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Investigating phase separation in amorphous solid dispersions via Raman mapping

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ABSTRACT

The bioavailability of poorly-water-soluble active pharmaceutical ingredients (APIs) can be significantly improved by so-called amorphous solid dispersions (ASDs). However, the long-term stability of ASDs might be impaired by API recrystallization and/or amorphous phase separation (APS). So far, no methods have been reported to quantify APS in ASDs. In this work, phase-separation kinetics as well as the compositions of the two amorphous phases evolving due to APS were quantitatively determined for the first time using confocal Raman spectroscopy. Raman spectra were evaluated via non-linear multivariate Indirect Hard Modeling and verified by differential scanning calorimetry and hot-stage microscopy. APS in water-free ASDs of ibuprofen and poly (DL-lactic-*co*-glycolic acid) was investigated considering the influence of temperature and polymer architecture (linear vs. star-shaped). Water absorbed at 40 °C and 75% relative humidity (RH) promotes APS which was quantified for formulations of felodipine/poly(vinyl pyrrolidone) and ibuprofen/poly(vinyl pyrrolidone).

1. Introduction

Poor water solubility and hence poor bioavailability of most newly-developed active pharmaceutical ingredients (APIs) can be improved by formulating them as amorphous solid dispersions (ASDs). In this well-established technique (Huang and Dai, 2014; Janssens and van den Mooter, 2009; Vo et al., 2013), the API is moleculary dissolved in a suitable polymer. Besides the unwanted API recrystallization during long-term storage, amorphous-amorphous phase separation (APS) might occur. The latter means that two amorphous phases evolve which may remarkably differ in the API content, finally leading to two coexisting amorphous phases one of them being API-rich and the other one being API-poor. APS is highly unwanted in API/polymer formulations and because of that, several research groups focussed on the characterization of this phenomenon. APS was e.g. reported for nifedipine in soluplus (Keratichewanun et al., 2015), itraconazole in hydroxpropyl methylcellulose (HPMC) (Purohit et al., 2017), telaprevir in various polymers (Li and Taylor, 2016), felodipine (FEL) in poly (acrylic acid) (Lin and Huang, 2010), ibuprofen (IBU) in poly (DL-lactic-*co*-glycolic acid) (PLGA) (Luebbert et al., 2017) and also in many polymer blends (Bikiaris et al., 2004; Karim et al., 1998; Kim et al., 2003; Stevenson et al., 2001). Furthermore, APS can be promoted by absorbed moisture. This is referred to as moisture-induced APS (MIAPS) and was experimentally reported especially for hydrophilic formulations (e.g. those containing poly(vinyl pyrrolidone) (PVP) (Lauer et al., 2013; Purohit and Taylor, 2015; Zhang et al., 2011; Marsac et al., 2010; Luebbert and Sadowski, 2017). APS and MIAPS occur faster than recrystallization-usually within several hours (Lauer et al., 2013; Qi et al., 2013; Lauer et al., 2011)- and thus dramatically affect the long-term stability of pharmaceutical formulations.

Fig. 1 depicts the schematic phase behavior of an API/polymer formulation (Huang and Dai, 2014; Luebbert et al., 2017; Lehmkemper et al., 2017; Tian et al., 2013; Prudic et al., 2014, 2015).

The solubility line describes the saturated (liquid) polymer/API mixture which is in equilibrium with the crystalline (solid) API. All formulations kept in the composition/temperature range below this line will eventually recrystallize whereas formulations stored in the composition/temperature range above this line are thermodynamically stable against recrystallization. The gray region in Fig. 1 depicts the APS region. All formulations located in the APS region will finally undergo APS forming an API-rich and an API-poor phase. At thermodynamic equilibrium, the final concentrations in the two phases for a specific temperature will be found on the right and left branches of this region (arrow a in Fig. 1). Quantifying the concentrations in the two

Abbreviations: API, active pharmaceutical ingredient; APS, amorphous-amorphous phase separation; ASD, amorphous solid dispersion; DSC, differential scanning calorimetry; FEL, felodipine; GA, glycolic acid; HSM, hot-stage microscopy; IBU, ibuprofen; IHM, Indirect Hard Modeling; LA, lactic acid; M, molecular weight; MIAPS, moisture-induced amorphous-amorphous phase separation; PG, hyperbranched poly glycerol; PLGA, poly(DL-lactic-*co*-glycolic acid); RH, relative humidity; T, temperature; w, weight fraction

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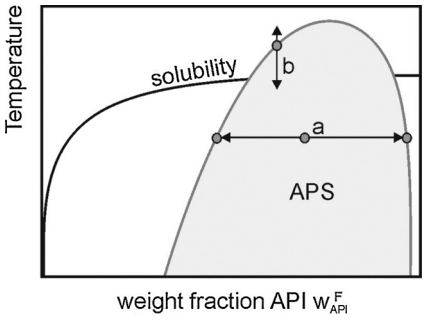

Fig. 1. Schematic phase behavior of API/polymer formulations with the solubility line and the APS region. The arrows a and b show the possible strategies to experimentally characterize APS.

evolving phases at a specific temperature will thus yield two coexisting points in the phase diagram. However, this measurement is challenging due to the high viscosity of those polymer-based formulations (leading to very slow demixing processes) and the small size of the evolving droplets (requiring measurement techniques with high spatial resolution).

Apart from this, an APS region can be characterized as shown by heating up (or cooling down) a formulation with a specific composition until crossing the APS border, e.g. by hot-stage microscopy (HSM) (arrow b in Fig. 1). This method is only applicable in case where the APS region ends at an experimentally-accessible temperature.

So far, APS was experimentally investigated by means of optical investigations (e.g. via light microscopy (Luebbert et al., 2017), fluorescense microscopy (Purohit et al., 2017) or atomic-force microscopy (Lauer et al., 2011; Walheim et al., 1997)), by differential scanning calorimetry (DSC) detecting the occurrence of two glass-transition temperatures in the heat flow signal (Lin and Huang, 2010; Kim et al., 2003; Lu and Zografi, 1998), spectroscopy (e.g. Raman (Stevenson et al., 2001; Padilla et al., 2011; Qian et al., 2010), nuclear magnetic resonance (Yuan et al., 2014), infrared (Li and Taylor, 2016; Purohit and Taylor, 2015)) or X-ray diffraction (Rumondor et al., 2009). Detecting APS reliably is nevertheless challenging, as the mentioned analytical techniques show a significant detection limit which is in many cases in the size of the evolving phases. As an example, DSC is not capable of detecting phase-separated domains smaller than 30 nm by resolving two glass-transition temperatures (Krause and Iskandar, 1977), Raman spectroscopy is limited by the spatial resolution of the optics (usually in the micro-meter range) and X-ray diffraction is not capable of quantifying the compositions in the coexisting phases at all. Moreover, none of the aforementioned publications focused on determining the equilibrium compositions of the two evolving phases. Only qualitative investigations whether or not APS occurs have been carried out so far. However, the quantitative information on the API equilibrium concentrations is of utmost importance as they determine the concentration range in which the formulation will eventually become inhomogeneous.

In this work, Raman spectroscopy and HSM were applied for measurements along arrow a and arrow b (Fig. 1), respectively, to investigate the equilibrium compositions of formulations undergoing APS. APS was quantified in water-free IBU/PLGA- formulations (Fig. 2d–e). The influence of polymer shape on APS was investigated by additionally studying APS in multi-arm star-shaped PLGA- formulations (Fig. 2e). MIAPS was quantified for FEL/PVP and IBU/PVP (Fig. 2c) formulations (after storage at 40 °C, 75% RH).

2. Experimental section

2.1. Materials

Racemic, crystalline (R,S)-IBU with a purity greater than 98% was purchased from TCI Deutschland (Eschborn, Germany), crystalline FEL (purity 99.7%, polymorph I) was purchased from Discovery Fine Chemicals (Wimborne, United Kingdom) and sodium chloride (purity > 99%) was obtained from VWR International (Darmstadt, Germany). The polymer PVP (Kollidon® K25) with a molecular weight of 25,700 g mol^{-1} was supplied by BASF (Ludwigshafen, Germany) while the poly (DL-lactic-*co*-glycolic acid) Resomer® RG752S (GA monomer content 25 mol%) was obtained from Evonik Pharma Polymers (Darmstadt, Germany). Star-shaped block copolymers P($G_{28}LLA_{10}$) and P($G_{68}LLA_{20}$) were synthesized as described in literature (Gottschalk et al., 2007) by the group of Prof. Holger Frey (Mainz, Germany). The star-shaped block copolymer properties and the core molecule properties (hyperbranched polyglycerol, PG) were determined by the supplier and are summarized in Table 1, namely the number-average molecular weight $\bar{M}_n$, the weight-average molecular weight $\bar{M}_w$, the z-average molecular weight $\bar{M}_z$,the average LLA arm length m and the average glycerol core number n.

All substances were used without further purification.

2.2. Preparation of formulations

In total 2 g solid (API and polymer) with different API weight fractions were weighted with an accuracy of ± 0.1 mg and then dissolved in 20 mL solvent. Acetone was used for formulations with the polymer PLGA while ethanol was used for formulations with PVP. The solvent was then removed via storage in a vacuum chamber for at least one week. Formulations were grounded with a mortar prior to the investigations. For DSC and HSM measurements, formulations with IBU weight fractions of w_{IBU} = 0.1; 0.3; 0.4; 0.6; 0.7; 0.9 were prepared.

2.3. Thermal analysis by HSM and DSC

HSM measurements were performed on a Linkam MS600 hot-stage (Tadworth, United Kingdom) in combination with a Leica DM4000M microscope (Wetzlar, Germany). The APS boundary was determined as schematically depicted by arrow b in Fig. 1 by subjecting formulations of different compositions to a heating rate of 2 K min^{-1}. Reaching the homogenous one-phase region was observed via the connected microscope.

Solubility temperatures and glass-transition temperatures were determined via a Q2000 DSC equipped with a RCS90 cooling device by TA Instruments (New Castle, United States). The instrument was calibrated using indium. Formulations were investigated by heating 10-20 mg in a standard aluminum pan with a sinusoidal heating ramp (heating-only mode, heat ramp 2 K min^{-1}, modulation amplitude 0.318 K min^{-1}). The peak offset temperature was considered as the solubility temperature. The solubility temperature was linearly extrapolated to a hypothetical heating rate of 0 K min^{-1} by determining the solubility peak offset temperatures of the total heat flow signal at heating ramps of 1 K min^{-1} and 5 K min^{-1} (Luebbert and Sadowski, 2017; Prudic et al., 2014). Formulations were then quench-cooled (10 K min^{-1}) and the glass-transition(s) were evaluated from the reversing heat flow signal of the second heating ramp. Each formulation was investigated in two measurements. The glass-transition temperatures could be determined with an accuracy of ± 0.71 K and solubility temperatures with ± 0.33 K.

2.4. Raman mapping

Raman mapping experiments were conducted on a HORIBA LabRAM Raman spectroscope (Bensheim, Germany) connected to an Olympus IX 71 Inverted Microscope (Tokyo, Japan). The experimental setup is schematically shown in Fig. 3 depicting the relevant components of the Raman spectroscope and the inverted microscope.

As can be seen in Fig. 3, the free space above the inverted microscope was used to expose the formulation to any desired storage