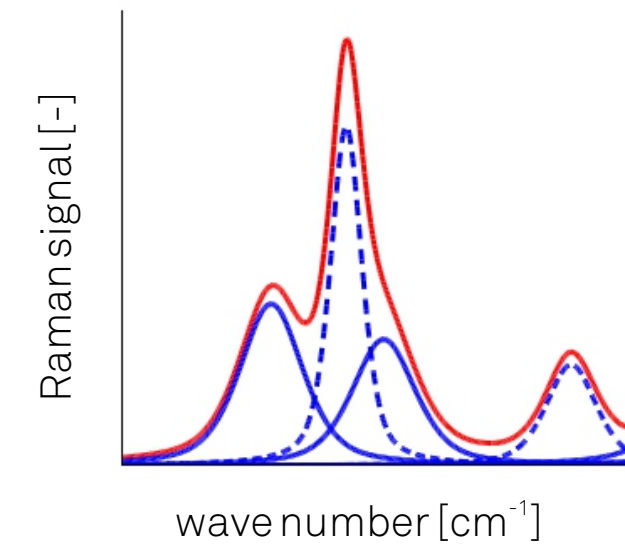
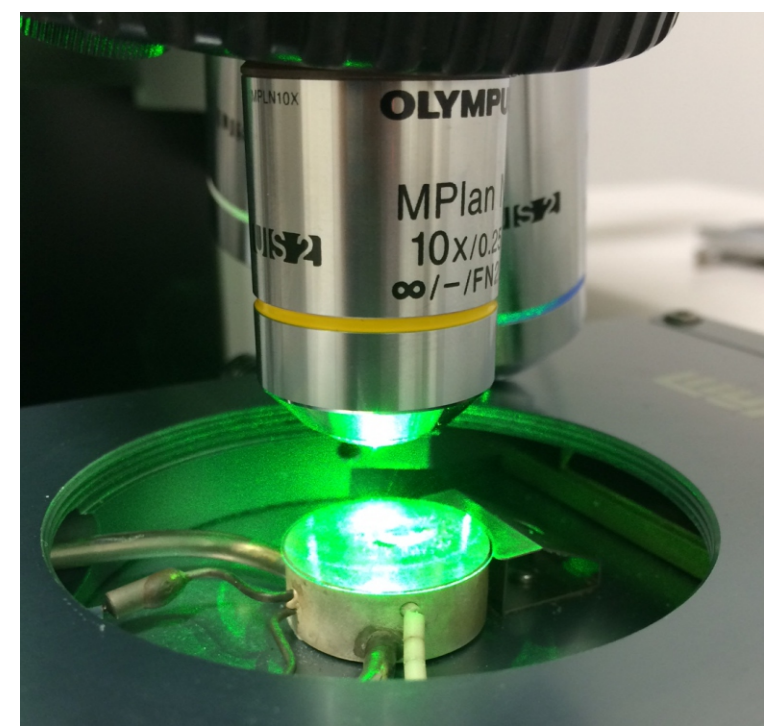
## Long-term stability tests

- Accelerated storage condition: 40°C, 75% RH
- Recrystallization behavior: PXRD
- Water sorption: gravimetric determination



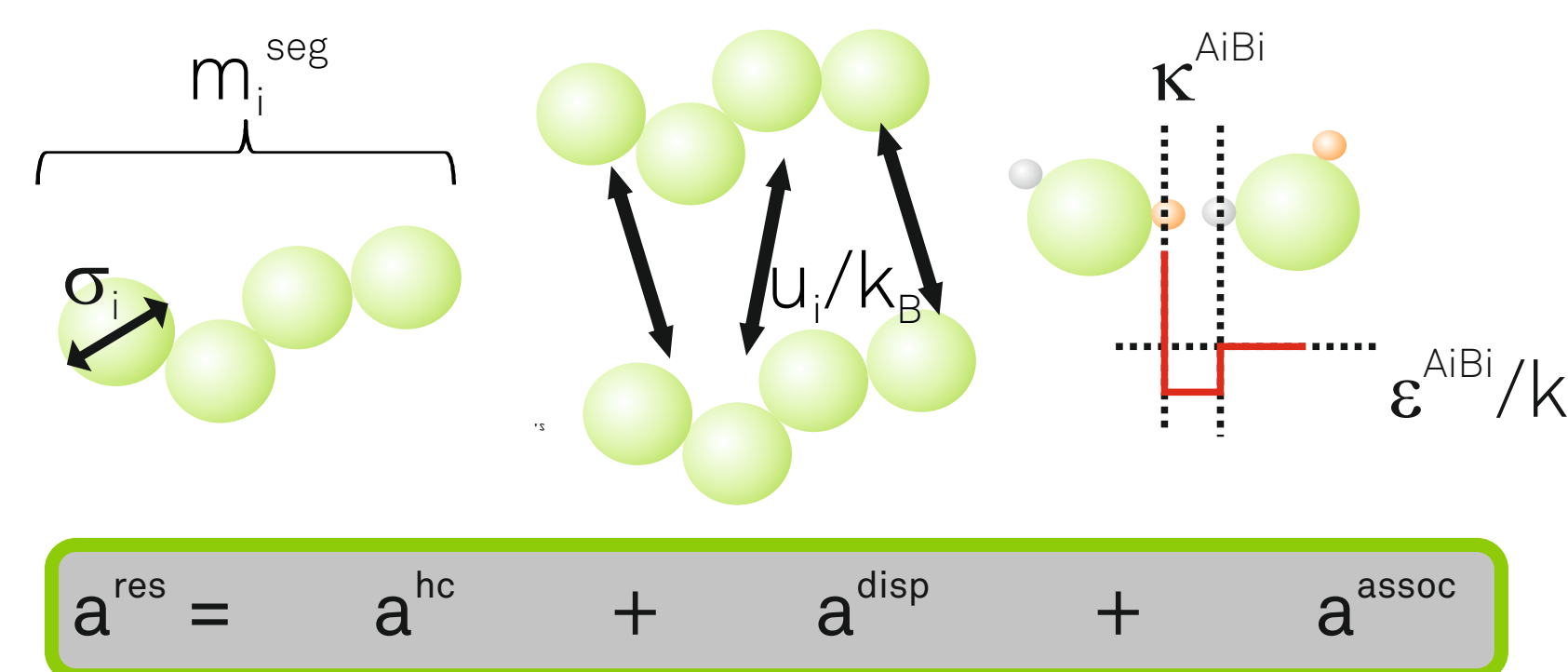
## Measurement of miAPS

Raman spectroscopy + Indirect Hard Modeling<sup>[1]</sup>



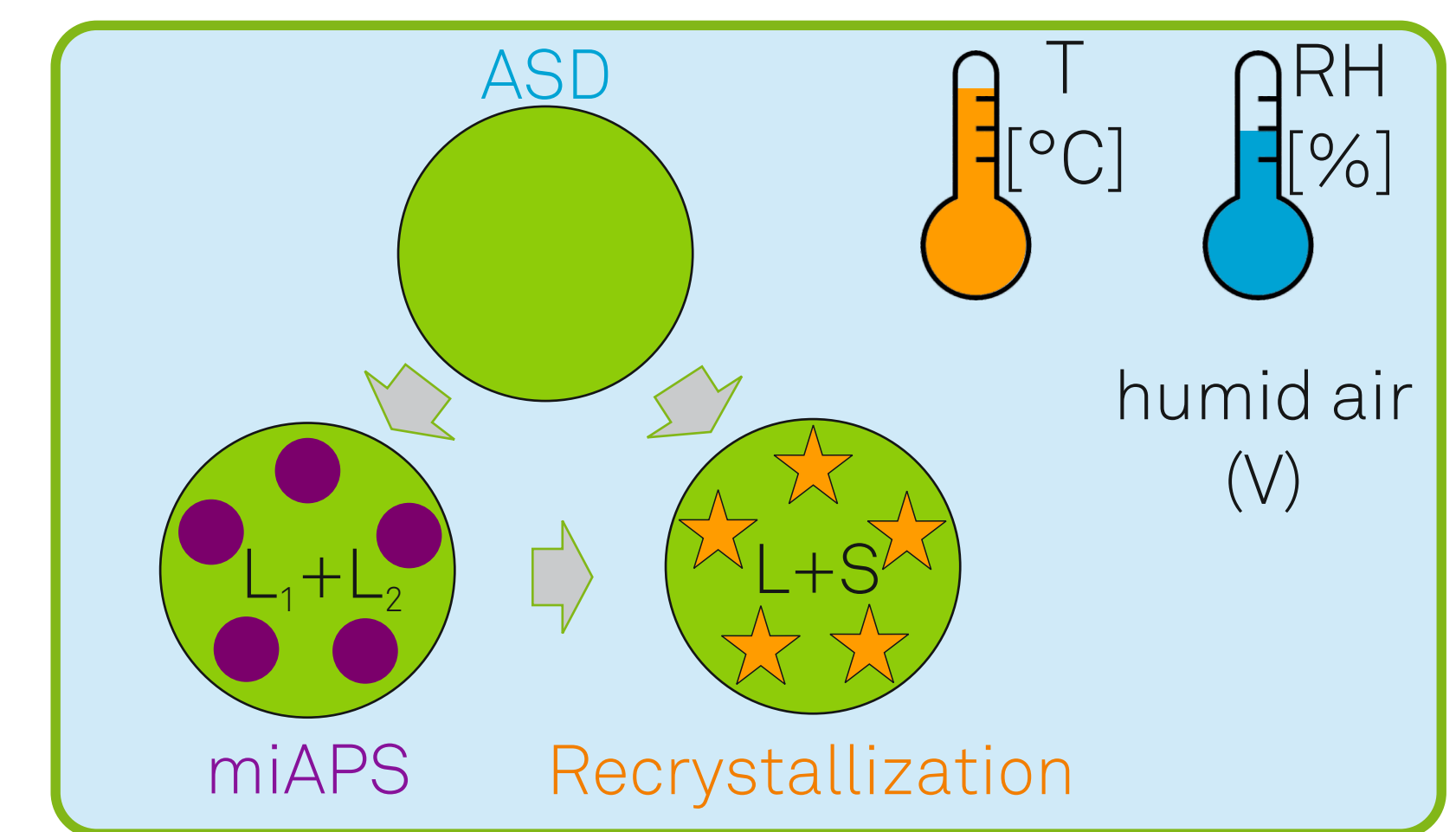
## Thermodynamic model PC-SAFT<sup>[2]</sup>

- Model for residual Helmholtz energy  $a^{\text{res}}$
- Five pure-component parameters
- Molecules considered as segmented chains
- Calculation of API solubility and APS



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

## Influence of humidity



Equilibrium of the humid air (V) with liquid (L) and solid (S) is considered to predict:

- Water sorption in the ASD
- Influence on API solubility<sup>[3]</sup>
- miAPS

METHODS

RESULTS

## Raman mapping

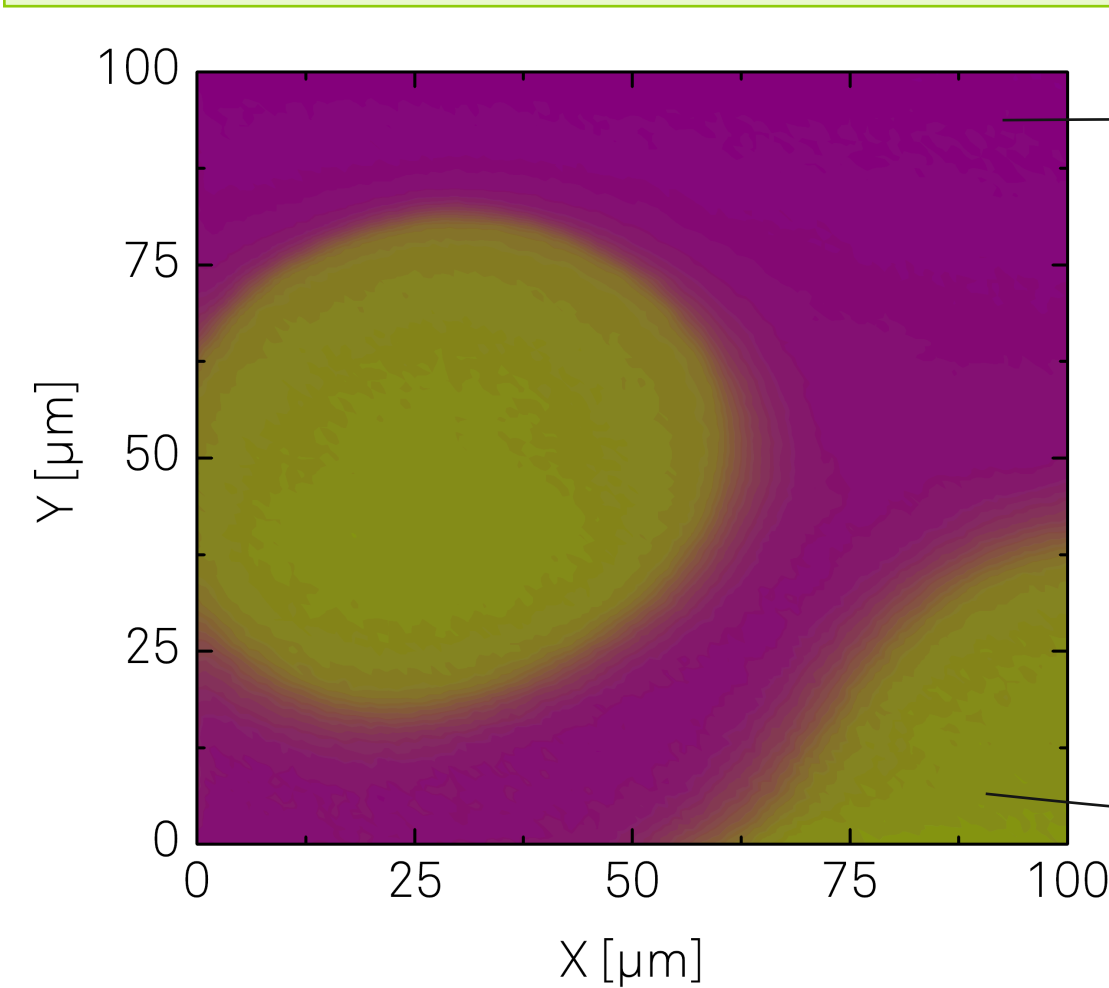


Fig. 1: Raman map of a PVP/IBU ASD exhibiting miAPS at 40°C and 75% RH

- In-situ measurement of concentrations in the two coexisting phases
- Spatially-resolved concentration profiles obtained
- 50 µm droplets with different IBU/PVP/water compositions observed

## Long-term stability tests and water sorption

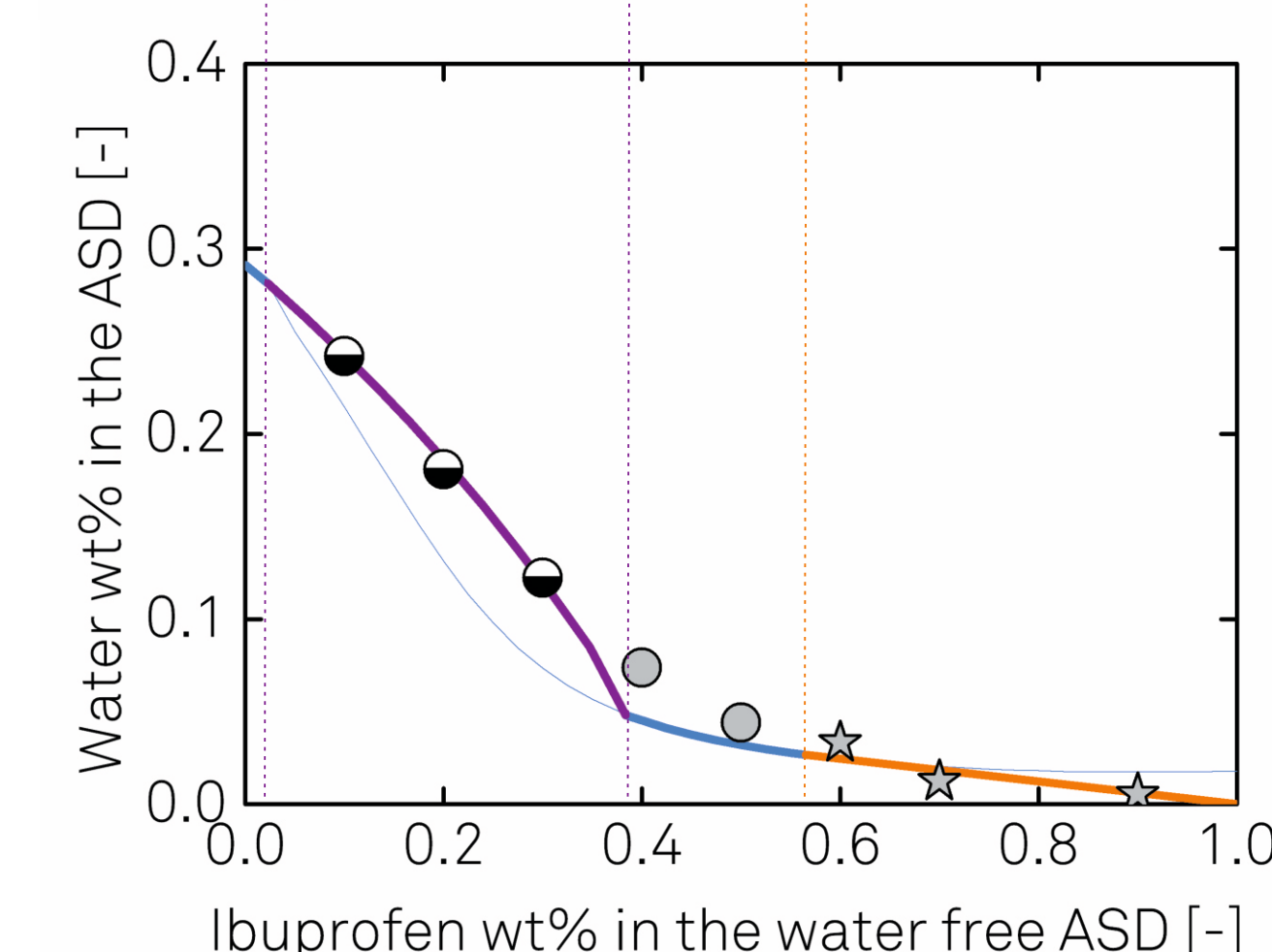
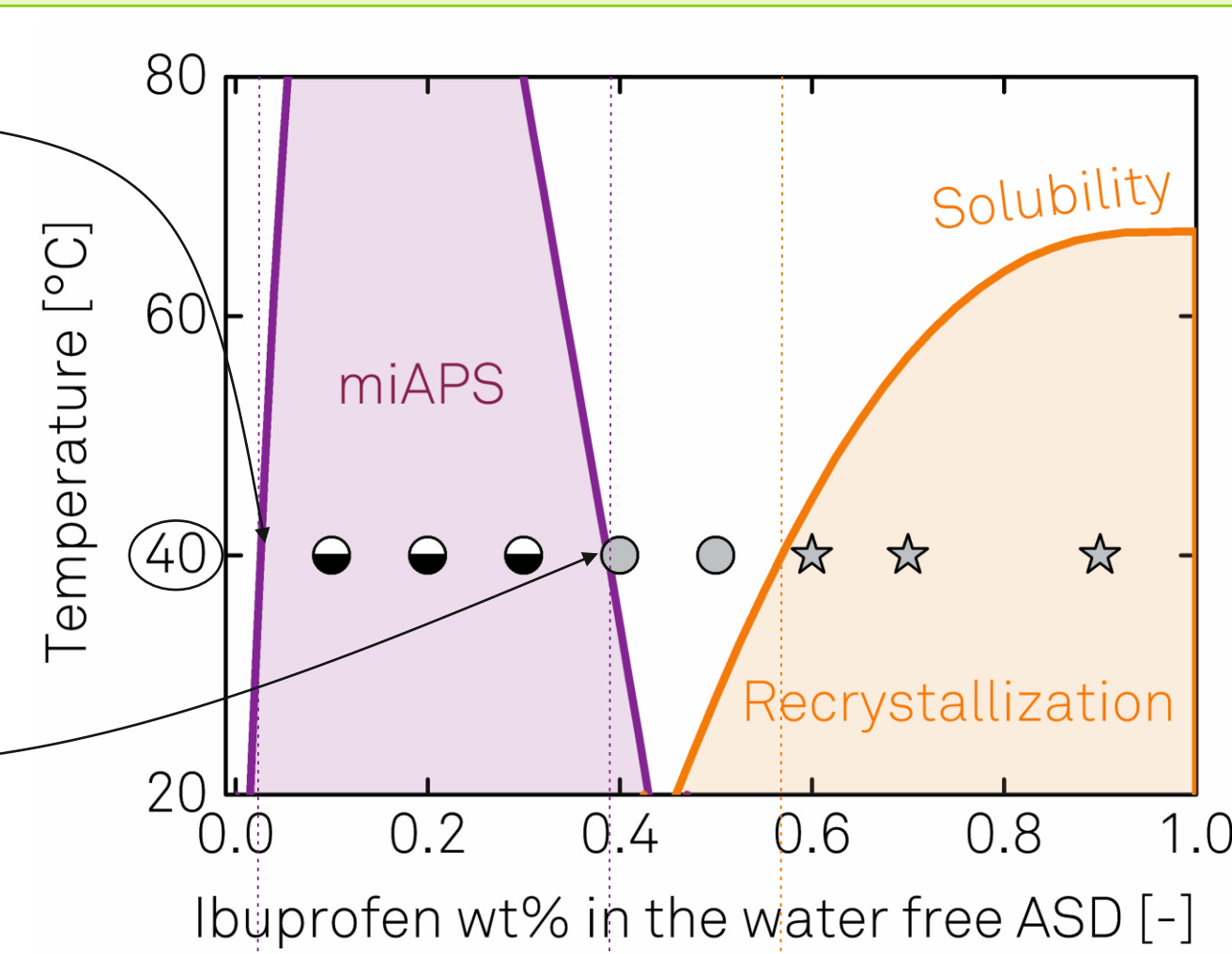
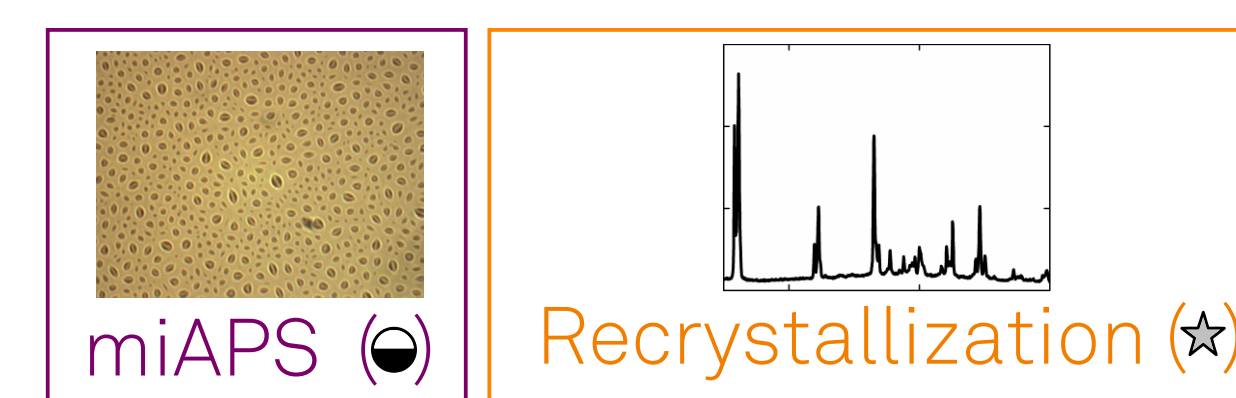


Fig. 2: (a) Predicted phase diagram of the System IBU-PVP at 75% RH. Areas are crystallization- (orange), miAPS- (purple), thermodynamically stable (white). (b) Predicted water sorption for the system IBU-PVP at T=40°C, 75% RH. Thin lines are metastable sorption values, thick lines thermodynamically stable. Symbols represent microscopically observed miAPS (●), recrystallization (★) and stable formulations (○).



Results of 2-years enduring long-term stability tests in accordance to predicted behavior

- Water sorption in formulations determined
- Recrystallization, miAPS and water sorption affect each other
- Water content in formulation depends on physical state: amorphous/ miAPS/ recrystallized

## Stability criteria

### Hydrophobic APIs promote miAPS

- miAPS is more likely to occur in hydrophobic BCS Class II-APIs like IBU or Felodipine

### High RH promotes miAPS

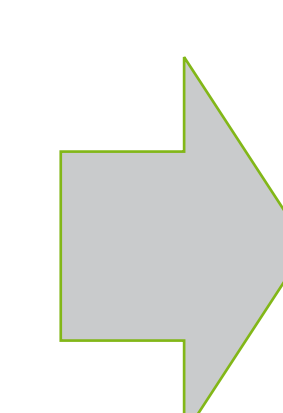
- High storage RH directly correlates with a bigger miAPS region

### Hydrophilic polymers promote miAPS

- ASDs containing hydrophilic polymers absorb more water leading to miAPS

## Conclusion

- This work studied the effect of RH on the thermodynamic stability of ASDs
- miAPS and crystallization were investigated experimentally and by thermodynamic predictions
- APS was quantified experimentally by confocal Raman microscopy



Results of long-term stability tests predictable