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Amorphous solid dispersions of piroxicam and Soluplus®: Qualitative and quantitative analysis of piroxicam recrystallization during storage

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ABSTRACT

The conversion of active pharmaceutical ingredient (API) from amorphous to crystalline form is the primary stability issue in formulating amorphous solid dispersions (SDs). The aim of the present study was to carry out qualitative and quantitative analysis of the physical solid-state stability of the SDs of poorly water-soluble piroxicam (PRX) and polyvinyl caprolactam-polyvinyl acetate-polyethylene-glycol graft copolymer (Soluplus®). The SDs were prepared by a solvent evaporation method and stored for six months at 0% RH/6 °C, 0% RH/25 °C, 40% RH/25 °C and 75% RH/25 °C. Fourier transform infrared spectroscopy equipped with attenuated total reflection accessory (ATR-FTIR) and Raman spectroscopy were used for characterizing the physical solid-state changes and drug–polymer interactions. The principal component analysis (PCA) and multivariate curve resolution alternating least squares (MCR-ALS) were used for the qualitative and quantitative analysis of Raman spectra collected during storage. When stored at 0% RH/6 °C and at 0% RH/25 °C, PRX in SDs remained in an amorphous form since no recrystallization was observed by ATR-FTIR and Raman spectroscopy. Raman spectroscopy coupled with PCA and MCR-ALS and ATR-FTIR spectroscopy enabled to detect the recrystallization of amorphous PRX in the samples stored at higher humidity.

1. Introduction

The number of poorly water soluble active pharmaceutical ingredients (APIs) and drug candidates has been growing significantly during past decade (Buckley et al., 2013; Lust et al., 2013a). One way to improve the apparent solubility of the poorly soluble drug molecules is to use amorphous solid dispersions (SDs) (Brouwers et al., 2009). The SD approach is a promising formulation strategy to improve the oral bioavailability of poorly water-soluble drugs (Kawabata et al., 2011) since APIs formulated in SDs have higher physical stability compared to pure amorphous compounds and they still have a faster dissolution compared to their crystalline counterparts. The other advantage of the SDs over the pure amorphous compounds is that the carrier polymer can solubilize the poorly water-soluble compound during dissolution and thus inhibit the recrystallization. Nevertheless the physical instability of SDs has to be taken into account during the formulation of these materials (Janssens and Van den Mooter, 2009). As different solid state forms can have different dissolution profiles and bioavailability (Lust et al., 2013a), it is important to monitor the solid-state stability of SDs during storage (Weuts et al., 2005).

The SD approach has been successfully used to stabilize the materials in amorphous form. The kinetic barrier or reduced molecular mobility, specific interactions between carrier polymer and API and molecular obstruction are factors that can stabilize the SDs (Vasconcelos et al., 2007). As molecular mobility governs the diffusion and surface integration, it influences the phase separation and subsequent crystallization of SDs (Janssens and Van den Mooter, 2009). The nucleation and crystal growth require correct orientation and conformation of the molecules, both of which are also governed by molecular mobility. Furthermore, the number of contacts between molecules that lead to the formation of hydrogen bonds depends on molecular mobility. Hence, the probability of crystallization is lower if the system has lower molecular mobility (Janssens and Van den Mooter, 2009). Some small molecules are known to increase the molecular mobility of amorphous systems

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(by acting as plasticizers), and they can promote crystallization (Hancock and Zografi, 1994; Heljo et al., 2012; Janssens and Van den Mooter, 2009). For hydrophilic polymers, water is well known to act as a plasticizer (Blasi et al., 2005; Lai et al., 1999). Hydrogen bonding and specific interaction between carrier polymer and API have been shown to stabilize the SDs (Bhugra and Pikal, 2008). Formation of the hydrogen bonds between an API and polymer can also inhibit the formation of hydrogen bonds between two API molecules. Also the relative bond strengths in the crystalline API compared to hydrogen bonds in the SD can affect the thermodynamic crystallization driving force (Janssens and Van den Mooter, 2009). As hydrogen bonding between an API and polymer can inhibit the diffusion of API molecules, it is evident that this also affects molecular mobility (Bhugra and Pikal, 2008).

Piroxicam (PRX) is a non-steroidal anti-inflammatory drug (Fig. 1). As PRX has low aqueous solubility and high permeability, it is a Class II drug in the Biopharmaceutics Classification System (Amidon et al., 1995). PRX has four different crystal forms: I, II, III and monohydrate (Kogermann et al., 2011; Vrecer et al., 2003). PRX can be obtained in amorphous form but it is highly unstable and recrystallizes very fast to a PRX anhydrate I (AH) (Kogermann et al., 2011,c; Sheth et al., 2004a,b,c,c). In water, AH recrystallizes as a monohydrate (MH), and at room temperature it takes more than 1 h for this process to start (Lust et al., 2013a; Paaver et al., 2012). Since AH and MH have completely different unit cell structures (Kojic-Prodic and Ruzic-Toros, 1982; Reck et al., 1988; Reck and Laban, 1990), the AH dissolves in a dissolution medium before it can recrystallize as a MH.

Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Solu-plus®) is a novel hydrophilic pharmaceutical excipient that is specially tailored to be applied as a carrier polymer in the SDs of poorly water-soluble APIs (Fig. 2). The glass transition temperature of Soluplus® is low 68 °C (Lim and Hoag, 2013), and to date it has been used for preparing SDs by melting method. Soluplus® is known to absorb water readily from air: at 40% relative humidity (RH) its water content is about 4% and at 75% RH about 12% by weight at ambient room temperature (Puncochova et al., 2014). Soluplus® has a relatively low critical solution temperature of 40 °C, and adding electrolytes to an aqueous solutions of Soluplus® can further lower the critical solution temperature and cause its salting out (Hughey et al., 2013).

A number of multivariate analysis methods coupled with vibrational spectroscopy have been successfully employed in the analysis of solid-state transformations of APIs (Aaltonen et al., 2007b; De Beer et al., 2009; Kogermann et al., 2007, 2008, 2011; Naelapää et al., 2012; Paaver et al., 2012; Romero-Torres et al., 2007). For example, principal component analysis (PCA) has been used in the qualitative analysis of solid-state forms during storage stability tests (Kogermann et al., 2011). For quantification of the solid-state transformations of APIs, partial least squares (PLS) regression has been widely exploited (Aaltonen et al., 2007a;

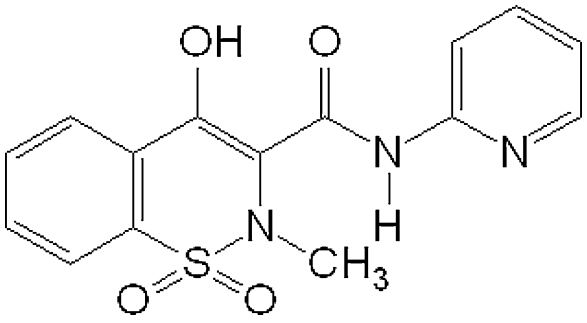

Fig. 1. Chemical structure of piroxicam (PRX).

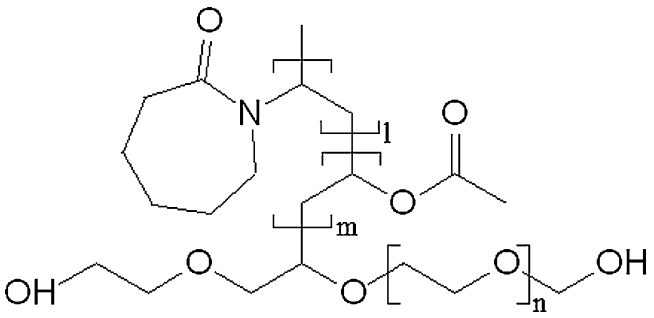

Fig. 2. Chemical structure of Soluplus®.

Paaver et al., 2012; Stephenson et al., 2001). The quantification of amorphous systems, however, can be challenging since most of multivariate analysis methods used for analysing spectroscopic data need the calibration based on instrumental measurements of calibration mixtures. As amorphous material can readily recrystallize when coming in contact with a crystalline matter, a method which does not need calibration models involving mixtures of crystalline and amorphous material would facilitate quantitative analysis. One method which can be used is multivariate curve resolution (MCR) as this method does not require a preliminary measurement of mixtures with specific composition (Christensen et al., 2013). MCR mathematically decomposes instrumental responses of mixtures into the contributions of pure components and calculates the concentration profiles of them. With MCR alternating least squares (MCR-ALS), the equation of MCR is solved iteratively by using alternating least squares method (Tauler, 1995). While MCR is commonly used to obtain quantitative information about the reagents during chemical reactions, lately it has also been successfully used to study complex phase transitions during dehydration (Christensen et al., 2013) and freeze-drying (De Beer et al., 2007). The general theory and application of MCR-ALS as a quantitative analysis tool for solid mixtures has been discussed in several papers (Azzouz and Tauler, 2008; Garrido et al., 2004, 2008).

The aim of this study was to investigate the physical solid-state stability and dissolution of SDs of PRX and Soluplus® graft copolymer immediately after preparation and during a short-term storage in different humidity and temperature conditions. Qualitative and quantitative analysis of PRX recrystallization during storage ®stability tests was carried out by means of Raman spectroscopy combined with PCA and MCR-ALS multivariate analysis methods. ATR-FTIR spectroscopy was used to study the recrystallization of PRX on the surface of SDs (in a powder form). In addition, the effects of PRX recrystallization on the dissolution behavior of SDs were also studied.

2. Materials and methods

2.1. Materials

PRX anhydrate I (AH) was purchased from Letco Medical, Inc., USA. Soluplus® was kindly gifted from BASF group. PRX monohydrate (MH) was obtained by recrystallisation from hot water. Physical mixtures of PRX AH and Soluplus® 1:4 (PM AH) and PRX MH and Soluplus® 1:4 (PM MH) were obtained by mixing them in a mortar with pestle using geometric dilution. The SDs of PRX and Soluplus® (1:4 weight ratio) were prepared by using a solvent evaporation method: 5 g of AH and 20 g of Soluplus® were dissolved in 250 ml of acetone. The solvent was gently evaporated at 40 °C by using a Rotovapor® rotatory evaporator (Büchi, Switzerland). The rotation speed of the 1000 ml flask used was set at 120 rpm. The SDs formed solid foam which was removed