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Solubility of crystalline organic compounds in high and low molecular weight amorphous matrices above and below the glass transition by zero enthalpy extrapolation

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ABSTRACT

Pharmaceutical applications which require knowledge of the solubility of a crystalline compound in an amorphous matrix are abundant in the literature. Several methods that allow the determination of such data have been reported, but so far have only been applicable to amorphous polymers above the glass transition of the resulting composites. The current work presents, for the first time, a reliable method for the determination of the solubility of crystalline pharmaceutical compounds in high and low molecular weight amorphous matrices at the glass transition and at room temperature (i.e. below the glass transition temperature), respectively.

The solubilities of mannitol and indomethacin in polyvinyl pyrrolidone (PVP) K15 and PVP K25, respectively were measured at different temperatures. Mixtures of undissolved crystalline solute and saturated amorphous phase were obtained by annealing at a given temperature. The solubility at this temperature was then obtained by measuring the melting enthalpy of the crystalline phase, plotting it as a function of composition and extrapolating to zero enthalpy. This new method yielded results in accordance with the predictions reported in the literature.

The method was also adapted for the measurement of the solubility of crystalline low molecular weight excipients in amorphous active pharmaceutical ingredients (APIs). The solubility of mannitol, glutaric acid and adipic acid in both indomethacin and sulfadimidine was experimentally determined and successfully compared with the difference between their respective calculated Hildebrand solubility parameters. As expected from the calculations, the dicarboxylic acids exhibited a high solubility in both amorphous indomethacin and sulfadimidine, whereas mannitol was almost insoluble in the same amorphous phases at room temperature.

This work constitutes the first report of the methodology for determining an experimentally measured solubility for a low molecular weight crystalline solute in a low molecular weight amorphous matrix.

1. Introduction

The use of amorphous molecular dispersions for drug delivery purposes is becoming of greater importance in the pharmaceutical industry (Ford, 1986; Serajuddin, 1999; Sethia and Squillante, 2003). These drug-excipient amorphous formulations are mainly used to improve the dissolution of poorly water soluble drugs (Hülsmann et al., 2000). Dispersing an active pharmaceutical ingredient (API) in an amorphous polymeric matrix at the molecular scale not only increases its solubility and dissolution rate but can also prevent its recrystallisation over time (Leuner and Dressman, 2000; Repka et al., 2008). Nevertheless, finding a suitable polymer and drug loading can be difficult. Indeed, in order to disperse a sufficient amount of API in the amorphous solid, the solubility of the crystalline API in the polymer must be sufficiently high (Marsac et al., 2006, 2009). Moreover, the drug loading should not exceed the solubility in order to avoid the recrystallisation of the API during the drug shelf-life (Qi et al., 2010), even though this unwanted phenomenon can be kinetically prevented in some cases (Marsac et al., 2006). Therefore, solubility is a key parameter and its accurate assessment is crucial for the development of amorphous dispersion formulations.

The determination of the solubility of a crystalline excipient in an amorphous API can also be of interest, as recently shown by Curtin et al. (Curtin et al., 2013a,b). They demonstrated the ability of crystalline low glass transition temperature (T_g) low molecular

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weight excipients to prevent the amorphisation of an API upon milling by reducing the T_g of the resulting composite. The authors highlighted that the efficiency of the process, arising from the T_g lowering effect, was highly dependent on the solubility of the excipient in the amorphous API.

The experimental determination of the solubility of an API in an excipient and vice versa is challenging. The most widespread method for the determination of the solubility of a crystalline compound in an amorphous polymer is known as the 'melting point depression' method (or scanning method). This thermal technique, introduced by Tao et al., is based on the measurement of the dissolution endpoint of solute/polymer mixtures prepared by milling (Tao et al., 2009). The plot of the dissolution endpoint as a function of composition gives the solubility curve of the crystalline solute in the amorphous polymer. However, the solubility cannot be experimentally measured below $T_g + 30\,^{\circ}C$ by this method because the high viscosity of polymers makes achieving equilibrium difficult (Tao et al., 2009). In order to circumvent this limitation and to enable the determination of solubility at temperatures closer to T_g, Tao et al. improved their protocol by annealing the solute/polymer mixtures over a long time (10 h) (Sun et al., 2010). Nonetheless this 'annealing method' could only be applied down to $T_g + 20\,^{\circ}C$ and the solubility below this temperature could only be predicted by determining the intersection between the T_g curve of the composite and the extrapolation of the solubility curve (Sun et al., 2010). Even though this technique is efficient and convenient for the determination of the solubility of an API in polymer above T_g, the typical storage temperature of a drug is usually below T_g.

Recently, the group of Descamps has designed a new protocol for the determination of the solubility of an API in a polymeric matrix (Mahieu et al., 2013). In this method, the saturated state is reached by demixing of supersaturated amorphous solid solutions and not by dissolution of crystalline drug into the amorphous polymer, as for the melting point depression method. According to Mahieu et al., the presence of a large amount of solute in the amorphous phase plasticizes the polymer (decreases the T_g) thus enhancing the molecular mobility and therefore speeds up the equilibration step. They validated this new technique against a previously described system, the solubility of which had been determined by Tao et al. through the annealing method (Sun et al., 2010). Nevertheless, as for the Tao et al. method, this promising new approach has only been used above the T_g so far.

As a thermodynamic property, the drug/polymer solubility is properly defined only above T_g, where the amorphous phase is a supercooled liquid at equilibrium. Below T_g, the supercooled liquid becomes a glass which relaxes and therefore, no thermodynamic solubility can be determined. However, since the glass relaxation is slow, an apparent solubility can be estimated (Qian et al., 2010). Marsac et al. developed a model in which they could calculate the Flory–Huggins interaction parameter, χ, from solubility measurements of the solute in the liquid low molecular weight polymer analog (Marsac et al., 2006). Despite the fact that this model enables the calculation of the solubility at temperatures below T_g, it works under the assumption that the drug–polymer and drug–monomer interaction parameters are the same. Furthermore this method is only applicable for polymers that have liquid monomers. More recently, Bellantone et al. published a new method for determining the solubility of a drug in a solid polymer near room temperature (Bellantone et al., 2012). They calculated the free enthalpy variation associated with the formation of the amorphous solid dispersion from the unmixed polymer and crystalline API from thermal analysis data. They determined the drug solubility in the polymer by calculating the minimum of the free enthalpy change versus the dissolved drug concentration.

An experimental method originally developed by Theeuwes et al. for the determination of the solubility in amorphous molecular dispersions above and below T_g seems promising (Theeuwes et al., 1974). This method is based on the principle that when a mixture has a drug–polymer composition above the solubility, the saturated amorphous solid phase is in apparent equilibrium with undissolved crystals of API. This fraction of unsolubilised drug will exhibit a melting endotherm upon differential scanning calorimetry analysis (DSC). The solubility is then obtained by plotting the measured melting enthalpy as a function of drug composition and extrapolating it to zero. This method has been extensively used to determine the minimum amount of polymer required to prevent API crystallization in amorphous dispersions prepared by spray drying (Corrigan, 1975) as well as for solubility purposes (Gramaglia et al., 2005; Qi et al., 2010) and has the potential to overcome the limitations of the other techniques.

This paper reports the development of a fast and standard method for the determination of the solubility of a crystalline organic compound in an amorphous polymer above and at T_g combining the benefits of the annealing method of Tao et al. and the thermal analysis reported by Theeuwes et al. The advantage of the technique presented in the current work lies in the production of a saturated amorphous phase ensured by the annealing step and the accuracy of the zero enthalpy extrapolation for the determination of its composition. The aim of this work is to validate this protocol against other results reported in the literature and to extend it to low molecular weight amorphous systems.

2. Materials and methods

2.1. Materials

Polyvinyl pyrrolidone (PVP) K15 ($M_w \approx 10{,}000\,g\,mol^{-1}$), PVP K25 ($M_w \approx 24{,}000\,g\,mol^{-1}$), sulfadimidine (SD) ($M_w = 278.33\,g\,mol^{-1}$), adipic acid (AA) ($M_w = 146.14\,g\,mol^{-1}$), glutaric acid (GA) ($M_w = 132.11\,g\,mol^{-1}$), mannitol (MN) ($M_w = 182.20\,g\,mol^{-1}$) and indomethacin (IM) ($M_w = 357.79\,g\,mol^{-1}$) were purchased from Sigma–Aldrich, Ireland.

2.2. Methods

2.2.1. Milling

Ball milling was performed with a PM 100 high energy planetary mill (Retsch, Germany) at room temperature, as previously described by Curtin et al. (Curtin et al., 2013b). 2.5 g of material were placed in stainless steel milling jars of 50 cm^3 volume with three stainless steel balls of diameter 20 mm, corresponding to a ball to powder mass ratio of 40:1. The speed of the solar disk was set at 400 rpm and the milling duration to 10 min.

2.2.2. Thermal analysis

Differential scanning calorimetry (DSC) experiments were conducted using a DSC Q200 (TA Instruments, United Kingdom) in hermetic pans with 1 pinhole and sample weights were between 2 and 6 mg with a heating rate of $20\,^{\circ}C\,min^{-1}$. Nitrogen was used as the purge gas. The instrument was calibrated for temperature and cell constant using high purity indium. Unless otherwise noted, the reported T_g is the midpoint temperature of the glass transition.

2.2.3. Powder X-ray diffraction

Powder X-ray diffraction (pXRD) measurements were performed on samples placed on a low background silicon sample holder using a Rigaku Miniflex II desktop X-ray diffractometer (Rigaku, Tokyo, Japan). The pXRD patterns were recorded from 5° to 40° on the 2θ scale at a step of $0.05^{\circ}\,s^{-1}$. The X-ray tube composed of Cu anode ($\lambda_{CuK\alpha} = 1.54$ Å), was operated under a voltage of 30 kV and current of 15 mA.