Stability of Pharmaceutical Co-Crystals Against Humidity Can Be Predicted

A thermodynamic approach for understanding co-crystal deliquescence and its consequences

Heiner Veith, Maximilian Zaeh, Christian Luebbert, Gabriele Sadowski

For the development of pharmaceutical products, the knowledge about their stability against relative humidity (RH) is crucial. Especially co-crystals (CC), composed from at least two components, present special challenges regarding physical stability at humid conditions. RH can lead to deliquescence and can induce dissociation and transformation to less-soluble solid-state forms of the consisting components. We developed an approach for predicting the CC transformations that may happen upon CC storage at certain RHs. The new approach allows to reliably predict the deliquescence and transformation of CCs even in the presence of common excipients like sugars used in pharmaceutical formulations.

The increasing utilization of CCs as pharmaceutical products intensifies the need for faster development times and predictive in-silico methods for predicting the stability of new products. For predicting the effects of humid conditions on CCs, we used the thermodynamic model PC-SAFT. Particularly, we calculated the deliquescence relative humidity (DRH), above which a crystal (be it a pure component or a CC) is going to be dissolved. As examples, the phase behaviors of the systems succinic acid (SA)/nicotinamide (NA), carbamazepine/nicotinamide, theophylline (TP)/citric acid (CA), and urea/glutaric acid were considered. Figure 1 shows the modeling result and the relevant DRHs for the system SA/NA. The pure CC was predicted to deliquesce above 99% RH (DRH_{CC}). If SA is present besides the CC, the DRH is lowered to 97.8% RH ($DRH_{CC/SA}$). This value further decreases in the presence of NA to 93.6% RH ($DRH_{CC/NA}$).

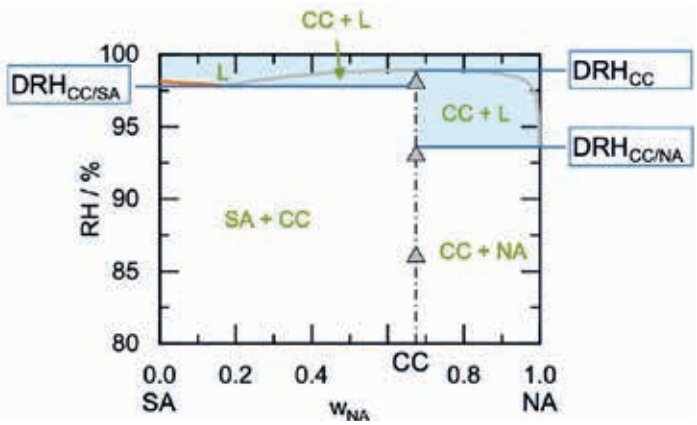

Figure 1: Phase behavior of succinic acid (SA) and nicotinamide (NA) forming a 2:1CC at 25 °C. Light blue areas show regions with deliquescence (L). DRH_{CC}, $DRH_{CC/SA}$, and $DRH_{CC/NA}$ show RHs above which the pure CC, the CC in contact with SA, and the CC in contact with NA dissolves. Triangles show storage conditions for the CC at 86, 93, and 98% RH.

The other systems were modelled accordingly. For the CC of TP and CA, deliquescence was predicted to occur above 99.3% RH. This value was predicted to remarkably decrease in the presence of CA to 79.3% RH which was also experimentally validated.

The modeling also allowed to predict the different behavior of so-called congruent or incongruent CC systems. Whereas deliquescence for congruent systems leads to recrystallization of the CC when decreasing RH below DRH, deliquescence for incongruent CC systems leads to crystallization of other crystal forms. These predictions were also verified experimentally, as shown in Figure 1.

For visualization of the deliquescence phenomenon, we used a RH chamber. Figure 2 shows a polarized-light picture of TP, CA, and their CC at 90% RH and 25 °C. CA with a predicted DRH of 79.4% RH and the CC contaminated with an CA impurity showed deliquescence at that conditions, whereas TP with a predicted DRH of 99.9% RH did not show deliquescence. This was in accordance with the predictions.

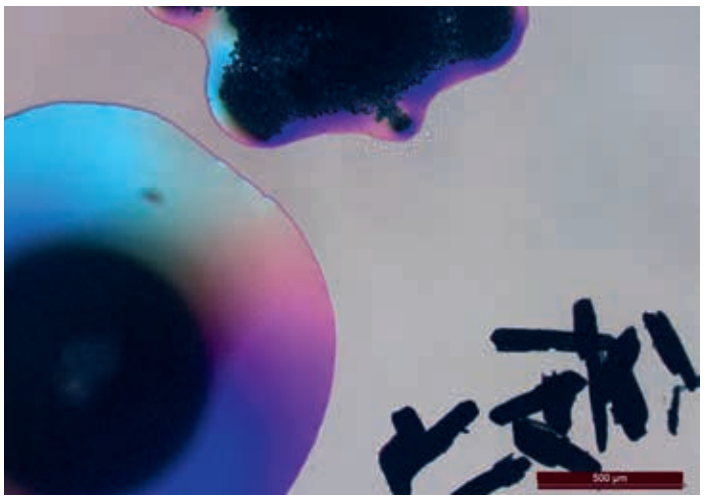

Figure 2: Polarized microscopic image of samples of the TP/CA CC, TP hydrate, and CA hydrate in the RH chamber. Sample positioning: top CC sample, bottom left CA, bottom right TP. Picture shows deliquescence at 90% RH and 25 °C for the CC and CA but not for TP.

Conclusively, we could show that PC-SAFT allows to predict DRHs as well as hydrate transformation RHs, which can also be found in the referenced paper. The new approach thus presents a valuable tool to shorten the development procedure for new pharmaceutical CC products.

Contacts:
maximilian.zaeh@tu-dortmund.de
gabriele.sadowski@tu-dortmund.de

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