

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

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INTRODUCTION

Most new active pharmaceutical ingredients (APIs) exhibit a very low solubility in water, leading to an insufficient absorption in the gastrointestinal tract and thus poor bioavailability. Several approaches exist to increase the bioavailability of APIs. A promising approach is to transform the -usually crystalline- API into its amorphous form, which is better water soluble, but also metastable against crystallization. The most common stabilizing strategy is to embed the amorphous API in a polymer matrix resulting in a so-called amorphous solid dispersion (ASD). However, as the API loading usually exceeds its solubility in the polymer, the API tends to recrystallize during storage. This is particularly true for humid storage conditions as the ASDs may absorb remarkable amounts of water which drastically decrease the solubility of the hydrophobic API in the ASD. Moreover, absorbed water also lowers the ASD glass-transition temperature thus decreasing both, the thermodynamic as well as the kinetic stability of ASDs.

METHODS

Water sorption measurements

ASDs composed of the API nifedipine (NIF) and the polymer poly (vinyl acetate) (PVAC) were prepared by spray drying. Directly after preparation, the ASDs (initial amorphous state confirmed by powder X-ray diffraction) were transferred to a magnetic suspension balance¹. In this device, the water sorption in the ASD was measured as function of time at fixed temperature and relative humidity (RH) conditions. ASDs with different drug loadings (70 wt% to 90 wt% NIF in the ASD) were exposed to different temperatures (30°C, 35°C, and 40°C) and RHs (60%, 75%, and 90%).

Thermodynamic calculations

In previous works we could show that the API solubility in ADSs in the absence² or presence^{3,4} of humidity can be predicted using the Perturbed-Chain Statistical Associating Fluid Theory⁵ (PC-SAFT). At humid storage conditions, the thermodynamic equilibrium between humid air, the amorphous API/polymer mixture and the crystallized API is considered to correctly describe the mutual influence of API crystallization and water sorption in the ASD³. In turn, this approach can be used to predict the amount of crystallized API as well as the concentration of the remaining amorphous part of the formulation if the amount of absorbed water is known from an experiment (depicted in Fig. 1).

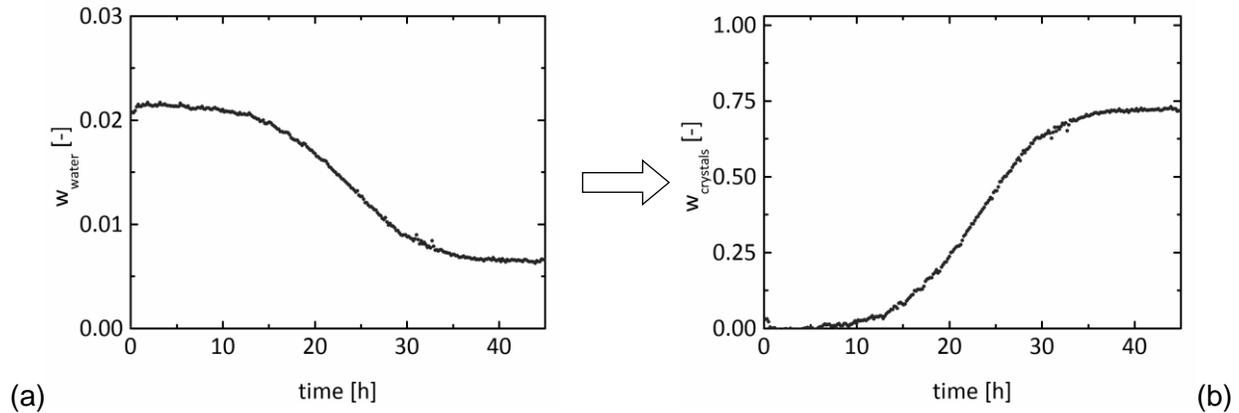


Fig. 1: (a) Experimental time-dependent water sorption of a nifedipine/ poly (vinyl acetate) ASD stored at 40°C, 75% RH and (b) amount of nifedipine crystals in the ASD calculated using PC-SAFT using the information from diagram (a)

RESULTS

Water sorption measurements

The water sorption was measured using a magnetic suspension balance at constant temperature and RH conditions. The result for an ASD with 80wt% NIF in PVAC is shown in Fig. 1a. Immediately after adjusting the RH to 75% RH, the sample absorbed 2.1 wt% water. This value remained constant for about ten hours, and then began slowly to decrease. This means that water was released from the ASD again, although the storage conditions were kept constant throughout the whole experiment. After 40 hours of storage, a second plateau was finally reached at a water content of 0.6 wt% which did not change anymore. This latter value almost quantitatively agrees to the predicted water sorption in a crystallized formulation (0.45 wt%). It is thus obvious to assume that the decrease in water sorption was caused by NIF crystallization. Moreover, the presence of crystals at the end of the experiment was confirmed by X-ray diffraction (Fig. 2b) while no crystals were present at the beginning of the experiment (Fig. 2a).

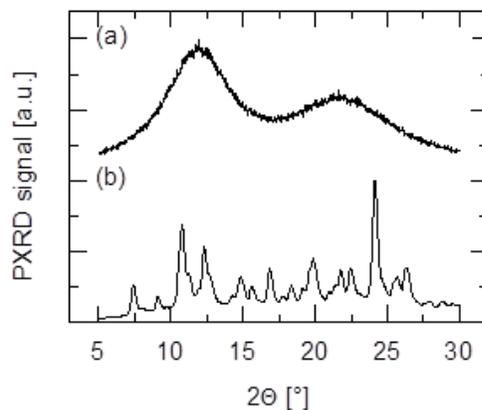


Fig. 2: X-ray diffractogram of the nifedipine (80 wt%)/ poly (vinyl acetate) ASD stored at 40°C, 75% RH obtained before (a) and after (b) the long-term water sorption experiment

Crystallization kinetics

Comparing the measured water sorption with the PC-SAFT predictions, reveals that the water sorption of the freshly-prepared formulation (2.1 wt% water) quantitatively corresponds to the predicted water sorption of an amorphous formulation, whereas the water sorption at the end of the experiment (0.6 wt%) quantitatively corresponds to the predicted water sorption in the ASD, which contains the equilibrium amount of crystallized NIF. For all experimental data points in between, a mass balance was performed using the measured water contents and the PC-SAFT predicted water sorption in the amorphous part of the ASD leading to the amount of crystals formed for every water-sorption data point (Fig. 1b). As expected, the amount of crystals equals zero at the beginning of the experiment and increases to 71% during storage. This value is quite close to the expected maximum amount of crystals (76%) at equilibrium (NIF molecules will crystallize until the NIF solubility in the PVAC/water system is reached).

Thus, the crystallization curve in Fig. 1b was obtained only using the water-sorption curve in Fig. 1a combined with the PC-SAFT modeled API solubility in the polymer/water system. The crystallization kinetics was investigated for different storage conditions. High storage RHs, high temperatures, and high NIF loadings were found to accelerate the crystallization velocity.

CONCLUSION

The API crystallization kinetics in ASDs can be determined only based on simple water-sorption measurements combined with a thermodynamic modeling without the need of additional measurements. It is worth mentioning that this method is completely calibration-free and thus a very cheap and easy method to estimate the amount of API crystals in an ASD.

KEYWORDS

Amorphous solid dispersion, crystallization kinetics, water sorption, PC-SAFT

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