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Polymer-mediated disruption of drug crystallinity

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Abstract

Ibuprofen (IB), a BCS Class II compound, is a highly crystalline substance with poor solubility properties. Here we report on the disruption of this crystalline structure upon intimate contact with the polymeric carrier cross-linked polyvinylpyrrolidone (PVP-CL) facilitated by low energy simple mixing. Whilst strong molecular interactions between APIs and carriers within delivery systems would be expected on melting or through solvent depositions, this is not the case with less energetic mixing. Simple mixing of the two compounds resulted in a significant decrease in the differential scanning calorimetry (DSC) melting enthalpy for IB, indicating that approximately 30% of the crystalline content was disordered. This structural change was confirmed by broadening and intensity diminution of characteristic IB X-ray powder diffractometry (PXRD) peaks. Unexpectedly, the crystalline content of the drug continued to decrease upon storage under ambient conditions. The molecular environment of the mixture was further investigated using Fourier transform infrared (FT-IR) and Fourier transform Raman (FT-Raman) spectroscopy. These data suggest that the primary interaction between these components of the physical mix is hydrogen bonding, with a secondary mechanism involving electrostatic/hydrophobic interactions through the IB benzene ring. Such interactions and subsequent loss of crystallinity could confer a dissolution rate advantage for IB.

Keywords: Ibuprofen; Polyvinylpyrrolidone; Amorphous; Hydrogen bonding; Physical mixing; Solid dispersion

1. Introduction

Solubilisation of poorly water soluble drugs continues to be a challenge within pharmaceutical formulation. Many compounds currently under development are Biopharmaceutical Classification System (BCS) Class II compounds, i.e. high permeability but poor solubility (Amidon et al., 1995). These physicochemical characteristics may be inherent in the chemical structure of the drug compounds but may also result from optimisation of lead compounds to enable site or receptor specificity. The dissolution rate in the aqueous environment of the gastrointestinal fluids is typically the rate limiting step for absorption of these drugs.

Since oral dosing is the desired administration route for most drugs and considering that tablets are the most widely used dosage form, drug dissolution is a prerequisite for absorption and clinical efficacy. Therefore improvements in the dissolution profile of these Class II drugs can greatly enhance the bioavailability of these compounds. Conversion of the molecule into a more soluble salt form, or identification of optimum polymorphic forms, are two common approaches for overcoming the problem of low solubility (Serajuddin, 1999). However, manipulation of the lead compound is not always possible, or if successful, will not necessarily lead to a product with sufficient stability for commercial use (Datta and Grant, 2004). Other strategies have therefore been developed to solubilise poorly soluble drugs.

Co-grinding is one such technique, i.e. the comminution of the drug and a carrier through high-energy milling. This results in size reduction of the active compound and can often facilitate conversion of the drug to an amorphous form (Mura et al., 2002). Both of these factors can positively affect the dissolution profile of the drug. Another effective technique for improving the dissolution properties and bioavailability of poorly water-soluble drugs is the inclusion of a drug within a solid dispersion (Shin et al., 1998; Leuner

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and Dressman, 2000). Solid dispersions are produced from drug-excipient mixtures either by co-crystallization from a common solvent, or by exposure to elevated temperatures that facilitate simultaneous melting and intimate mixing of the components (Craig, 2002). Both methods result in dispersion of the active compound within the carrier matrix at solid state (Chiou and Riegelman, 1971).

Co-grinding and solid dispersions may solubilise the drug through excipient facilitated wetting, dispersion due to excipient swelling, decreased drug particle size, and/or improved kinetics due to stabilisation of the amorphous form of the drug. However solid dispersions can have disadvantages, such as a lack of suitable co-solvents or lack of miscibility in the molten state, toxicity due to residual solvent, degradation of thermolabile compounds, sublimation of drug or carrier, or polymorphic transition of the drug resulting in loss of activity (Ford, 1986; Hancock and Zografi, 1997). Co-grinding can also result in thermal degradation of drug compounds as the highly energetic nature of the process can considerably increase the temperature of the product. The formation of "fines" can also have a detrimental effect on subsequent processing to produce solid dosage forms. Developing alternative methods of dry solubilisation is therefore desirable.

Cross-linked polyvinylpyrrolidone (PVP-CL) is a polymeric carrier commonly used within oral formulations, including solid dispersions (Leuner and Dressman, 2000). It is widely used as a disintegrant due to its highly hydrophilic character, rapid water uptake and excellent swelling properties upon contact with solvents (Moneghini et al., 2000). Cross-linked polyvinylpyrrolidone has also been successfully used as an excipient for co-grinding, creating an amorphous form of the drug shown to be stable after 1 year (Shin et al., 1998). Also, in excipient compatibility studies (Botha and Lotter, 1989a,b, 1990a,b) it was reported that decreased drug melting endotherms were seen upon co-grinding with both linear, and/or cross-linked forms of the polymer, as measured by differential scanning calorimetry.

Decreased crystallinity has also been noted for drug compounds combined with cross-linked polyvinylpyrrolidone in physical mixes (Fujii et al., 2005; Williams et al., 2005); similar results were not observed for other excipients, e.g. microcrystalline cellulose. Whilst strong molecular interactions between active pharmaceutical ingredients (APIs) and carriers within delivery systems would be expected on melting, through solvent depositions or through co-grinding, this is not the case with less energetic mixing. These systems therefore confer some of the previously described solubility advantages of solid dispersions without exposing the drug molecules to the same manufacturing stresses associated with heat or solvents.

In depth examination of this phenomenon has not yet been reported and no mechanisms have been elucidated. Within the context of this paper, we have explored the novel interaction between cross-linked polyvinylpyrrolidone and crystalline poorly water-soluble drug compounds. Here ibuprofen (IB), a non-steroidal anti-inflammatory BCS Class II drug was used as a model compound. This is one of the compounds noted to interact with cross-linked polyvinylpyrrolidone (Williams et al., 2005); interactions were also noted within solid dispersions with the linear form of the polymer (Sekizaki et al., 1995; Martinez-Oharriz et al., 2002).

Thermal and X-ray diffraction methods have been used to assess drug crystallinity within samples. In addition to melting transitions, glass transition temperature (T_g) of a polymer and subsequent drug mixtures can usually be measured by differential scanning calorimetry (DSC). When an interaction occurs between the two compounds a single T_g will be observed at a temperature between the two T_gs of the individual compounds as the drug acts as a plasticizer for the polymer (Cilurzo et al., 2002). This data can therefore provide an indication of the degree of interaction of two compounds and the stability of the combined systems (Nair et al., 2001; Corrigan et al., 2004). In contrast to linear polyvinylpyrrolidone that shows a defined T_g using DSC (temperature dependant on chain length), the cross-linked polyvinylpyrrolidone displays only broad changes in thermal character over a wide temperature range. It was not possible to investigate the T_g of this polymer by either thermomechanical analysis or dynamic thermomechanical analysis as the polymer is insoluble in all solvents preventing the casting of a thin film required for both techniques. No T_g has been reported for cross-linked polyvinylpyrrolidone by the two main manufacturers (BASF and ISP) and none has been found in a review of current literature. This prevented the use of T_g in characterising this system. Accordingly, ibuprofen crystallinity has been used to assess the stability of the physical mix systems and spectroscopic methods have been pursued to probe the mechanisms for the interaction explored here.

2. Materials and methods

2.1. Materials

Ibuprofen (IB) (Wessex Fine Chemicals), Fig. 1a, an anti-inflammatory, analgesic and antipyretic agent, was chosen as a model BCS Class II compound. It exists as a colourless crystalline solid with no reported polymorphs, and pK_a of 5.3, implying low aqueous solubility in acidic pH media (Herzfeldt and Kummel, 1983). IB was sieved to obtain a particle size range of 90–150 μm, thereby enhancing flowability and reducing potential variations in results due to particle size. The melting

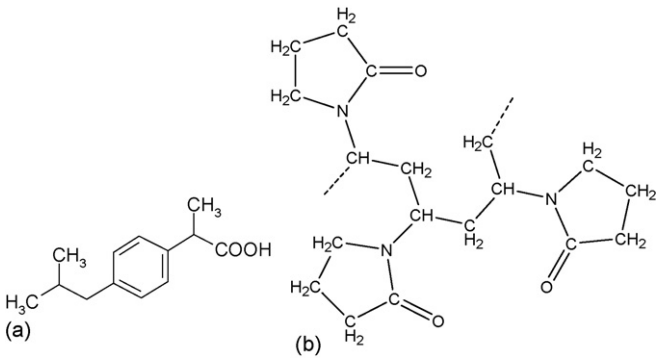

Fig. 1. Molecular structure of (a) model BCS Class II drug ibuprofen (IB) and (b) cross-lined polyvinylpyrrolidone (PVP-CL).