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Following mechanical activation of salbutamol sulphate during ball-milling with isothermal calorimetry

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ABSTRACT

Formulation of actives for pulmonary delivery with dry powder inhaler devices frequently requires a particle size reduction step. The high-energy forces imparted to a material during milling, as well as reducing particle size, can cause a significant change in physicochemical properties, in particular mechanical activation of the surface (manifested as generation of amorphous regions) which can affect formulated product performance. It is not clear whether particle size reduction occurs prior to, or concomitantly with, generation of amorphous content. In this study the formation of amorphous content with time in crystalline salbutamol sulphate was quantified with isothermal gas perfusion calorimetry as the sample was ball-milled. The data showed that the most particle size reduction occurred initially ($d_{0.5}$ dropping from 12.83 ± 0.4 to 4.2 ± 0.4 within 5 min). During this time period, no detectable amorphous content was observed. Between 5 and 15 min milling time the particle size distribution remained relatively constant but the amorphous content increased non-linearly with time. After 20 min milling time the particle size increased slightly. The data suggest that particle size reduction occurs initially upon application of a force to the crystal. Once maximum particle size reduction has occurred the crystal absorbs the force being applied and the crystal lattice becomes disordered. After extended milling the conditions in the ball mill (heat and/or humidity) may cause crystallisation of some of the amorphous material resulting in particle–particle fusion. It would appear that the ball-milling process could be optimised to achieve the desired particle size distribution but without any loss of crystalline structure.

1. Introduction

Delivery of active principals via the pulmonary route is an increasingly popular strategy, but presents a number of unique formulation challenges, in particular the fact that only small particles (between 2 and 5 μm) can be successfully deposited in the lower respiratory tract. Powders with such a small particle size distribution can be difficult to aerosolise because of their intrinsic cohesiveness, caused by their large surface area to mass ratio, irregular morphology, disordered surface chemistry, electrostatic charge and the fact that gravitational forces acting on particles of this size are not as dominant as other physical forces.

One approach is to formulate actives for delivery with a dry powder inhaler (DPI) device. Here, the small drug particles are located on the surface of a larger, crystalline carrier (typically lactose), bound by a force of adhesion. The aggregates, by virtue of larger physical dimensions, have better flowability and are easier to aerosolise. When the patient inspires, the turbulent air-flow causes deaggregation of the drug and carrier. The large carrier particles impact the back of the throat while the micronised drug enters the airways (Telko and Hickey, 2005).

Such an approach is convenient, because the inhaler device is breath actuated and hence the aerosolisation step is coordinated with inspiration (a common problem with pressurised metered dose inhalers (pMDI)). However, product performance is critically dependent upon the force of adhesion, which is in turn dependent upon the surface properties, mentioned above, of the active and carrier. It follows the method by which the active is prepared can control final product consistency (Chow et al., 2007). Particle engineering approaches such as antisolvent precipitation (Murnane et al., 2008), solution atomisation and crystallisation by sonication (SAX, Pitchayajittipong et al., 2009), supercritical fluid processing (Schiavone et al., 2004) and spray-freeze-drying (Amorji et al., 2007) have been employed, but these can be complex to design and difficult to scale to commercial batch manufacture.

A more generally used approach is milling, wherein a force is applied to large crystalline particles to achieve particle size reduction. Ball mills or air-jet mills are common designs. In the former

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case ceramic or metal balls are placed in a container with the sample and whole apparatus is rotated; the size, weight and number of balls can be varied as can the number of revolutions per minute and the total milling time. In the latter case compressed air is used to agitate particles, causing size reduction by particle attrition; the pressure of the air can be varied and centrifugal force determines when the particles are ejected from the mill. Since milling is a high-energy process, crystalline particles may become partially disordered (or amorphous) during size reduction, particularly at their surfaces (so called mechanical activation, Brodka-Pfeiffer et al., 2003a). While milling is easier to scale to industrial manufacture, the processes that lead to particle size reduction, and their effect on the physicochemical properties of the milled material, in particular at the surface, are not totally understood. On a commercial scale, this means it may well be the case that the milling process is optimised on particle size parameters alone, when surface factors may in fact be more important in ensuring consistency of product performance (Jones et al., 2008). As a consequence, milled material may often be 'conditioned' prior to formulation (with humidity, time and/or temperature) as this is seen empirically to produce a more consistent product (Brodka-Pfeiffer et al., 2003b).

While it is not possible to prevent the changes in surface chemistry caused by milling, quantifying the changes that occur is the first step in understanding, and ultimately controlling, these surface effects. Here, we show with isothermal microcalorimetric data, how some of the physicochemical properties of a model inhalation drug, salbutamol sulphate, change with increasing milling time and correlate the results with particle size distribution data to construct a simple model of the processes that occur during milling.

2. Materials and methods

Salbutamol sulphate (SS) was obtained from Micron Technologies Ltd (UK). Acetone (ACS grade) was purchased from Aldrich (UK). Aqueous solutions were prepared in deionised water.

Because the SS sample arrived micronised, it was recrystallised prior to commencement of experimentation, both to remove any amorphous content and to increase the particle size distribution. SS (35 g) was dissolved in water (110 mL) at 25 °C with continuous stirring and the solution was cooled to 0 °C in an ice bath. Acetone (2000 mL) was then poured slowly into the solution to precipitate SS crystals. The crystals were filtered, washed with acetone and dried in a vacuum oven at 40 °C for 1 week. Thermogravimetric measurements (Pyris 6, Perkin-Elmer Ltd) were performed on the SS crystals to confirm attainment of complete dryness during this time period (data not shown). The crystallinity of the sample was confirmed with powder X-ray diffraction (PXRD, Philips PW1730/10), Fig. 1, which showed the existence of the stable Form I. Scanning electron micrographs (Phillips XL-30) of the initial and recrystallised SS samples also confirmed the existence of Form I crystals (Fig. 2).

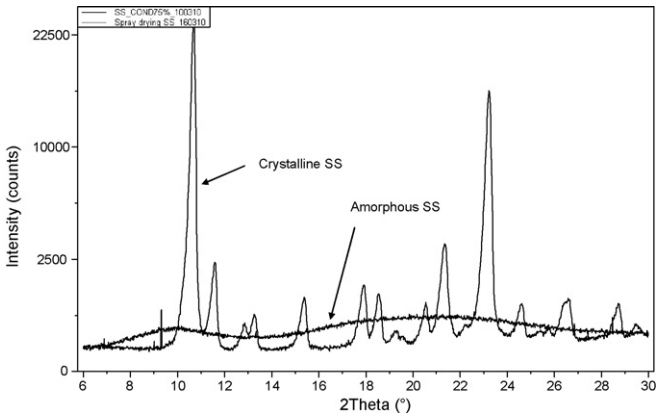

Fig. 1. PXRD patterns of recrystallised SS, showing the presence of Form I and spray-dried SS.

Amorphous SS was prepared by spray-drying. An aqueous solution of SS (5%, w/v) was spray-dried (Buchi B-191 mini-spray-drier) in accordance with the methodology of Columbano et al. (2002). XRPD measurements confirmed that the sample was amorphous, Fig. 1.

Extent of disorder was quantified with isothermal calorimetry (IC, TAM, TA Instruments UK). Samples (20 mg) were loaded into the ampoule (4 mL total volume) and allowed to equilibrate at 25 °C under 0% relative humidity (RH). The RH was then increased to 90% for a period of 8 h before being reduced to 0% for a further 8 h. Data were recorded with the dedicated software package Digitam 4.1. The instrument was calibrated with the electrical substitution method prior to use and operated on an amplifier setting of 1000 μW. The reference channel contained an empty stainless steel ampoule. A calibration curve was prepared by mixing crystalline and amorphous SS in appropriate ratios. All experiments were repeated in triplicate.

Ball-milling of SS was performed with a Fritsch Planetary Ball mill, Pulverisette 5 (Idar-Oberstein, Germany). The mill consisted of a ceramic jar (300 mL volume) containing ceramic balls (10) of diameter 2 cm. Drug (500 mg) was weighed and poured into the jar in which the balls had already been placed. Samples were milled at 100 rpm for various periods of time up to 20 min. Immediately following milling, the milled SS was analysed with IC for amorphous content quantification.

Particle size distribution was determined by laser diffraction (Mastersizer S, Malvern Instruments UK, equipped with a small volume stirred cell and 100 mm lens). Samples (ca. 5 mg) were suspended in a cyclohexane-lecithin solution (0.1%, w/v) and sonicated with a PUL 55 Sonicator (Kerry Ultrasonics, UK) at 50 Hz for 1 min prior to drop-wise addition to the sample cell to achieve a laser

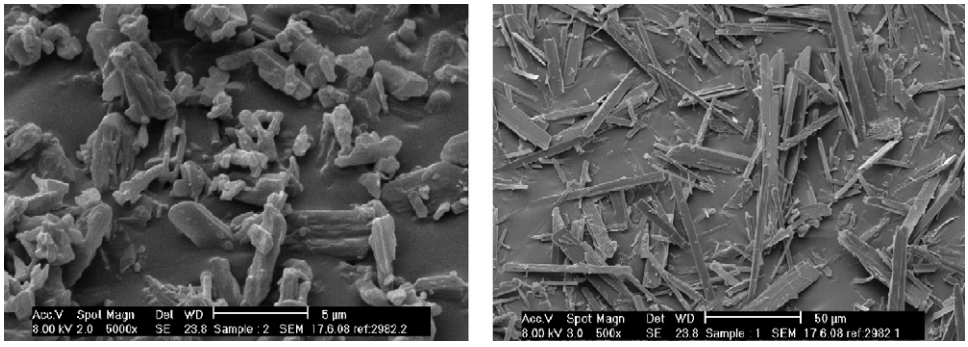

Fig. 2. SEM images of SS as received (left) and post-crystallisation (right).