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Comparison of the physical stability and physicochemical properties of amorphous indomethacin prepared by co-milling and supercritical anti-solvent co-precipitation

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ABSTRACT

Recently, amorphization methods are used to enhance the dissolution of poorly water-soluble drugs. There are a number of different methods to generate amorphous drug substances such as solvent deposition, co-milling (COM), spray-drying, melt-quenching and supercritical fluids technology. In this study, the effectiveness of a low-cost and easily scalable process COM was compared with the high-cost and precision-controlled supercritical anti-solvent (SAS) process to amorphize indomethacin (IDMC) with a water-soluble polymer excipient poly(vinylpyrrolidone) (PVP) to improve the physical stability of the IDMC amorphous form. Both COM and SAS precipitation were conducted at IDMC to PVP ratios of 60:40, 50:50 and 20:80. The untreated COM and SAS powders (before and after storage) were characterized using scanning electron microscopy (SEM, morphology), X-ray powder diffractometry (XRD, crystallinity), thermogravimetric analysis (TGA, composition), gravimetric vapour sorption (GVS, moisture isotherms), Fourier-transform infrared spectroscopy (FTIR, drug–polymer interactions), inverse gas chromatography (IGC, surface energetic and structural relaxations) and Raman mapping (RM, spatial distribution). Accelerated physical stability stress tests were also conducted on COM and SAS co-precipitates in open pans at 75%RH/40 °C in order to evaluate their physical stability. SAS co-precipitates with PVP contents more than 40 wt.% were X-ray amorphous form and remained stable after more than 6 months of storage at 75%RH/40 °C. COM powders with PVP contents less than 50 wt.% re-crystallized after 7 days of storage at 75%RH/40 °C. FTIR spectra suggested that hydrogen bonding formed between PVP amide carbonyl and IDMC carboxylic acid hydroxyl groups for all COM and SAS co-precipitates. Therefore, the amorphous phase present in COM and SAS co-precipitates could be stabilized by the intermolecular hydrogen bonds between IDMC and PVP which improved its physical stability against re-crystallization. IGC studies also revealed that different preparation methods used to generate the amorphous form have an effect on its physical stability in terms of surface structural relaxation as well as having different surface energetics. Overall the surface structural relaxation of SAS co-precipitate was slower than COM samples indicating that SAS co-precipitate was physically more stable than COM sample. Finally, this work has demonstrated the potential of using PVP as a suitable "amorphous inducing and stabilizing" agent for a poorly water-soluble drug such as IDMC using co-milling and SAS processes.

1. Introduction

Recently, the increase in the number of newly discovered poorly water-soluble drug candidates has heightened the interest in developing new patents and novel techniques to improve aqueous-solubility. The uses of amorphous forms of active pharmaceutical ingredients (APIs) in various solid formulations have received considerable attention to enhance/improve aqueous solubility. The amorphous form of API is desirable mainly due to the advantages of solubility, dissolution rate and better compression characteristics that it offers over crystalline forms [1]. Hancock and Parks [2] reported that the experimental solubilities of amorphous solids are at least 2–4 times greater than their crystalline counterparts. However, the amorphous form is thermodynamically unstable as compared to its crystal and has the tendency to revert back to its crystalline form, especially during storage at different temperatures and relative humidities [3]. Therefore, the key approach is to use amorphous solid dispersion to attain good physical stability as well as enhanced dissolution and bioavailability. This

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system utilized crystallization inhibitors such as additives together with the APIs [4–7] to generate a single-phase amorphous mixture. These additives/inhibitors are usually hydrophilic carriers (polymers or sugars) and could inhibit re-crystallization and generate a more stable amorphous solid as well as increase the wetting property of APIs. There are a number of different methods to generate amorphous APIs such as solvent deposition [8], co-milling (COM) [9,10], melt-extrusion [11,12], spray-drying [13], melt-quenching [14] and supercritical fluids technology [15–18].

Among the various methods that can generate the amorphous form, milling is a common unit operation employed for particle reduction which is a relatively low-cost and easily scalable [19,20] manufacturing process. In order to improve the milling efficiency, a favourable method using a co-milling drug with additives/polymers has been successfully applied [21–23]. Various amorphous solid dispersions were generated by co-milling poly(vinylpyrrolidone) (PVP) with ibuprofen, sulfathiazole, phenothiazone, acridine, chloranil and vitamin K3 [24–26]. Recently, Deepak et al. [27] investigated the amorphization of indomethacin (IDMC) using co-milling with six pharmaceutical silicates, and the co-milled amorphous indomethacin was physically stable for 3–6 months at 40 °C/75%RH.

Currently, a new approach using supercritical fluids technologies for particle design of pharmaceutical materials is being actively pursued due to its major advantages over conventional pharmaceutical processing such as high purity of products, ability to control particle size and narrow particle size distribution, ability to process thermo-labile materials, a potential for a single-step process, and a solvent content that is within pharmacopoeia standards can be reached rather easily [18,28,29]. Recently, the supercritical anti-solvent (SAS) process has been used to generate the amorphous form of APIs. Sethia and Squillante [30] generated carbamazepine solid dispersion in PVP prepared using conventional solvent evaporation and a supercritical carbon dioxide (Sc-CO_2) process. It was reported that the intrinsic dissolution of carbamazepine solid dispersion in PVP generated by Sc-CO_2 process was 4-fold higher as compared to its crystalline form. Kluge et al. [31] studied the effect of phenytoin to PVP ratios using precipitation with the compressed anti-solvent (PCA) process and obtained X-ray amorphous co-formulations at PVP contents of 60 wt.% and above. Besides that, these amorphous co-formulations remained stable after 1 year of storage at ambient conditions. Previously, our group prepared X-ray amorphous IDMC–PVP co-precipitates using the SAS process [6]. The SAS co-precipitates were stored at 75%RH/40 °C and remained stable in the X-ray amorphous form for more than 6 months. The SAS processed IDMC and SAS co-precipitates enhanced the dissolution rate of IDMC as compared to the crystalline pure IDMC [6].

It has been reported that the choice of processes used to prepare the amorphous form has influence on its physical stability in terms of enthalpic relaxation and crystallization behaviour [32]. In addition, structural relaxation of amorphous materials is believed to be the precursor to re-crystallization. Bhugra et al. [33,34] reported that there is a relationship between the structural relaxation and the onset time of the re-crystallization. Amorphous materials undergo structural relaxation to dissipate excess energy during ageing/storage because of their higher energy state as compared to the equilibrium state [35,36]. Moreover, it is also known that re-crystallization starts to occur at the surface of amorphous materials. Crowley and Zografi [37] reported that smaller particles of amorphous IDMC and IDMC–PVP solid dispersion re-crystallized faster as compared to the larger particles, indicating surface-mediated nucleation occurred. Recently, Hasegawa et al. [38] investigated the structural relaxation of amorphous IDMC–PVP solid dispersion using inverse gas chromatography (IGC) and concluded that structural relaxation at the surface occurred faster as compared to the bulk. Ke et al. [39] also investigated the effect of preparation methods on surface structural relaxation using IGC and reported that the surface has higher molecular mobility than the bulk in all systems prepared. Hence, it will be advantageous and useful to investigate the surface structural relaxation of amorphous materials to predict/understand its tendency to re-crystallize which is important for formulation design and product manufacturing. Therefore, the aim of this study is to investigate the surface properties and nature/structural relaxation of amorphous solid dispersion generated by SAS and COM processes using IGC. Besides that, the physicochemical properties and physical stability under accelerated storage conditions (40 °C/75%RH) of powders prepared by COM are compared with our previous studies using SAS co-precipitation process [6].

2. Materials and methods

2.1. Materials

γ-Indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid), IDMC (Fluka) and poly(vinylpyrrolidone), PVP (molecular weight 360,000, Sigma) were used as received. IDMC, a poorly water soluble (<0.01 μg/mL in water from Merck Index, 2006) and non-steroidal anti-inflammatory drug (NSAID) which is classified as a class II drug in the Biopharmaceutical Classification System (BCS), has low bioavailability and high permeability. IDMC is used as a painkiller and for treating inflammatory conditions such as arthritis, osteoarthritis, alkylosing spondylitis and other disorders. It has a molecular weight of 357.79 g/mol. IDMC exists in two known polymorphic forms of α and γ-indomethacin. The γ-phase (triclinic, plate morphology) form constituting the monotropic system is thermodynamically more stable than the α-phase (monoclinic, acicular habit) [40]. In the monoclinic form, 6 molecules of IDMC with three different conformations are packed in a unit cell, whereas for a unit cell of the triclinic form, two molecules of the same conformation and dimerization are formed by hydrogen bonding between carboxylic acid functional groups [41]. The melting point of the α form is 155 °C with a heat of fusion of 91 J/g, whereas the γ form melts at 161 °C with a heat of fusion of 110 J/g [41]. The decomposition temperature of IDMC is 220 °C [41].

PVP is an amorphous polymer with molecular weights (MW) ranging from 2500 to 3,000,000. It is classified according to the *K* value, which is calculated using Fikentscher's equation [42]. The glass transition temperature (T_g) of PVP is high and depends on molecular weight and moisture content. The high T_g of PVPs may render them unsuitable for the preparation of solid dispersions by the hot melt method [43]. They are soluble in a wide variety of organic solvents and are particularly suitable for the preparation of solid dispersions by the solvent method [43]. PVP is a water-soluble, hydrophilic and hygroscopic polymer made from the monomer N-vinylpyrrolidone. Besides that, PVP also possesses chemical and biological inertness, low toxicity, high media compatibility, cross-linkable flexibility and other unique properties. The PVP used in this study has a T_g of 177 °C. The chemical structures of IDMC and the PVP repeating unit are shown in Fig. 1.

2.2. Preparation of physical blends

The physical blends (PB) of different IDMC to PVP ratios (20:80, 60:40, 50:50 w/w) were prepared in a turbula mixer (Turbula® T2F) at 49 rpm for 45 min. Each PB was characterized immediately after harvesting the samples from the glass vessels at the end of the mixing process.