available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevier.com/locate/ejps

The effect of crystal morphology and mill type on milling induced crystal disorder

V. Chikhalia[a], R.T. Forbes[a,*], R.A. Storey[b,1], M. Ticehurst[b]

[a] Drug Delivery Group, School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK
[b] Pharmaceutical R&D, Pfizer Global R&D, Sandwich, Kent CT13 9NJ, UK

ARTICLE INFO

Article history:
Received 11 November 2004
Received in revised form 27 July 2005
Accepted 4 August 2005
Available online 24 October 2005

Keywords:
Milling
Amorphous
Disorder
Solution calorimetry
Morphology
Habit
Succinic acid

ABSTRACT

Milling is a key process in the preparation of many solid dosage forms. One possible milling induced change is the production of small levels of disorder or amorphous material found predominantly at the surface of a powder, which could lead to significant chemical and physical instability. The influence of crystal habit on this change was investigated using β-succinic acid, in plate like and needle like morphologies. β-Succinic acid crystals with these habits were processed in a ball mill and a jet mill. SEM images indicated jet milled material was finer than the ball milled product. Powder X-ray diffraction of the milled powders revealed an amorphous halo at lower angles and peak broadening suggesting disorder though this could not be quantified accurately. In addition, a partial conversion during milling to the alpha form was noted. Quantitation of the alpha form in the milled powders indicated it was present at <2% (w/w). Plate and needle shaped particles had similar heats of solution pre-milling, however, all milled powders had lower heats of solution compared to the unmilled powers. The contribution of the alpha polymorph to the lower heats of solution was calculated to be insignificant. Therefore, the reduced heat of solution is attributed to a loss in crystallinity. The largest decreases were seen in the plate like morphology. These findings suggest that β-succinic acid crystals with plate like morphology are more prone to crystallinity loss on milling compared to the needle like morphology. The mill type has also been shown to influence the final crystallinity.

1. Introduction

Solution crystallisation of pharmaceuticals is well documented and understood. Altering crystallisation conditions allows for control over particle shape, polymorphic form and particle size. However, it is often difficult to achieve a narrow size distribution through crystallisation alone and therefore milling is commonly used for this purpose. A reduced particle size can have a significant effect on increasing the bioavailability of a product, in some cases doubling it (Atkinson et al., 1962; Prescott et al., 1970). Where the drug is to be delivered to the lung, for example, using metered dose inhalers, particles are required to be in the respirable size fraction (typically 2–10 μm) (Patton and Platz, 1992), which is usually achieved by milling. The milling process is extremely inefficient (Parrot, 1990) and, due to the high energy input, the milled powder may be of reduced crystallinity and may contain disordered regions (Krycer and Hersey, 1980). These regions are thought to be concentrated on the surface of particles which have amorphous characteristics (Ward and Schultz, 1995). The amorphous phase is thermodynamically unstable compared to a crystalline counterpart. When sufficient energy is provided

* *Corresponding author*. Tel.: +44 1274 234653; fax: +44 1274 234769.
E-mail address: r.t.forbes@brad.ac.uk (R.T. Forbes).
[1] Present address: AstraZeneca Pharmaceuticals, Macclesfield, UK.
0928-0987/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2005.08.013

so that the energy barrier to crystallisation is overcome, the resultant crystalline product may impart different functionality and performance, such as altering flow properties and bringing about aggregate formation.

The relationship between internal crystal structure and derived habit from sublimation and solution processes are well understood (Berkovitchyellin, 1985; Winn and Doherty, 2000). Particle shape has been shown to affect the flow properties and tableting performance of ibuprofen, with plate like particles, having better flow properties and tableting properties compared to needle like particles (Gordon and Amin, 1984). Habit modification has been explored towards the improvement of the performance of pulmonary formulations. The carrier morphology of lactose in a dry powder formulation has been shown to affect the respirable fraction of salbutamol sulphate (Zeng et al., 2000). In their study, lactose morphology was characterised by elongation ratio. An increase in elongation ratio of lactose crystals produced an increase in the respirable fraction. This is thought to occur as a result of the lower relative aerodynamic diameter of the more elongated particles which may be easier to aerosolise.

The effect of particle shape upon milling induced changes is investigated here, as the literature shows very little information in this area. β-Succinic acid was used as a model compound because it is well known that its habit can be modified by altering crystallisation solvent (Davey et al., 1982). The effect of mill type on the milling induced solid state properties of the product was also evaluated.

2. Materials and methods

2.1. Crystallisation of plate shaped crystals

Based on the methods of Davey et al. (1982), sufficient β-succinic acid (Sigma–Aldrich, Poole) was dissolved in distilled water at 45 °C, in a 1 l jacketed vessel, to produce a supersaturated solution (degree of supersaturation, $s = 2.0$ at 22 °C). The supersaturated solution was allowed to equilibrate for 30 min, whilst being stirred at 150 rpm, using an overhead stirrer. The liquor was then cooled at 40 °C/h to 22 °C, using a chiller thermo circulator (Model 02CTCV, Conair/Churchill, Uxbridge, Middlesex). Once at the final temperature, the liquor was filtered using a sintered glass funnel and the crystallised product washed with chilled acetonitrile (4 °C) (BDH chemicals, Poole). The product was vacuum dried at 800 mbar at 45 °C overnight.

2.2. Crystallisation of needle shaped crystals

Sufficient β-succinic acid (Sigma–Aldrich) was dissolved in isopropanol (Sigma–Aldrich) at 55 °C in a 500 ml conical flask for 30 min, to produce a supersaturated solution, ($s = 2$ at 22 °C). The flask was then transferred to a water bath at 22 °C, for 1 h under gentle agitation. The liquor was then filtered using a sintered glass funnel and the crystallised product washed with ice cold acetonitrile (BDH chemicals). The product was vacuum dried at 800 mbar at 45 °C overnight.

2.3. Crystallisation of α-succinic acid

The method of preparation of the α polymorph is based upon the work of Dupré La Tour (1932). One gram of β-succinic acid was placed into a glass ampoule and sealed using an ampoule sealer. The sealed ampoule was transferred to a small glass vessel, containing Dow Corning Silicone fluid, sufficient to immerse the body of the ampoule. The glass vessel was then subjected to the following temperatures in an oven, 200 °C for 2 h, 190 °C for 2 h, 180 °C for 2 h, 140 °C for 12 h, 80 °C for 2 h and 40 °C for 2 h. The powder was then stored at room temperature.

2.4. Preparation of physical mixtures

One gram physical mixtures of α and β forms of succinic acid were prepared, using sieve fractions <125 μm. Physical mixtures were Turbula® mixed for 15 min at the slowest speed.

2.5. Milling

Ball milling was performed using a Pascal Engineering ceramic ball mill. Approximately 10 g of material was milled, using ceramic balls 3 cm in diameter, for 2 h at 60 rpm. Jet milling of powders was performed using an in house microniser. Inlet and outlet pressures were set to 45 and 65 psi. Approximately 10 g of material was milled and the product stored over silica gel.

2.6. Differential scanning calorimetry (DSC)

Thermal properties of samples were determined using a Perkin-Elmer Series 7 DSC (Perkin-Elmer Ltd., Beaconsfield, UK). Samples between 3 and 5 mg were heated in hermetically sealed stainless steel pans at a rate of 10 °C/min under a dry nitrogen flow of 20 ml/min over a temperature range of 25–220 °C. For fast DSC work, the same parameters as above were used, though the heating rate was set to 50 °C/min.

2.7. Thermogravimetric analysis (TGA)

Analyses were performed on a Perkin-Elmer TGA Series 7 (Perkin-Elmer Ltd.). Samples between 3 and 4 mg were heated from 30 °C at 10 °C/min to 200 °C under nitrogen flow at 20 ml/min.

2.8. Powder X-ray diffraction (PXRD)

X-ray powder diffraction patterns of samples were obtained using a Siemens D5000 diffractometer (Siemens, Karlsruhe, Germany), using Cu Kα radiation ($\lambda = 1.5418$ Å). Samples were scanned over an angular range of 2–50° 2θ, with a step size of 0.05° and a count time of 3 s per step. Samples were rotated at 30 rpm during analyses. The generator was set to 40 kV and 30 mA.

The method of polymorph quantification by PXRD is based upon work performed by Suryanarayanan (1989, 1990). Physical mixtures were scanned over an angular range of 21–23° 2θ. The 2θ region of 21.5–22.5° provided sufficient angular range for the integration of the unique α peak, present at 22° 2θ. Back-