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Influence of polymer content on stabilizing milled amorphous salbutamol sulphate

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ABSTRACT

The study investigates the influence of polyvinyl pyrrolidone (PVP) concentration on stabilizing the amorphous form of salbutamol sulphate (SS) before and after storage under ambient and elevated humidity conditions. Different mass ratios of SS and PVP (0–90 wt%) were co-milled using a planetary ball mill. X-ray powder diffraction (XRPD), high sensitivity differential scanning calorimetry (HSDSC), dynamic vapor sorption (DVS), infrared spectroscopy (FT-IR), scanning electron microscopy (SEM) and Raman microscopy (RM) were used to analyze the stability of the co-milled mixtures against heat and humidity treatments as well as storage at different humidity conditions. Prior storage, DSC and DVS analyses revealed that re-crystallization of amorphous SS was suppressed above PVP content of 33 wt%. Probable hydrogen bond interaction between SS and PVP was found in FT-IR analysis. XRPD diffractograms and SEM analysis showed stability against re-crystallization was achieved in the co-milled mixtures with a minimum PVP content of 80 wt% after storage. Homogeneous distribution of SS and PVP from RM analysis showed fine clustering of SS and PVP, suggesting the formation of an amorphous dispersion at molecular level. The results provide insights on the application of thermal and humidity treatments, accelerated stability testing and investigations on drug–excipient interactions to predict the minimum ratio of an excipient for stabilizing the amorphous state of a milled API.

1. Introduction

One of the major challenges of the pharmaceutical industry is to improve the water solubility of new chemical entities (NCEs) under development. Low water solubility and poor oral bioavailability affect the inherent efficacy of the NCEs (Vasconcelos et al., 2007). Hence, the amorphous form of the drug is desirable as it can have advantages of solubility, dissolution rate and better compression characteristics over the less soluble crystalline form (Yu, 2001), but not always. However, amorphous form of the drug is often associated with stability problems as it is thermodynamically unstable and tends to re-crystallize to stable but less soluble crystals under temperature and humidity stress encountered during accelerated storage conditions designed for testing pharmaceutical preparations (Vasconcelos et al., 2007). Thus, stabilization of an amorphous form of drug is particularly desirable for pharmaceutical products. For practical purposes, it is important to optimize a subtle balance between amorphization and stabilization (Watanabe et al., 2001), by application of techniques such as melt quenching, spray drying, melt extrusion to formulate stable amorphous drug–excipient dispersions (Miyazaki et al., 2004; Ghebremeskel et al., 2006; Pokharkar et al., 2006). Co-grinding or co-milling with excipients has also been recently studied to prepare amorphous materials that are more prone to degradation either by heat or solvent which preclude other preparation methods (Crowley and Zografi, 2002; Watanabe et al., 2003). Bahl and Bogner reported the improvement in the dissolution profile of indomethacin on co-grinding with silicates (Bahl and Bogner, 2008; Bahl et al., 2008). They previously reported the effects of humidity and drug–excipient ratios on the stability of amorphous indomethacin as a co-ground mixture (Bahl and Bogner, 2006). A stable amorphous indomethacin–silica alloy was formed due to plasticization of amorphous drug leading to mechanical transfer of drug to silicate, vapor phase mass transfer and water in facilitating particle–particle surface migration of

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the drug to the silicate. Other studies showed that the higher glass transition temperature and greater viscosity of polymers gave rise to a more stable amorphous drug mixture (Hancock et al., 1995; Hancock and Zografi, 1997). For instance, polyvinyl pyrrolidone (PVP), a hydrophilic polymer inhibited re-crystallization and stabilized the amorphous dispersions (Aso et al., 1996; Watanabe et al., 2003; Cirri et al., 2004). However, a major concern with the use of PVP is its hygroscopic nature. PVP has been reported to have an equilibrium moisture content of 27.8 wt% at 25 °C/75% RH and classified as "very hygroscopic" (Umprayn and Mendes, 1987). The hygroscopic nature of PVP could be detrimental when it is used to stabilize dispersions. Marsac et al. (2008) observed that 25 wt% PVP in the presence of water increased the nucleation rate of the solvent evaporated amorphous nifedipine–PVP molecular dispersions leading to re-crystallization. Vapor sorption studies indicated that pure amorphous nifedipine with a moisture uptake of around 1–2 wt% showed a significant increase in moisture uptake up to 6 wt% when PVP content was increased from 0 to 25 wt%. In an Atomic Force Microscopy study, Mahlin et al. (2006) found that the more PVP present in spray-dried lactose–PVP increased the propensity of moisture-induced re-crystallization. The glass transition temperature (T_g) of pure amorphous lactose was below 25 °C at 40% RH. This RH referred to as the critical crystallization RH increased steadily with more PVP in the composite mixture. PVP when used at high concentrations impaired the stability of co-formulated amorphous phase. On the other hand, Shakhtshneider's group (2007b) recently reported that lower PVP content resulted in less stable cryogenic co-ground mixture of indomethacin and PVP. Concentrations of PVP above 50 wt% was required to keep the amorphous indomethacin stable for 10 months. However, indomethacin–PVP solid dispersions prepared by solvent evaporation technique did not show any re-crystallization even at 20 wt% PVP. The authors suggested that amorphous forms prepared by grinding may contain crystalline seeds or nuclei which facilitated re-crystallization at low PVP concentrations.

Physical stabilization of the amorphous form is affected by several factors. Controlling molecular mobility, inter- and intramolecular interactions and variations in processing conditions play an important role (Bhugra and Pikal, 2008). With reference to drug–polymer systems, the stability of the amorphous form primarily depends on factors such as drug and polymer interaction, viscosity of polymer and glass transition temperature of the mixture (Choksi et al., 2008). In addition, the presence of polymer has been shown to increase the activation energy towards crystallization and could act as a physical barrier against crystallization. Although T_g serves as an important indicator of crystallization tendency, modes of molecular mobility not reflected by T_g should also be considered. This was clearly observed in case of amorphous solid dispersions of PVP with drugs such as nifedipine and felodipine, where T_g alone could not explain the reduced rate of crystallization in the presence of polymer and water (Marsac et al., 2008). On the other hand, PVP–indomethacin cryoground systems (Shakhtshneider et al., 2007b) were found to show an elevated T_g but at higher concentration of PVP (>50 wt%). Similar results were reported in case of PVP–piroxicam cryoground systems (Shakhtshneider et al., 2007a). Apart from factors discussed above, intra- and intermolecular hydrogen bonding interactions also play a key role in achieving stable amorphous dispersions. Miyazaki et al. (2004) attributed the ability of polyacrylic acid (PAA) to stabilize amorphous dispersions of acetaminophen to the strength of interaction between hydroxyl group of acetaminophen and the carboxyl group in PAA in comparison to PVP. Tang et al. (2002) investigated the differences in hydrogen bonding tendencies in the crystalline and amorphous states of seven dihydropyridines analogues. The authors concluded that for some compounds, hydrogen bonding was stronger in the crystalline state while for others, it was stronger in the amorphous state. A strong relation of hydrogen bonding in molecules to molecular mobility was also found in case of acetaminophen glass (Gunawan et al., 2006). This meant that the strength of the hydrogen bonding could significantly impact the structural relaxation time, i.e. the molecular mobility and hence impact the tendency to crystallize. Hence, a precise knowledge of such interactions could be useful if the acceptor or donor groups are targeted by polymeric excipients in order to achieve physical stabilization. Hydrogen bonding has also been reported in case of PVP–drug co-ground systems. Hydrogen bonding with PVP has played an important role in stabilizing amorphous co-ground systems of drugs such as indomethacin, piroxicam and sulphathiazole (Boldyrev et al., 1994; Shakhtshneider et al., 2007a,b).

However, investigations into the minimum ratio of PVP required to stabilize the amorphous form of milled pharmaceutical actives are lacking. Thus, the objective of this study is to understand the influence of the proportion of PVP for stabilizing amorphous co-milled SS before and after storage under ambient and elevated humidity conditions. The degree of crystallinity and the re-crystallization tendency of the co-milled mixtures were evaluated using X-ray powder diffractometry (XRPD), high sensitivity differential scanning calorimetry (HSDSC) and dynamic vapor sorption (DVS) respectively. Fourier transformed infrared spectroscopy (FT-IR) was used to study possible chemical interactions between the drug and polymer. Raman microscopy (RM) was utilized to map the spatial distribution of drug and excipient in the co-milled mixture. Scanning electron microscopy (SEM) analysis of co-milled mixtures kept under ambient and elevated humidity conditions (75% RH) was conducted to study the effect of re-crystallization on particle agglomeration and morphological changes.

Salbutamol sulphate (SS) is the model compound as a fully X-ray amorphous form could be obtained easily on ball milling (Balani et al., 2009), and this could readily undergo moisture-induced amorphous to crystalline transition at 60–70% RH (Balani et al., 2009; Brodka-Pfeiffer et al., 2003b). The stability of amorphous SS is dependent on storage conditions as the T_g of SS is influenced by relative humidity and temperature (Burnett et al., 2004). Brodka-Pfeiffer et al. (2003a,b) reported that the amorphous content of partially micronized SS decreased significantly from 7.7 to 2.5 wt% when stored for 24 h at ambient conditions of 25 °C and 45% RH. Storage at accelerated conditions of 40 °C and 75% RH resulted in complete re-crystallization within 5 h (Brodka-Pfeiffer et al., 2003a).

2. Materials

SS (≥99% purity) was purchased from Junda Pharmaceutical Co. Ltd. (Jiangsu, PR China). Polyvinyl pyrrolidone K-30 (PVP, M_w range 29,000–55,000, 99% pure) was purchased from (Sigma–Aldrich, Singapore). All other reagents and chemicals used were of analytical grade.

3. Methods

3.1. Ball milling

Sieved fraction (75–250 μm) of crystalline SS (cSS, non-milled) was prepared using Retsch Sieve Shaker (Retsch GmbH, Rheinische Straße, Haan, Germany) set at amplitude of 2.5 mm for 10 min. Milling of cSS was carried out using Fritsch Pulverisette 5 (Fritsch GmbH Pulverisette 5, Idar-Oberstein, Germany), a planetary ball mill equipped with stainless steel jar and balls (diameter 10 mm). As PVP is amorphous in nature, no prior milling was required. The mass ratio of ball to sample was kept at 50:1 (Parrott, 1974). The rotation speed was set at 300 rev min^{-1} and a milling duration of