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Reducing mechanical activation-induced amorphisation of salbutamol sulphate by co-processing with selected carboxylic acids

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ABSTRACT

The unintentional generation of amorphous character in crystalline active pharmaceutical ingredients (APIs) is an adverse consequence of mechanical activation during dosage form manufacture. In this study, we assess and compare the ability of low glass transition temperature (T_g) dicarboxylic acids to mitigate amorphisation of a model API, salbutamol sulphate (SS), on both co-milling and co-mixing.

SS processed alone, as well as co-milled and co-mixed composites of the API with glutaric acid (GA), adipic acid (AA) and pimelic acid (PA) were characterised by powder X-ray diffraction (pXRD), differential scanning calorimetry (DSC) and dynamic vapour sorption (DVS).

Milling and dry mixing of SS both resulted in pXRD amorphous materials. No amorphous content of SS was detected by DVS on co-milling with 50% (w/w) GA, while amorphisation was more than halved, relative to the API milled alone, on co-milling with 50% (w/w) AA and PA, respectively. Co-mixing with each excipient also resulted in a decrease in API amorphicity, although the extent of reduction was considerably less compared to the co-milling experiments.

The solubility ($Sol_{excipient}$) of each excipient in amorphous SS was determined by thermal methods. No further reduction in API amorphisation was achieved on co-mixing with 50% (w/w) excipient, compared to concentrations corresponding to the solubility of each excipient in the amorphous API (Sol_{GA} = 36%, Sol_{AA} = 21%, Sol_{PA} = 22%). PXRD confirmed gradual dissolution over time of GA in amorphous SS on co-mixing. In contrast to co-mixing, co-milling SS at excipient weight fractions above their respective solubilities in the amorphous drug resulted in further reductions in API amorphisation. This is thought to be due to the generation of a molecular dispersion of amorphous API, supersaturated with excipient, thereby leading to a more pronounced composite T_g lowering effect.

The results indicate that co-processing with low T_g excipients is an effective strategy at minimising amorphisation of an API on mechanical activation.

1. Introduction

It is well recognised that subjecting drugs to routine pharmaceutical unit operations can result in changes to the solid state properties of the material (Morris et al., 2001; Lin et al., 2010). This can result in the transformation of a highly ordered crystalline material to a disordered, high energy amorphous state (Feng et al., 2008; Patterson et al., 2007). An amorphous system, despite its advantages of enhanced solubility and dissolution rate, will be thermodynamically metastable relative to its crystalline form and can revert back to the lower energy state with time. This can have serious implications in terms of manufacturability, processability and stability (Hancock and Zografi, 1997; Yu, 2001).

Mechanical activation is a term used to describe the increase in free energy of a solid on mechanical processing, and is generally assumed to arise from operations such as milling, grinding, compaction and compression, which results in breakage or fracture of a solid (Hüttenrauch et al., 1985). However it was shown by Mosharraf and Nyström (1999), that 'gentler' operations such as dry mixing can activate solids. The authors noted a considerable change in the solid state structure of griseofulvin on mixing, which also resulted in an increase in solubility. More recently, Hockerfelt et al. in 2009 reported that griseofulvin could be completely amorphised by dry blending without particle breakage.

Milling, when compared to dry mixing, is a considerably more energetic process and is known to amorphise several APIs (Gusseme et al., 2008; Willart et al., 2012, 2001). Balani et al. (2010) noted that amorphisation of milled salbutamol sulphate could be reduced by

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co-milling the API with crystalline excipients, such as α lactose monohydrate, adipic acid and magnesium stearate. They suggested that the effects observed were associated with the presence of excipient acting as seed crystals, coupled with a temperature increase from the milling operation. We demonstrated that co-milling sulfadimidine with a series of low glass transition temperature (T_g) excipients was an effective strategy to minimise amorphisation of the drug (Curtin et al., 2013). It was highlighted that excipients which showed good solubility in the API exerted a T_g lowering effect, resulting in composite T_g values lower than that of the API alone, which could mitigate amorphisation of the API. In contrast, a crystalline excipient (malic acid) which displayed very poor solubility in the API was found to promote amorphisation of the drug.

In this work we evaluate and compare, for the first time, the influence of two mechanical operations on a model API co-processed with low T_g excipients. The objective of the study was to compare the effect of two different modes of mechanical activation (milling and dry mixing) on salbutamol sulphate (SS) and to see if co-processing with low T_g excipients could prevent or minimise amorphisation of the API. SS was chosen because of its high glass transition temperature (120 °C) and its known propensity to amorphise when milled (Balani et al., 2010; Griesdale et al., 2011; Brodka-Pfeiffer et al., 2003). The excipients chosen were glutaric acid, adipic acid and pimelic acid based on their structural similarity and their low glass transition temperatures according to the $T_g = T_m \times 0.7$ rule (Fukuoka et al., 1989; Kerc and Srcic, 1995). Their respective solubilites in amorphous SS were determined by thermal methods. Freeze drying was used to produce amorphous API:excipient systems which enabled composite T_g values to be determined. The milled and dry mixed API, as well as the API:excipient co-processed systems were characterised with respect to their X-ray diffraction, thermal and vapour sorption properties.

2. Materials and methods

2.1. Materials

Salbutamol sulphate (SS) raw material (molar weight (Mw) = 576.70 g mol^{-1}) was purchased from Camida Ltd. (Clonmel, Ireland). Adipic acid (AA) (Mw = 146.14 g mol^{-1}), glutaric acid (GA) (Mw = 132.11 g mol^{-1}), and pimelic acid (PA) (Mw = 160.17 g mol^{-1}) were purchased from Sigma–Aldrich, Ireland. Glass beads of diameter 5 mm were purchased from Sigma–Aldrich, Ireland. Ethanol (99.5%, v/v) was purchased from Corcoran Chemicals, Ireland. Water, ultra-pure, was prepared from a Millipore Elix advantage water purification system. Acetonitrile, HPLC grade, was purchased from Fisher Scientific (Ireland). Triethylamine was purchased from Sigma Aldrich, Ireland.

2.2. Methods

2.2.1. Milling

Ball milling of SS and excipients was performed with a PM 100 high energy planetary mill (Retsch, Germany) at room temperature. 2.5 g of material was 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 disc was set at 400 rpm. Every 20 min of milling was followed by a pause period of 10 min to avoid overheating (Curtin et al., 2013). Total milling time was kept constant at 3 hours (h) corresponding to an effective milling time of 2 h. SS was co-milled with GA at different weight percentages of excipient (X_{GA} = 5, 20, 35, 50%). SS was also co-milled with 21% and 50% (w/w) AA, and 22% and 50% (w/w) PA. API:excipient co-processed systems are named in accordance to the % weight fraction of each component. For instance SS95:GA5 refers to a system composition of 95% (w/w) SS and 5% (w/w) GA. All milling experiments were performed at least in duplicate.

2.2.2. Dry mixing

Dry mixing experiments were performed using a Turbula mixer operating at 64 rpm (360 ml tubes, W.A. Bachofen, Switzerland) based on the method used previously by Hockerfelt et al. (2009). The API and API:excipient fractions were mixed with glass beads in the weight proportion 1:99 of powder to beads. A total powder content of 0.78 g was used for the dry mixing experiments. Experiments were performed at different times, ranging from 2 h to 24 h. SS was dry mixed with each excipient at a concentration corresponding to its solubility in the amorphous drug. The 24 h mixes were also performed at 50% (w/w) excipient. All mixing experiments were performed at least in duplicate.

2.2.3. Freeze drying

API:excipient mixtures of various weight fractions ranging from 95:5 to 50:50 were dissolved in deionised water and stirred for 24 h at room temperature to yield aqueous solutions with a concentration of 5% (w/w) total solid. The solutions were then sonicated for 10 min and filtered through a 0.45 μm syringe filter to ensure the absence of any residual crystals. The resulting aliquots (5 ml) were then poured into 50 ml plastic tubes, which were immersed in liquid nitrogen for 15 min and then loaded into a VirTis wide mouth filter seal glass flasks and attached to one of the manifold ports of a benchtop VirTis 6K freeze-dryer model EL (SP Scientific, USA). A Vacuum of 29–31 mTorr was obtained by the use of an Edwards 5 RV5 rotary vane dual stage mechanical vacuum pump (Edwards, England). After 48 h of freeze drying the tubes were removed and capped. This was performed in duplicate for all mixtures.

2.2.4. Spray drying

PA was spray dried as a solution in ethanol/water 7:3 (v/v) using a Buchi-290 Mini Spray Dryer, as previously described (Curtin et al., 2013). The inlet temperature was maintained at 78 °C, outlet temperature was between 42–49 °C and a feed concentration of 0.4% (w/v) was used. Spray drying was performed in the open mode configuration using compressed air as the drying medium with a pump rate of 30% (8 ml/min), aspirator setting of 100% and air flow of 40 mm (473 l/h).

2.2.5. 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), as previously described (Curtin et al., 2013). The pXRD patterns were recorded from 5° to 40° on the 2 theta scale at a step of 0.05° 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. PXRD patterns were recorded at least in duplicate.

For quantification of crystalline content by pXRD, the amorphous standard was prepared by milling the API for 2 h and the crystalline reference standard was obtained by placing SS as received in the DVS at 90% RH until no mass loss events were observed in the kinetic profile. The method employed was based on the method reported by Clas et al. (1995). Zinc oxide was used as an internal standard to determine if there were variations in peak position and intensity.

Different weight fractions of crystalline SS (X_c) (X_c = 0.2, 0.25, 0.5, 0.75, 0.9) were prepared by mixing the relevant quantities of crystalline and amorphous reference samples (total mixed sample weight 100 mg) with 10 mg zinc oxide using an agate mortar and