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Production of cocrystals in an excipient matrix by spray drying

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ABSTRACT

Spray drying is a well-established scale-up technique for the production of cocrystals. However, to the best of our knowledge, the effect of introducing a third component into the feed solution during the spray drying process has never been investigated. Cocrystal formation in the presence of a third component by a one-step spray drying process has the potential to reduce the number of unit operations which are required to produce a final pharmaceutical product (e.g. by eliminating blending with excipient). Sulfadimidine (SDM), a poorly water soluble active pharmaceutical ingredient (API), and 4-aminosalicylic acid (4ASA), a hydrophilic molecule, were used as model drug and coformer respectively to form cocrystals by spray drying in the presence of a third component (excipient). The solubility of the cocrystal in the excipient was measured using a thermal analysis approach. Trends in measured solubility were in agreement with those determined by calculated Hansen Solubility Parameter (HSP) values. The ratio of cocrystal components to excipient was altered and cocrystal formation at different weight ratios was assessed. Cocrystal integrity was preserved when the cocrystal components were immiscible with the excipient, based on the difference in Hansen Solubility Parameters (HSP). For immiscible systems (difference in HSP $>$ 9.6 $MPa^{0.5}$), cocrystal formation occurred even when the proportion of excipient was high (90% w/w). When the excipient was partly miscible with the cocrystal components, cocrystal formation was observed post spray drying, but crystalline API and coformer were also recovered in the processed powder. An amorphous dispersion was formed when the excipient was miscible with the cocrystal components even when the proportion of excipient used as low (10% w/w excipient). For selected spray dried cocrystal-excipient systems an improvement in tableting characteristics was observed, relative to equivalent physical mixtures.

1. Introduction

It has been shown that the reason less than 1% of drug candidates make it to market is not only due to a lack of efficacy, safety or an unfavourable side effect profile, but also due to poor biopharmaceutical properties (Aakeröy Cb Fau - Aakeröy et al., 2009; Cook et al., 2014). It has been suggested that drug discovery strategies, such as high throughput screening, are increasingly leading to lead candidates which have unfavourable physicochemical properties (Lipinski et al., 2012). Many of these compounds have poor aqueous solubility, which can lead to a low dissolution rate (Hörter and Dressman, 2001). Over half of marketed drug products are formulated as salts to modify the physical properties of the active pharmaceutical ingredient (API). However, a major limitation of this approach is the requirement of the API to possess a basic or acidic ionisable group. Pharmaceutical cocrystals offer an alternative to salt forms as a means of improving the solubility, dissolution and bioavailability of poorly water soluble drugs. Cocrystals of an API and coformer are formed by noncovalent, freely reversible interactions, and so the presence of an ionisable group is not a necessity. The solubility and dissolution rate of an API in a cocrystal are improved by lowering the lattice energy and/or increasing the solvent affinity (Thakuria et al., 2013). Cocrystallisation of an API can confer a number of advantages over other formulation strategies such as amorphisation. One of the major limitations of amorphous forms is the fact that they are thermodynamic unstable, making them prone to conversion to the lower energy crystalline forms (Hancock et al., 1995).

Various methods exist to produce cocrystals. Common approaches include grinding and solution methods. However, a disadvantage of solution methods to produce cocrystals can be the formation of single component crystals when crystallised from an incongruently saturating solution (Qiao et al., 2011). Spray drying is commonly used to produce amorphous solid dispersions (Van den Mooter et al., 2001; Zhao et al.,

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2012) but also, in some instances, results in the formation of crystalline materials (Kumar et al., 2015). This technique has been shown to be a viable and scalable method to produce pure cocrystals from both congruent and incongruently saturating solutions. Carbamazepine-glutaric acid, theophylline-nicotinamide, urea-succinic acid and caffeine-glutaric acid all formed pure cocrystals when spray dried from an incongruently saturating solutions. Further to this, the urea-succinic acid 1:1 cocrystal was discovered and consistently generated in pure form by spray drying. Cocrystallisation of this system did not occur by slurry or reaction crystallisation methods (Alhalaweh and Velaga, 2010).

The approach of using Hansen Solubility Parameters (HSP) calculated using the group contribution method has enabled the prediction of solid-solid solubility of pharmaceutical materials (Greenhalgh et al., 1999; Hancock et al., 1997). For drug-excipient combinations, a $\Delta\delta t$ (i.e. difference in HSP) of less than 7.0 $MPa^{1/2}$ is considered to be indicative of significant miscibility, while a $\Delta\delta t$ of greater than 10.0 $MPa^{1/2}$ denotes a lack of miscibility and limited ability to form glass solutions (Forster et al., 2001; Greenhalgh et al., 1999).

Calculation of the HSP of drug and coformer and the difference in HSP values for the two components can be used as a tool to predict the success of cocrystal formation on spray drying. It has been shown that, in order for an API to form a cocrystal with a coformer, the two molecules must be miscible at a molecular level, with the difference in HSP being less than 7 $MPa^{0.5}$ (Mohammad et al., 2011). However, to the best of our knowledge, the effect on cocrystal formation of introducing a third (excipient) component into the feed solution during the spray drying process has never been investigated, nor has the relative differences in HSP between excipient and cocrystal components been probed in relation to success or otherwise of cocrystal formation on spray drying.

The hypothesis underlying this work is that a larger difference in HSP between the cocrystal components and the excipient will promote cocrystal formation during spray drying in the presence of a carrier excipient, as the cocrystal components will not be miscible with the excipient, and so will remain phase separated from the excipient but still interact with one another. In contrast, excipients which have a similar HSP to the cocrystal components may be miscible and may not allow for cocrystal formation to occur, rather there may be a high probability that an amorphous dispersion of individual coformer molecules, rather than a cocrystal suspension would form within the carrier.

The aim of this work was to investigate the impact of including a carrier excipient on cocrystal formation during the spray drying process. A range of pharmaceutical excipients were selected and co-spray dried with the cocrystal components. Solid state characterisation was performed as well as solubility studies of the cocrystal in the excipient using a thermal analysis approach. Dissolution studies were performed from constant surface area disks.

The feasibility of co-spray drying cocrystals and a third component, carrier excipient, in order to reduce the number of unit processes to produce a final pharmaceutical product was investigated by compaction studies.

2. Materials

Sulfadimidine (SDM), 4-aminosalicylic acid (4ASA), mannitol, chitosan (average molecular weight 50,000–190,000), glycine, polyvinyl alcohol (PVA) (average molecular weight 70,000-100,000), dextran (average molecular weight 68,800), hydroxypropyl methylcellulose (HPMC) (4,000 cP) and polyvinylpyrrolidone K15 (PVP) were purchased from Sigma-Aldrich (Ireland). Microcrystalline cellulose (MCC) Avicel® CL-611 was a gift from FMC Biopolymer, Belgium. Soluplus® was a gift from BASF, Germany. Inulin with an average degree of polymerisation of 11 (Fruitafit® HD) was a gift from Sensus, Netherlands. Ethanol was supplied by Corcoran Chemicals (Ireland). Water was purified and filtered using an Elix 3 connected to a Synergy UV system (Millipore, UK). All other chemicals used were of analytical grade.

3. Methods

3.1. Preparation of cocrystals

3.1.1. Spray drying

A 1% w/v solution of SDM and 4-ASA was prepared using ethanol as solvent. The solution was sonicated to dissolve the cocrystal components completely. An equal volume of 1% w/v excipient aqueous solution (inulin, mannitol, glycine, PVA (heated to 60 °C), HPMC, PVP and Soluplus) or suspension (MCC, chitosan and dextran) was added to the 1% solution of SDM and 4-ASA. The solution with the cocrystal components was mixed with the excipient solution/suspension prior to spray drying. The resultant solutions/suspensions were spray dried using a Büchi B-290 Mini Spray Dryer operating in the open mode. The solutions/suspensions were delivered to a 2-fluid atomization nozzle using a peristaltic pump at a pump speed of 30% (9–10 ml/min) and the aspirator was operated at 35 m^3/h. The flowmeter for the standard 2-fluid nozzle was set at 4 cm, which is equivalent to 667 normlitres per hour (Nl/h) of gas flow at standard temperature and pressure conditions ($p = 1013.25$ mbar and $T = 273.15$ K) (Büchi Labortechnik, 93001). The inlet temperature was set at 105 °C (outlet temperature between 68–72 °C) for the systems which contained excipient in deionised water and 78 °C (outlet temperature between 50–57 °C) for the spray drying of cocrystal in ethanol alone. Based on whether cocrystal formation occurred at this ratio of cocrystal component to excipient (i.e. 1:1%w/w), the ratio of cocrystal components to excipient was altered to assess the maximum ratio of excipient:cocrystal components which would allow cocrystal formation.

For comparison purposes, physical mixtures of cocrystal and excipients were prepared using an agate mortar and pestle.

3.1.2. Solvent evaporation

Equimolar proportions of SDM and 4ASA were dissolved in 60 ml of acetone to give a 0.01 M solution and stirred until complete dissolution was achieved. The resulting solution was placed in a fumehood and allowed to evaporate for 72 h (Serrano et al., 2016a).

3.2. Solid state characterisation

3.2.1. Powder X-ray diffraction

Powder X-ray analysis was performed using a Miniflex II Rigaku diffractometer with Ni-filtered Cu Kα radiation (1.54 Å). The tube voltage and tube current used were 30 kV and 15 mA, respectively. The PXRD patterns were recorded (n = 3) for 2 theta ranging from 5° to 40° at a step scan rate of 0.05° per second. Rigaku Peak Integral software was used to determine peak intensity for each sample using the Sonneveld-Visser background edit procedure.

3.2.2. Differential scanning calorimetry (DSC)

DSC was performed using a Mettler Toledo DSC 821e instrument under nitrogen purge. Powder samples (4–6 mg) were placed in aluminium pans (40 µl), sealed, pierced to provide three vent holes and heated at a rate of 10 °C/min in the temperature range of 25 to 250 °C. Temperature and enthalpy were calibrated using indium as standard. The DSC was controlled by Mettler Toledo STARe software (version 6.10) working on a Windows NT operating system. All reported temperatures refer to onset of melting.

3.2.3. Solubility of cocrystal in excipient

Physical mixtures of cocrystal and excipient were prepared by mixing in a pestle and mortar at different weight ratios. The melting enthalpy of the crystalline phase was determined by DSC (as described above) and plotted as a function of excipient weight fraction. The