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Mitigating unwanted amorphisation: A screening method for the selection of suitable excipients

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ABSTRACT

Co-processing an active pharmaceutical ingredient (API) with a low Tg excipient has been previously reported to be an effective strategy for preventing drug amorphisation on milling. This technique relies on the ability of the excipient to form a molecular dispersion with the amorphous API during the milling process. The presence of the excipient within the amorphous phase induces a reduction of the Tg. Hence, the molecular dispersion becomes less stable than the amorphous API alone and recrystallises upon milling. The objective of this study was to develop a screening method for the selection of suitable excipients to prevent amorphisation, based on two criteria: the Tg of the excipient and the solubility of the excipient in the amorphous API. The ability of the excipients to induce Tg reduction was first assessed by measuring the Tg of the amorphous composite by thermal analysis and comparing it with that of the pure API (griseofulvin). A predicted ability for mitigation of amorphisation upon milling was then deduced from these observations for each excipient and assessed against experimental results. The same excipients were then studied with regard to their expected solubility in another amorphous API (budesonide) by Hildebrand solubility parameter calculations in order to evaluate their capacity to form an amorphous composite with the drug. The predicted effects of the excipients on comilling were compared with the amorphous content of the processed API.

The screening method as applied to both APIs showed good agreement with the experimental results and were shown to be efficient for the selection of the most appropriate excipient. This approach revealed that the two key parameters involved are the Tg of the excipient and the ability of the API to form an amorphous molecular dispersion with the excipients. This work confirms and completes our previously published results on the mitigation of the amorphisation by comilling with low Tg excipients and constitutes the first report of the use of a polymeric additive for this purpose.

1. Introduction

Milling is a unit process commonly used in the pharmaceutical industry for particle size reduction (Yu, 2001). This technique imparts a lot of energy into a pharmaceutical system and can lead to the generation of amorphous content (Gusseme et al., 2008; Willart and Descamps, 2008). Various studies have been carried out to promote the production and retention of this amorphous character, due to its enhanced solubility and bioavailability compared to the crystalline form (Pokharkar et al., 2006; Shah et al., 2006). However, due to the inherent physical instability and chemical reactivity associated with this amorphous state, there is, conversely, also a keen interest in avoiding this, often unintentionally generated, high energy state and retaining the crystallinity of active pharmaceutical ingredients (APIs) upon milling (Yu, 2001; Hancock and Zografi, 1997).

Co-processing with crystalline excipients of low glass transition temperatures (Tg) has previously been shown to reduce the amorphisation of salbutamol sulphate and sulfadimidine (Balani et al., 2010; Curtin et al., 2013a, 2013b). Curtin et al. have hypothesised that the amorphous API produced during the process (milling or dry blending) dissolves the crystalline low Tg excipient thus generating an amorphous composite with a lower glass transition temperature compared to the drug alone (Curtin et al., 2013a, 2013b). This Tg reduction induces a decrease of the stability of the two-component amorphous phase and can trigger the recrystallisation of the composite during the process, resulting in the production of a physical mixture of crystalline API and crystalline excipient. The Tg of the excipient therefore appears to be the key parameter which determines its ability to reduce or prevent amorphisation. The affinity between the API and the excipient is also a criterion of primary importance since the latter has to be at least partially soluble in the amorphous API in order to exert its Tg lowering effect, as shown by Curtin et al. (2013b).

To further investigate this topic, a series of crystalline excipients were tested for their ability to mitigate the amorphisation of two model APIs on processing: griseofulvin and budesonide. These two

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APIs were chosen because of their high glass transition temperature (ca. 90 °C) and their known propensity to amorphise when milled (Willart et al., 2012; Dudognon et al., 2006). The ability of the excipients to induce a reduction in Tg were first assessed by thermal analysis on griseofulvin and compared with their efficiency for preventing the amorphisation of the API by comilling. A screening method was deduced from these observations and then assessed on systems formed by the same excipients and another API, budesonide. The purpose of this study was to design a predictive model for screening crystalline excipients that can selectively reduce or prevent unwanted amorphisation upon co-processing.

2. Materials and methods

2.1. Materials

Griseofulvin (GF) (Mw = 352.77 $g \cdot mol^{-1}$), budesonide (BD) (Mw = 430.53 $g \cdot mol^{-1}$), glutaric acid (GA) (Mw = 132.11 $g \cdot mol^{-1}$), adipic acid (AA) (146.14 $g \cdot mol^{-1}$) mannitol (MN) (Mw = 182.20 $g \cdot mol^{-1}$), poly(ethylene glycol) (PEG) (Mw = 4000 $g \cdot mol^{-1}$), methanol (Mw = 32.04 $g \cdot mol^{-1}$) and chloroform (Mw = 119.38 $g \cdot mol^{-1}$) were purchased from Sigma-Aldrich, Ireland. Xylitol (XY) (Mw = 152.15 $g \cdot mol^{-1}$) was obtained from Lancaster Synthesis, England. The thin layer chromatography (TLC) plate was purchased from Riedel de Haen, Germany.

2.2. Methods

2.2.1. Milling

Ball milling was performed using 2.5 g of material in a PM 100 high energy planetary mill (Retsch, Germany) at room temperature, as previously described by Curtin et al. (2013a). Griseofulvin and budesonide were milled for 17 and 18 h for systems respectively.

2.2.2. Thermal analysis

Differential scanning calorimetry (DSC) experiments were conducted using a DSC Q200 (TA Instruments, United Kingdom) as previously described (Curtin et al., 2013a). Unless otherwise noted, the reported Tg is the midpoint temperature of the glass transition (n = 2).

2.2.3. 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., 2013a).

2.2.4. Preparation of API/excipient amorphous composites

API/excipient mixtures (50/50 *w/w*) were milled as described in the previous section and subsequently melted on a heating plate under a nitrogen atmosphere. The resulting materials were then quenched to 25 °C. pXRD was used to verify the absence of crystalline API. The Tg of the resulting amorphous phase was then determined by DSC as described above (n = 2).

2.2.5. Hildebrand solubility parameter

The Hildebrand solubility (δ) parameters were determined utilising the Fedors' group contribution method (Fedors, 1974) by means of the following equation:

$$\delta = (\Delta E_v / V_m)^{1/2} \quad (1)$$

where ΔEv is the energy of vaporisation and Vm is the molar volume.

2.2.6. Dynamic vapour sorption (DVS)

Sorption isotherms and kinetic profiles of the milled solids were obtained using DVS (Advantage, Surface Measurement Systems, Alperton, UK) as previously described (Curtin et al., 2013a, 2013b). The temperature was 25.0 ± 0.1 °C and water and ethanol were used as the probe vapours for GF and BD systems respectively. The samples were dried at 0%P/P_0 and then subjected to step changes of %P/P_0 up to 90% and 80% for GF and BD respectively, and the reverse for desorption. Amorphous content was determined using Eq. (2):

$$\%\ \text{amorphous content} = 100\ x\ \frac{\Delta m \cdot m_s}{m_d} \cdot \frac{1}{\Delta m_{100}} \quad (2)$$

Where Δm is the difference in the mass uptake (%) of the API between the first and second sorption cycles at a system specific %P/P_0, m_s is the sample mass in the DVS, m_d is the mass of the API in the overall sample mass, and Δm_{100} is the difference in mass uptake (%) between the first and second sorption cycles of the fully amorphous standard (GF sample milled at 4 °C). The amorphous content was defined as the mass percentage of amorphous API.

All DVS experiments were performed at least in duplicate.

2.2.7. High performance liquid chromatography analysis (HPLC)

The chemical integrity of melt-quenched samples was determined using a Shimadzu HPLC Class VP series with a LC-10AT VP Pump, SIL-10 AD VP autosampler and SCL-10VP system controller for GF, GA, AA and MN and a Waters HPLC equipped with a Waters 1525 binary HPLC pump and a Waters 717 Plus autosampler for XY. The mobile phases were vacuum filtered through a 0.45 μl membrane filter (Pall Supor-450) and consisted of methanol/purified water 70/30 (*v/v*) for GF (Trotta et al., 2003), water (purified) for MN and XY (British pharmacopoeia, 2007 and 2013) and a phosphoric acid solution (pH = 2.1) for GA and AA (Amharar et al., 2014). Separation was performed on TSK-Gel 6000PWXL (30 cm length, 7.8 mm diameter, pore size 13 μm) and TSK-Gel 3300PWXL (30 cm length, 7.8 mm diameter, pore size 6 μm) columns with elution carried out isocratically at temperatures of 50 °C and 40 °C for MN and XY respectively (British Pharmacopoeia, 2007, 2013). For GA and AA a LiChrosorb RP-10 column (250 mm length, internal diameter 4 mm, and particle size 10 μm) was used at room temperature with isocratic elution. Separation was performed on a Luna C18 (250 mm length, diameter 4.6 mm, particle size 5 μm) for GF with elution carried out isocratically and at room temperature (Trotta et al., 2003). UV detection was used at a wavelength of 245 nm for GF and at 210 nm for GA and AA using a SPD-12A VP UV–Vis detector. A flow rate of 1 ml/min was used for GA and AA and 0.8 ml/min for GF. A Waters 410 Differential Refractometer held at a temperature of 50 °C with a flow rate of 0.5 ml/min was used for the detection of MN. The detection of XY was performed on a Waters 2414 Differential Refractometer held at 40 °C with a flow rate of 1 ml/min.

Class-VP 6.10 software was used for peak evaluation.

2.2.8. Thin layer chromatography (TLC)

Thin layer chromatography was used to assess the thermal stability of PEG (Padfield et al., 1990). Analyses were carried out on TLC aluminium plates (20 × 20 cm, 0.2 mm layer thickness) precoated with silica gel (254 nm). The sample volumes for all experiments were 5 μl. The mobile system used was methanol:H_2O:Chloroform (70:24:6, *v/v/v*). The TLC plate was developed until a 12 cm migration distance of the solvent from the start line was achieved. Iodine vapour was used for spot detection. The development distance of the samples were compared with that of raw PEG and the expected degradation products (lower molecular weight analogues).

2.2.9. Nomenclature

The system formed by a mixture of the API A and the excipient B is denoted AB. If this mixture contains X % *w/w* of B, the resulting solid is denoted ABX. For example GFGA50 stands for a mixture of 50% of GF and 50% *w/w* of GA. It is acknowledged that the term 'solubility' cannot be used on amorphous systems below Tg because these systems are not