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Moisture-induced phase separation and recrystallization in amorphous solid dispersions

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ABSTRACT

Active Pharmaceutical Ingredients (APIs) are often dissolved in polymeric matrices to control the gastrointestinal dissolution and to stabilize the amorphous state of the API. During the pharmaceutical development of new formulations, stability studies via storage at certain temperature and relative humidity (RH) have to be carried out to verify the long-term thermodynamic stability of these formulations against unwanted recrystallization and moisture-induced amorphous–amorphous phase separation (MIAPS). This study focuses on predicting the MIAPS of API/polymer formulations at elevated RH. In a first step, the phase behavior of water-free formulations of ibuprofen (IBU) and felodipine (FEL) combined with the polymers poly(vinyl pyrrolidone) (PVP), poly(vinyl acetate) (PVAC) and poly (vinyl pyrrolidone-co-vinyl acetate) (PVPVA64) was determined experimentally by differential scanning calorimetry (DSC). The phase behavior of these water-free formulations was modeled using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). Based on this, the API solubility and MIAPS in the above-mentioned formulations at humid conditions was predicted in perfect agreement with the results of two-year lasting stability studies at 25 °C/0% RH and 40 °C/75% RH. MIAPS was predicted and also experimentally found for the FEL/PVP, FEL/PVPVA64 and IBU/PVP formulations, whereas MIAPS was neither predicted nor measured for the IBU/PVPVA64 system and PVAC-containing formulations. It was thus shown that the results of time-consuming long-term stability tests can be correctly predicted via thermodynamic modeling with PC-SAFT.

1. Introduction

Most recently-developed active pharmaceutical ingredients (API) have a low solubility in water (Vo et al., 2013; Baghel et al., 2016). This can lead to a poor dissolution behavior and bioavailability in the gastrointestinal tract when administered in an solid oral dosage form. This biovailability limit can be avoided by transfering the API into its amorphous state. To prevent recrystallization of this metastable state, the amorphous API is usually dissolved in a siutable polymer matrix. Such formulations, often denoted as amorphous solid dispersions (ASDs), are state-of-the-art for poorly water-soluble APIs and many formulations based on this technique are already on the market (Vasconcelos et al., 2007).

API/polymer formulations long-term stable against recrstallization are usually found by trial-and-error or applying statistical design of experiments (Basalious et al., 2011). Time-consuming long-term stability tests are carried out via storage at defined storage temperatures and relative humidities (RH) afterwards choosing the best performing formulation.

However, it was already shown that the long-term thermodynamic stability against API crystallization at dry conditions (Knopp et al., 2015a,b; Sun et al., 2010; Zhao et al., 2011; Tian et al., 2013; Prudic et al., 2014a) and humid conditions (Prudic et al., 2015a; Lehmkemper et al., 2017) can be reliably estimated by considering the thermodynamic phase diagram of an API/polymer formulation. Thermodynamic models like the Flory-Huggins-Theory (Flory, 1942) (FHT) or the Perturbed-Chain Statistical Associating Fluid Theory (Gross and Sadowski, 2001) (PC-SAFT) were already successfully applied to calculate the solubility of APIs in dry polymers (Prudic et al., 2014a,b, 2015b; Lin and Huang, 2010; Tao et al., 2009). To estimate the kinetic stability, the glass-transition temperature of a fully amorphous API/polymer formulation can be correlated by empirical approaches like the

Abbreviations: API, active pharmaceutical ingredient; APS, amorphous-amorphous phase separation; ASD, amorphous solid dispersion; DSC, differential scanning calorimetry; FEL, Felodipine; FHT, Flory-Huggins-theory; HSM, hot-stage microscopy; IBU, ibuprofen; MIAPS, moisture-induced amorphous–amorphous phase separation; PC-SAFT, perturbed-chain statistical associating fluid theory; PXRD, powder x-ray diffraction; PVAC, poly(vinyl acetate); PVP, poly(vinyl pyrrolidone); PVPVA64, poly(vinyl pyrrolidone-co-vinyl acetate); RH, relative humidity

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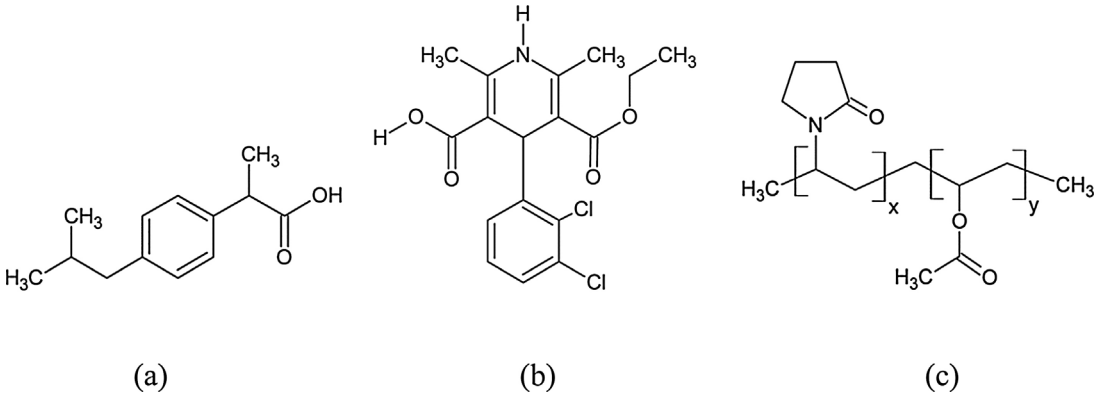

Fig. 1. Chemical structures of the investigated APIs IBU (a), FEL (b) incorporated in the polymers (c) PVP (monomer x), PVAC (monomer y) and PVPVA64 (both, monomers x and y).

Gordon-Taylor-Equation (Gordon and Taylor, 1952).

Besides recrystallization, also amorphous–amorphous phase separation (APS) might occur in dry formulations of API and excipient. APS is the formation of two coexisting amorphous phases, which is from thermodynamic point of view exactly the same as a liquid–liquid demixing (e.g. known from water/oil mixtures). In pharmaceutical ASD formulations, APS leads to a splitting into an API-rich and a polymer-rich phase causing highly-unwanted inhomogeneities in the formulation (Prudic et al., 2014b; Lin and Huang, 2010). It is worth mentioning that this APS is not directly related to API recrystallization as the formed API-rich phase must not necessarily undergo recrystallization (Goetsch et al., 2017; Espitalier et al., 1995; Rashid et al., 2014).

APS was e.g. reported in Felodipine (FEL)/poly(acrylic acid) (Lin and Huang, 2010), Indomethacin-citric acid (Lu and Zografi, 1998), poly(vinyl pyrrolidone) (PVP)/Dextrane (van Eerdenbrugh et al., 2012), and in Ibuprofen (IBU)/poly(lactic-co-glycolic acid) (Luebbert et al., 2017).

During the development of new formulations, stress tests at elevated RH need to be carried out to assure the long-term stability and required shelf life of the formulation. The absorbed moisture causes a dramatic decrease in glass-transition temperature of a formulation due to the low glass-transition temperature of water which has been widely investigated for pharmaceutical excipients (Yoshioka et al., 1994) as well as for API/polymer formulations (Oksanen and Zografi, 1990; Ahlneck and Zografi, 1990). Long-term studies also revealed that the recrystallization of pure APIs (Andronis et al., 1997; Andronis and Zografi, 1998) and of APIs dissolved in polymers (Prudic et al., 2015a; Marsac et al., 2008; Donnelly et al., 2015) is accelerated at high RH. Recurring powder x-ray diffraction measurements (PXRD) of amorphous formulations revealed the impact of storage RH and Temperature on the start of recrystallization in studies by Greco et al. (Greco et al., 2012) or Lehmkemper et al. (Lehmkemper et al., 2017).

The moisture absorbed from humid atmosphere may also induce APS in formulations which are fully miscible in the dry state, also refered to as moisture-induced amorphous phase separation (MIAPS) (Marsac et al., 2010). This phenomenon was qualitatively observed e.g. via differential scanning calorimetry (DSC) by Vasanthavada et al. (Vasanthavada et al., 2005, 2004), via transmission electron microscopy and atomic force microscopy by Marsac et al. (Marsac et al., 2010) and by polarized light microscopy, atomic force microscopy and nano-thermal analysis in a study of Qi et al. (Qi et al., 2013). Marsac et al. and Qi et al. investigated the MIAPS of FEL in PVP and found that MIAPS occurs at elevated RH within several hours subsequently followed by recrystallization. Rumondor et al. found MIAPS in formulations of hydrophobic APIs with PVP and poly (vinyl pyrrolidone-co-vinyl acetate) (PVPVA64) while formulations with hydroxypropylmethyl celluloses did not exhibit MIAPS (Rumondor et al., 2011).

Although MIAPS in formulations has been so far investigated qualitatively (MIAPS occuring “yes or no”), no approach exists at the moment to determine the API concentrations in the two amorphous phases and therewith the inhomogeneity of the formulations resulting from the water uptake at humid conditions. To the best of our knowledge, this work will for the first time report thermodynamic phase-equilibrium calculations for the MIAPS in API/polymer formulations and thus allow for a detailed understanding of this phenomenon.

The thermodynamic model PC-SAFT will be applied to predict the MIAPS in formulations of FEL and IBU in PVP, PVPVA64, and poly (vinyl acetate) (PVAC). This model has already been succesfully used to thermodynamically model the solubility of APIs in organic solvents (Paus et al., 2015a; Ruether and Sadowski, 2009), in aqueous media at variying pH (Cassens et al., 2013) and in the presence of various excipients (Paus et al., 2015b). The API solubility has been already modeled and even predicted in water-free (Prudic et al., 2014a,b, 2015b) and water-containing (Prudic et al., 2015a; Lehmkemper et al., 2017) polymer formulations and the dissolution of APIs (Paus et al., 2015d,c; Paus and Ji, 2016) and API/polymer formulations (Ji et al., 2015) could be described by combining PC-SAFT with a two-step chemical-potential gradient model.

Applying PC-SAFT for liquid-liquid-equilibrium calculations allowed for predicting the solubility of amorphous APIs in water (Paus et al., 2015a) and also the partitioning of APIs in demixed solvents for the optimization of extraction processes (Laube et al., 2015). Furthermore, amorphous demixing in numerous polymeric (API-free) systems has already been accurately modeled using PC-SAFT (Gross and Sadowski, 2001; Kleiner et al., 2006; Peters et al., 2012).

In this work, FEL and IBU were investigated as model substances. PVP, PVAC and the copolymer PVPVA64 were used as polymeric excipients. The chemical structures of all investigated compounds are given in Fig. 1.

Formulations of all six API/polymer combinations were prepared by spray drying and solvent evaporation. They were stored at 25 °C, 0% RH and at 40 °C, 75% RH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003). The long-term stability of amorphous formulations was monitored by recurring PXRD-measurements for two years and compared to the predicted phase diagrams of the humid ASDs.

2. Thermodynamic phase behavior of ASDs at elevated humidity

ASD formulations absorb water from the sourrounding humid atmosphere resulting in a ternary mixture of API, polymer, and water. The thermodynamic phase behavior of this mixture might be quite different from the one of the water-free API/polymer formulation as shown in Fig. 2.

The phase diagram for the water-free formulation depicted in Fig. 2a schematically shows the solubility line of the API in the polymer. All formulations located left of the solubility line are