technische universität dortmund
Biochemical and Chemical Engineering

DDiC Drug Delivery innovation Center

invite

Thermodynamic and kinetic stability of amorphous solid dispersions

Friederike Wolbert[1,2], Christian Luebbert[2] and Gabriele Sadowski[2]

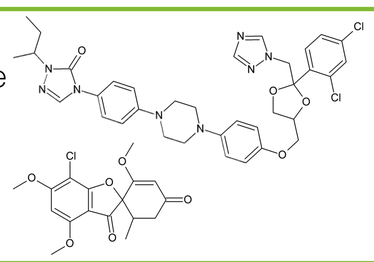
[1]INVITE GmbH, CHEMPARK, Geb. W32, 51373 Leverkusen, Germany
[2]TU Dortmund University, Laboratory of Thermodynamics, Emil-Figge-Str. 70, 44227 Dortmund, Germany,
Phone: +49 (231) 755-2635, Fax: +49 (231) 755-2572, gabriele.sadowski@tu-dortmund.de

Motivation

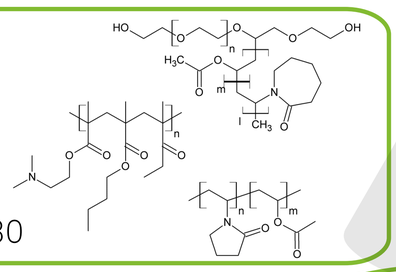
Many newly developed active pharmaceutical ingredients (APIs) show low solubility in water and may require an enabling formulation in order to achieve sufficient bioavailability. One powerful formulation option for that purpose is a so-called amorphous solid dispersion (ASD), a formulation in which the amorphous API is embedded in a polymer matrix to prevent crystallization. However, not all ASDs are thermodynamically stable and will thus crystallize, at least after infinite time. The time span of crystallization is influenced by various factors like the storage conditions (temperature, relative humidity (RH)). Knowing the crystallization velocity of thermodynamically metastable ASDs at long-term storage conditions (25°C/60% RH or 40°C/75% RH) is highly relevant for the determination of at least kinetically stable API/polymer combinations and compositions.[1]

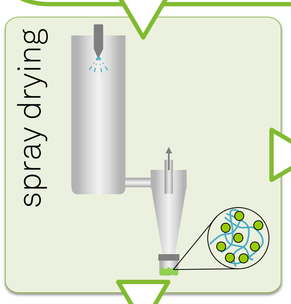
Preparation and analytic methods

APIs:
Itraconazole (ITR)
Griseofulvin (GRI)

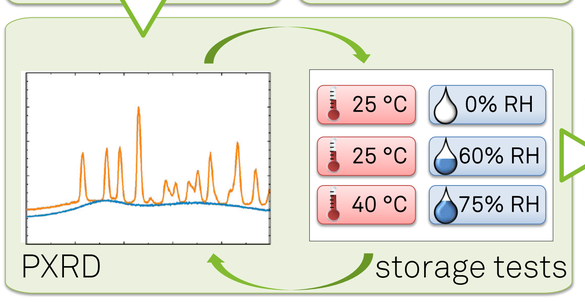


Polymers:
Soluplus®
Eudragit® EPO
Plasdone™ S630





solubility and glass transition



long-term stability

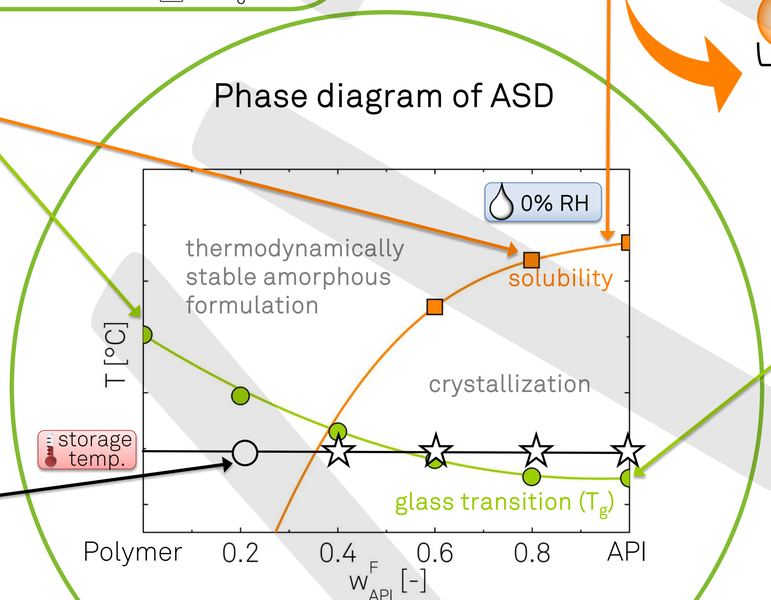


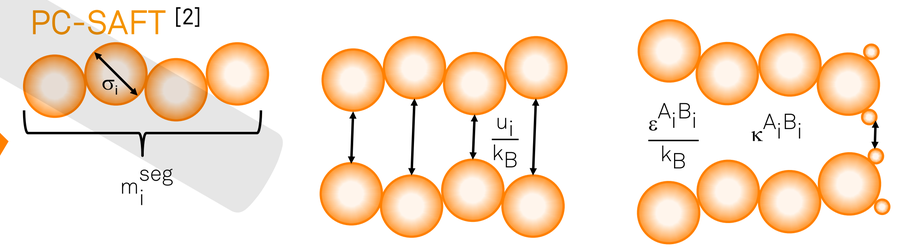
Figure 1: Schematic ASD phase diagram showing the solubility (orange) and T_g (green) experimentally determined (symbols) and modeled (solid line). Black symbols represent ASDs stored at certain storage conditions. Circle means the ASD is amorphous – star means the ASD is crystallized.

Modeling

Solubility equation

$$x_{API}^{L} = \frac{1}{\gamma_{API}^{L}} \exp\left(-\frac{\Delta h_{0i}^{SL}}{RT}\left(1-\frac{T}{T_{API}^{SL}}\right)-\frac{\Delta c_{p,i}^{SL}}{R}\left(\ln\left(\frac{T_{0i}^{SL}}{T}\right)-\frac{T_{0i}^{SL}}{T}+1\right)\right)$$

PC-SAFT [2]



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

Kwei-equation [3]

$$T_g^{mix} = \frac{\Sigma_i K_i w_i T_{g,i}}{\Sigma_i K_i w_i} + \frac{1}{2}\Sigma_i \Sigma_{j\neq i} q_{ij} w_i w_j \qquad K_i = \frac{\rho_1 T_{g,1}}{\rho_i T_{g,i}}$$

PC-SAFT was used to predict the solubility of the APIs in the polymers in the absence and presence of water. The Kwei-equation was used to predict the glass transition temperature (T_g) in the absence and presence of water.

Results

Influence of the polymers Soluplus®, Eudragit® EPO and Plasdone™ S630

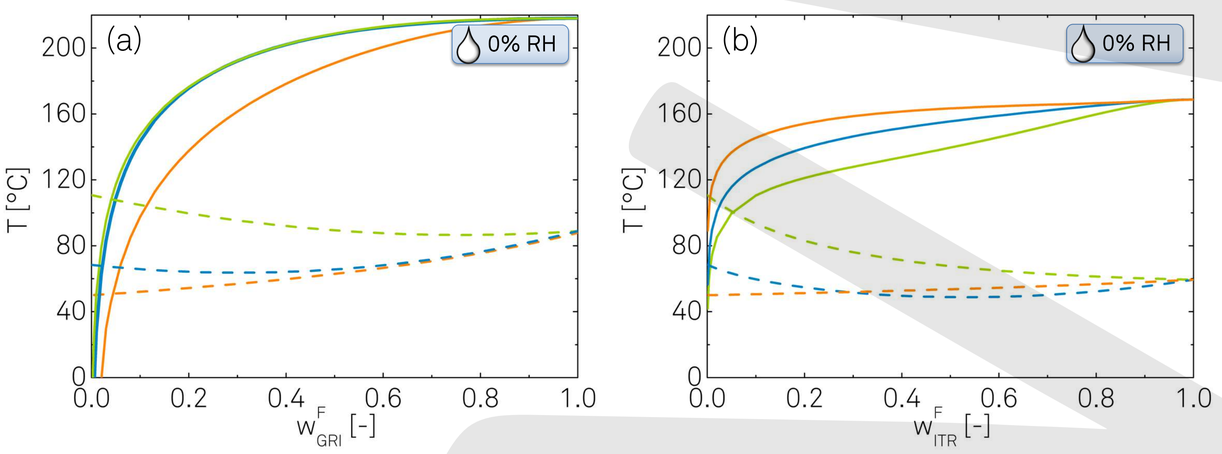


Figure 2: Comparison of solubility (solid line, modeled with PC-SAFT) and T_g (dashed line, modeled with Kwei-equation) of (a) GRI ASDs and (b) ITR ASDs with the three different Polymers: Soluplus® (green), Eudragit® EPO (orange) and Plasdone™ S630 (blue).

Solubility of ITR and GRI in all polymers is very low at ambient temperature

Influence of relative humidity (RH)

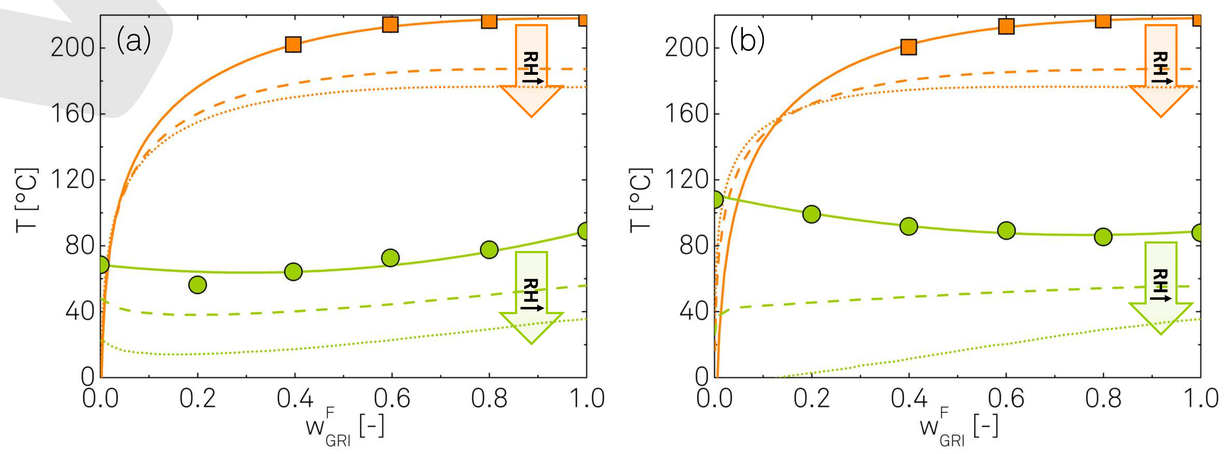


Figure 3: Solubility (orange, modeled with PC-SAFT) and T_g (green, modeled with Kwei-equation) of (a) GRI/Soluplus® and (b) GRI/Plasdone™ S630 ASD influenced by RH (0% RH (solid line), 60% RH (dashed line), 75% RH (dotted line)). The symbols are experimentally detected solubilities and T_gs.

RH has a minor influence on the solubility but a huge influence on the glass transition temperature

Long-term stability of GRI in Soluplus®

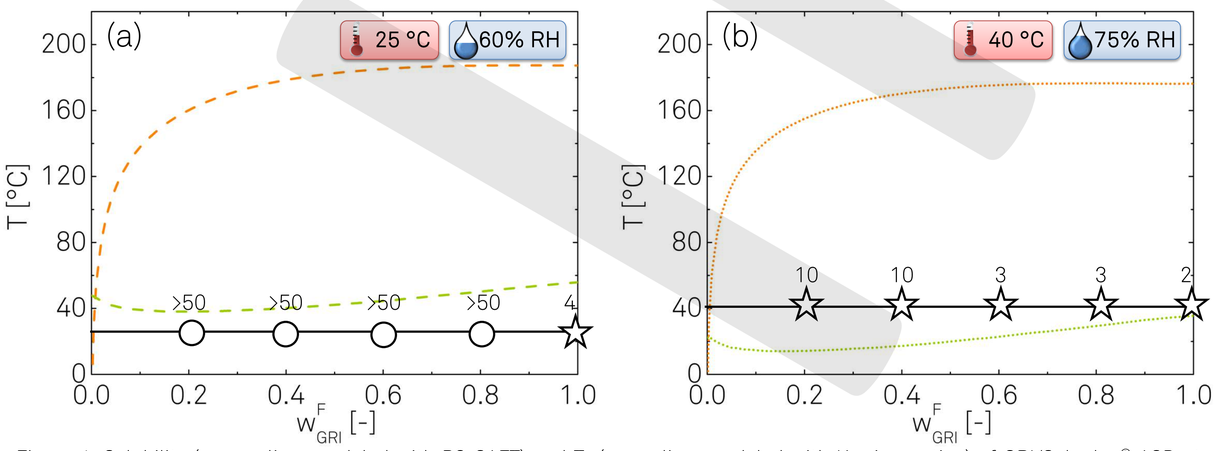


Figure 4: Solubility (orange line, modeled with PC-SAFT) and T_g (green line, modeled with Kwei-equation) of GRI/Soluplus® ASD at (a) 60% RH and (b) 75% RH. Symbols represent ASDs stored at (a) 25 °C/60% RH and (b) at 40 °C/75% RH. Circle means the ASD is still amorphous – star means the ASD is crystallized. The numbers show the time span (in days) till crystallization.

Crystallization kinetics of ASDs is strongly influenced by storage conditions and API content

Conclusion

Within this work, the phase diagrams of ASDs influenced by relative humidity could successfully be modeled with the PC-SAFT equation of state (solubility) and the Kwei-equation (glass transition temperature). It was found, that the Itraconazole and Griseofulvin ASDs are thermodynamically unstable in the entire composition range from 20 – 80 wt% at all storage conditions. All investigated ASDs are expected to crystallize in a certain time span (or are already crystallized). This shows the high need for an investigation of the crystallization kinetics of ASDs in order to estimate their true shelf life.

References:

[1] Prudic, A.; Ji, Y.; Luebbert, C.; Sadowski, G. *Eur. J. Pharm. Biopharm.*, **2015**, *94*, 352–362.
[2] Gross, J.; Sadowski, G. *Ind. Eng. Chem. Res.*, **2001**, *40*, 1244–1260.
[3] Kwei, T.K. *Journal of Polymer Science Part C: Polymer Letters*, **1984**, *22*, 307–313.

Additional Informations?