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The impact of material attributes and process parameters on the micronisation of lactose monohydrate

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ABSTRACT

Dry powder inhalers (DPIs), which are important medicines for drug delivery to the lungs, require drug particles in the respirable size range of 1–6 μm for optimal lung deposition. Drugs administered by the oral route also derive benefit from particles in this size range owing to their large surface area to volume ratio, which provides potential for rapid dissolution. Micronisation used in the production of particles, however often leads to heterogeneous product containing mechanically activated surfaces with amorphous content. This study was therefore carried out to evaluate the effect of particle properties of three grades of lactose monohydrate, with sizes above and below the brittle–ductile transition (dcrit) and their interaction with process variables on the quality of micronised material. Following an experimental design, the impact of three factors (grinding pressure, injector pressure and feed rate) on the particulate attributes of micronised powders produced from the different size grades was assessed. Processing conditions were shown to be important determinants of powder properties only for the coarsest starting material. Ultrafine material was achieved by processing finer grade feed stock below dcrit. However the resultant product was more crystalline and transformed on heating to the anhydrous state with markedly reduced onset temperature with lower energy surfaces than powders produced from larger sized starting material. Thus the propensity for micronisation of lactose monohydrate can be altered through control of starting materials and optimal settings for process variables.

1. Introduction

Particle size reduction is a widely used technique to improve the performance of active pharmaceutical ingredients (APIs) through enhancement of dissolution, mixing, and compaction behaviour. Dry powder inhalers (DPI) also require drug particles in the respirable range (1–6 μm) for optimal lung deposition (Pritchard, 2001). Different technologies are available for producing drug particles in this size range, including micronisation, spray drying, spray freeze drying, supercritical antisolvent methods, emulsion based methods and conventional crystallisation, although it is micronisation which still dominates the landscape from a commercial manufacturing perspective.

Micronisation using fluid air jet milling is a well-established method for yielding micron size particles for orally administered and inhaled drugs. The micronisation process involves acceleration and impact of particles causing self-attrition, fracture and subsequent size reduction (Chow et al., 2007).

Micronisation has advantages over other milling processes, such as low metal contamination through absence of moving parts. The size reduction of heat sensitive materials is also possible as temperature increases are markedly less than those experienced using other mechanical comminution processes. This assures easy cleaning, simple operation and allows adjustments in process parameters to produce varying grades of material, from coarse to ultrafine in one product stream (Patel et al., 2008).

There are a number of different micronisation approaches that are widely used and differ in the methods by which pressurised gas is used to reduce the particle size. These include: spiral jet mills, loop mills, and fluid bed opposed jet mills (Patel et al., 2008).

Previous research in this area has revealed several issues associated with micronisation, which reduces the attractiveness of this approach for size reduction. Problems include an inability to precisely control particle size, morphology, crystallinity and surface characteristics (Ticehurst et al., 2000) alongside high-energy consumption (Gommeren et al., 2000). The forces generated during micronisation have the potential to induce lattice defects, weaken intermolecular bonds in crystalline materials and alter the physical and chemical stability of crystalline materials (Huttenrauch, 1978; Ticehurst et al., 2000). Production of amorphous content predominantly at particle surfaces can also occur with consequent agglomeration of particles providing difficulties in

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downstream processing, product performance and stability (Price and Young, 2004). The likelihood of polymorphic transformation is also increased, which has the potential to modify the physicochemical and mechanical properties of the processed materials (Garnier et al., 2008). In addition to affects on the physical integrity of pharmaceutical powders, the propensity for micronisation is also known to be influenced by the point at which materials demonstrate plastic deformation under stress rather than brittle fragmentation. This phenomenon is termed the brittle–ductile transition (dcrit) and is specific for each material (Roberts, 1991). For lactose monohydrate, this transition is believed to occur below 23.7 μm (Roberts, 1991). It is therefore useful to determine changes in micronisation behaviour at sizes above and below this critical particle size. APIs at sizes below this point often demonstrate reduced potential for mechanically induced size reduction due to predominance of ductile behaviour.

Investigations into the milling of lactose monohydrate by Kwan et al. (2004) showed that increases of milling frequency and impact velocity lead to improved efficiency of particle size reduction. Chen et al. (2004) observed high milling efficiency when processing lactose monohydrate at reduced batch sizes. A relationship was also observed by Young et al. (2007) between milling times, the percentage of fines (below 15 μm) produced and amorphous content generated. It was shown that increased milling time was responsible for reduced particle size and increased amount of amorphous content. Garnier et al. (2008) however suggested that grinding also plays a role in decreasing the dehydration onset temperature for lactose monohydrate, through changes in crystal structure. In this regard, Newell et al. (2001) showed that ball milling increased the dispersive surface energy of lactose monohydrate (41.6 mJ/m^2) compared to crystalline starting material (31.2 mJ/m^2), whilst Vromans et al. (1986) claimed that dehydration of lactose monohydrate was a surface dependent phenomenon.

Owing to the clear dependence of micronised particle attributes on the properties of the feedstock and the associated processing parameters, a study has been conducted to establish an understanding of the interplay between these variables. The intention of this study was to identify strategies to control the particle characteristics of micronised lactose monohydrate and to determine whether this compound can be micronised below its brittle–ductile transition.

2. Materials and methods

2.1. Materials

Three sieved batches of lactose monohydrate were used in micronisation studies. Respitose-SV003 (D50 = 60 μm) and Respitose-SV010 (D50 = 105 μm) were supplied by DMV Fonterra, Netherlands. L-Dcrit (below brittle–ductile transition, D50 = 13.93 μm) was produced in-house (University of Bradford) by sieving SV010 using a 20 μm sieve (Retsch, UK).

2.1.1. Probes for IGC

2.1.1.1. Non-polar probes. The non-polar probes used (n-alkanes) in inverse gas chromatography (IGC) for this project were as follows:

Hexane, 99+% purity, Lot No. – I1012384, BDH Laboratory Supplies, Poole, England
Heptane, 99+% purity, Lot No. – 50228042, Sigma–Aldrich, Gillingham, England
Octane, 99+% purity, Lot No. – CO04654BO, Aldrich Chemical Company. WI, USA
Nonane, 99+% purity, Lot No. – EO08280AO, Aldrich Chemical Company. WI, USA

2.1.1.2. Polar probes. Polar probes used in these studies were as follows:

Chloroform, 99+% purity, Batch No. – 0565673, Sigma–Aldrich, Gillingham, England
Acetone, 99+% purity, Lot No. – 9307A, Sigma–Aldrich, Gillingham, England
Ethylacetate, 99+% purity, HPLC Grade, Sigma–Aldrich, Gillingham, England
Tetrahydrofuran, (THF) 99+% purity, Lot No. – 13540 (Rathburn Chemicals Ltd.), Scotland

2.1.2. Materials for IGC column preparation

Methanol, for HPLC, Batch No. – 0886933, BDH Laboratory Supplies, Poole, England
Toluene (low in sulphur), Lot No. – 7270S, BDH Laboratory Supplies, Poole, England
Dimethylchlorosilane, Lot No. – 55H1218, Aldrich, Gillingham, England

Compressed gases:

Compressed hydrogen, BOC Ltd., Surrey, UK (used in IGC)
Compressed Nitrogen, BOC Ltd., Surrey, UK (used in IGC and DVS)
Compressed Air, BOC Ltd., Surrey, UK (used for micronisation and IGC).

2.2. Methods

2.2.1. Micronisation

The micronisation behaviour of each sieved batch of lactose monohydrate was evaluated through means of an experimental design using the FPS Spiral Jetmill (FPS, Italy) (Fig. 1). The influence of the three process variables (GP = grinding pressure, IP = injector pressure and FR = feed rate) at two levels (H = high and L = low) on the quality attributes of micronised powder was evaluated. The levels defined for each of the process parameters in the experimental design are given in Table 1. For each experiment, 5 g samples of each grade of lactose monohydrate were processed. Feed rates were determined using samples at the highest and lowest settings of the speed controller from the experiments carried out in triplicate. Powder was collected at 1 minute intervals and the weight determined using a standard balance. Grinding and injector pressure were set using the appropriate regulator with pressure display, calibrated using an external pressure gauge (accuracy ±1.6%).

Injector pressure, grinding pressure and feed rate were adjusted to provide the conditions stated in Table 2. Samples were collected from the collection vessel at the end of the experiments and stored over phosphorous pentoxide to avoid moisture mediated transformation before characterisation. For all experiments, the moisture

Table 1
High and low values of GP, IP and FR for SV003, SV010 and L-Dcrit.

Exp. No.	GP	IP	FR
1	–	–	–
2	–	–	+
3	–	+	+
4	+	+	+
5	+	+	–
6	+	–	–
7	+	–	+
8	–	+	–

("+" = high level processing condition and "–" = low level processing condition).