

A Calorimetric Method for Optimising Milling of Pharmaceuticals

Mansa Dennison¹, Simon Gaisford^{1,2}, Matthew Jones¹ & Mark Saunders²

¹Department of Pharmaceutics, School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, UK

²Synectix Pharmaceutical Solutions Ltd, Tredomen Business and Technology Centre, Ystrad Mynach, Hengoed, CF82 7FN, UK

Summary

Background: The hypothesis is that generation of disordered regions during milling of pharmaceuticals can be monitored with isothermal calorimetry.

Methods: Salbutamol sulphate was milled for various periods of time; particle size was determined with laser diffraction and extent of disorder was quantified with isothermal calorimetry.

Results: The data showed that milling resulted initially in a reduction in particle size. No disorder in the sample was detected during this time. Further milling did not cause additional particle size reduction but extent of disorder increased. At longer milling times particle size was seen to increase and extent of disorder decrease.

Conclusions: It is proposed that at long milling times the heat and humidity in the mill cause recrystallisation of the disordered regions.

Introduction

The small particle sizes required for pulmonary delivery frequently mean that size-reduction steps (such as milling) are required during processing of constituents prior to formulation. As has been discussed in the literature [1], the mechanical forces imparted to a crystalline material during milling result primarily in a reduction in particle size, as the material fractures. Eventually there comes a point at which the bulk material can no longer fracture and maximum particle size reduction has been achieved. Post this point, the mechanical force applied is absorbed and dissipated by the sample, resulting in surface dislocations and eventually generation of amorphous regions; so called process-induced disorder. These changes in the surface of the material act to alter the surface energy, which impacts significantly upon dry powder inhaler (DPI) product performance. In addition, disordered material is thermodynamically unstable and will relax over time, ultimately crystallising; the balance of forces that is so important in modulating product performance thus changes from batch-to-batch and within one batch over time. Consistent product performance over time can be assured only when no significant disordered regions exist on the milled drug.

The hypothesis to be tested here is thus that with an increase in milling time, there will become a point at which the particle size reduction of a crystalline material stops and formation of process-induced disorder starts. It is proposed that isothermal calorimetry can be used to monitor the formation of these disordered regions and, consequently, to optimise the milling process.

The specific aims and objectives were thus;

- To ball-mill crystalline salbutamol sulphate for increasing periods of time and use isothermal calorimetry to quantify the extent of any disorder,
- To measure the particle size distributions of the milled salbutamol sulphate samples
- To determine whether particle size reduction occurs before, or concomitantly with, formation of disordered regions
- To demonstrate that isothermal calorimetry can be used to optimise the milling time

Materials and Methods

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

SS (35 g) was dissolved in water (110 mL) at 25 °C with continuous stirring. Acetone (2000 mL) was then poured slowly into the solution to precipitate SS crystals. These were filtered, washed with acetone and dried in a vacuum oven at 40 °C for 1 week. The crystallinity of the SS was confirmed with powder X-ray diffraction (PXRD, Philips PW1730/10) and differential scanning calorimetry (DSC, Perkin-Elmer Pyris 1)

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 in [2]. XRPD and DSC measurements confirmed that the sample was amorphous.

Extent of disorder was quantified with isothermal calorimetry (IC, TAM, TA Instruments UK) [3]. Samples (20 mg) were loaded into the ampoule and allowed to equilibrate at 25 °C under 0% relative humidity (RH). The RH was then increased to 90%, causing the disordered regions to crystallise with a concomitant release of heat. The heat output was quantitatively proportional to the extent of disorder. A calibration curve was prepared by mixing crystalline and amorphous SS in appropriate ratios.

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 2cm. Drug (500 mg) was weighed and poured over the jar in which the balls had already been placed. Samples were milled at 100 rpm for various periods of time up to 1 h. Immediately following milling, the milled SS was analysed with IC for amorphous content quantification. The particle size distribution was determined with laser diffraction spectroscopy (Mastersizer, Malvern Instruments UK).

Results and discussion

The calibration curve obtained of SS amorphous content versus measured heat was linear, Figure 1. It was thus possible to quantify extents of disorder in milled SS samples, although it should be noted that the use of this type of calibration curve has some limitations [3]. Principally, the material used to prepare the calibration curve (a mixture of wholly amorphous and wholly crystalline particles) is physically distinct from the study material, which in this case will have disordered regions (that is, a combination of crystal dislocations and amorphous areas) forming a corona around an otherwise crystalline substrate. The magnitude of this effect will vary according to the sample studied. In the case of lactose [4] significant issues arise because of the existence of 2 anomers and 3 crystal forms and the effect of muta-rotation must be considered. For salbutamol sulphate the case is simpler and hence confidence in the correlation between the data sets is higher. However, since the calibration curve was prepared with totally amorphous material (because it was spray-dried), the values reported below for milled SS samples are expressed in amorphous content (% w/w) but it is noted that this term really means extent of disorder and accounts for crystal dislocations as well as true amorphous regions.

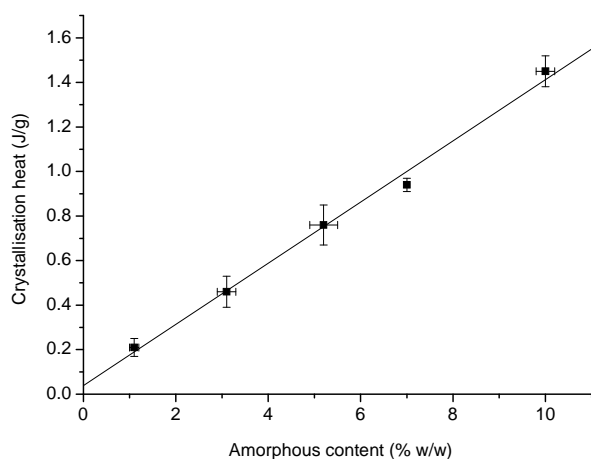


Figure 1: Calibration plot of amorphous content versus heat of crystallisation for salbutamol sulphate.

SS samples were milled for various time periods up to 1 h. The average particle size and extent of disorder data are plotted in Figure 2. It is clear that the data support the hypothesis proposed; over short milling times there is a sharp reduction in particle size, with no increase in extent of disorder detected with the calorimeter. After ca. 5 min milling time, the particle size distribution remains constant and there is a concomitant increase in extent of disorder.

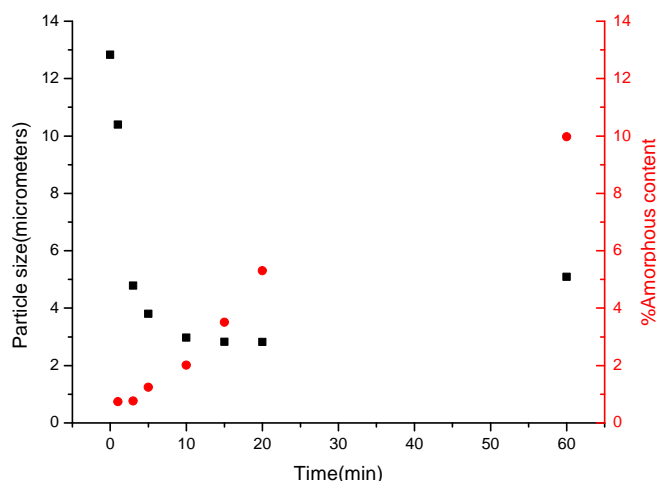


Figure 2: Particle size and amorphous content data as a function of milling time for ball milled salbutamol sulphate.

At longer milling times, the extent of disorder starts to reach a plateau while the particle size starts to increase. It is likely that at these longer milling times the conditions in the mill are such that the ambient RH or, more likely, temperature become sufficiently high to cause some crystallisation of the amorphous regions. This in turn would tend to cause particle agglomeration. Since extended milling will result in continual formation of disordered regions, it seems likely that the system will reach a dynamic equilibrium, with both amorphous content and particle size remaining constant. Of course, these limiting values may not be ideal from the perspective of DPI product performance. Further study could correlate DPI product performance with extent of disorder and hence the calorimeter could be used to optimise the milling process of the drug prior to formulation.

Summary

The data show that milling of a crystalline pharmaceutical results initially in a reduction in particle size with no measurable surface disorder. Continued milling does not reduce particle size further; rather, the surface of the material becomes disordered. This disorder will act to change the surface energy and, as a direct consequence, DPI product performance. Controlling this process starts with being able to monitor the formation of these disordered regions. The study has shown that isothermal calorimetry has the potential to accomplish this.

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