International Journal of Pharmaceutics 408 (2011) 58–66

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

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

M.H. Shariare*, M. de Matas, P. York, Q. Shao

Institute of Pharmaceutical Innovation, University of Bradford, UK

ARTICLE INFO

Article history:
Received 9 November 2010
Received in revised form 19 January 2011
Accepted 24 January 2011
Available online 2 February 2011

Keywords:
Particle size
Micronisation
Lactose monohydrate
Crystallinity
Inverse gas chromatography

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

* Corresponding author. Tel.: +44 1274410346; fax: +44 1274236155.
E-mail addresses: m.h.shariare@bradford.ac.uk, mridul_pharmju@yahoo.com (M.H. Shariare).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.01.047

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).

Fig. 1. The spiral jetmill (FPS, Italy).

content of supplied compressed air was 2–6% RH, which was measured using a hand held hygrometer (Testo 610, Testo, UK).

2.2.2. Particle size analysis

Particle size distribution was determined for starting materials and processed samples using a laser diffraction particle size analyser (Sympatec HELOS and RODOS dry dispersion unit, Sympatec Instruments, UK). 15–20 mg of samples were fed into the analyser using an air pressure of 2 bar at a feed rate of 20 mm/s. Trigger conditions used for both starting and micronised batches were 5 s at an optical concentration of 1%. All samples were analysed in triplicate (Table 3).

2.2.3. Thermogravimetric analysis (TGA)

The weight loss on heating and dehydration onset temperature for samples of lactose monohydrate (starting materials and processed samples) was determined using the thermogravimetric analysis module of the TA instruments Q5000 series thermal analysis system (TA Instruments, West Sussex, UK). Samples (1–5 mg) were analysed in an open aluminium pan attached to the microbalance with heating in the temperature range 25–300 °C using a scanning rate of 10 °C/min. Measurements were carried out in triplicate and the sample weight was monitored by the microbalance throughout the experimental period to an accuracy of ±1 μg. The TGA module was calibrated using a nickel standard. All samples were analysed in triplicate.

Table 2
High and low values of GP, IP and FR for SV003, SV010 and L-Dcrit.

Lactose grade	Level	Process variables		
		GP	IP	FR
SV010	High (+)	8 bar	8 bar	Maximum (4.075 g/min)
	Low (−)	5 bar	5 bar	Minimum (0.800 g/min)
SV003	High (+)	8 bar	8 bar	Maximum (2.500 g/min)
	Low (−)	5 bar	5 bar	Minimum (0.475 g/min)
L-Dcrit	High (+)	8 bar	8 bar	Maximum (1.240 g/min)
	Low (−)	5 bar	5 bar	Minimum (0.375 g/min)

2.2.4. Differential scanning calorimetry (DSC)

Thermal properties of the starting material and processed samples were determined using the DSC module of the TA Instruments Q2000 series thermal analysis system (TA Instruments, West Sussex, UK) calibrated using a pure indium standard (melting point 156.6 °C) and tested using a zinc standard (melting point 419.5 °C) under nitrogen purge. Samples (1–5 mg) were analysed in pierced and crimped aluminium pans. The samples were then heated under a stream of nitrogen gas from 25 to 250 °C with a scanning rate of 10 °C/min. All samples were analysed in triplicate.

2.2.5. Scanning electron microscopy (SEM)

SEM analysis of starting material and processed samples was undertaken using a Quanta 400 SEM (FEI Company, Cambridge, UK) to produce high-resolution images of particles. Samples were analysed at a variety of magnifications with direct data capture of the images onto a personal computer. Calibration of the SEM was performed using a gold grid standard supplied with the instrumentation.

2.2.6. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction was used to detect any changes in solid form occurring following micronisation. Analysis of the samples was carried out using a Bruker D-8 powder diffractometer (Bruker, Kahlsruhl, Germany) at room temperature. Samples were placed into a plastic sample holder with zero background and levelled using a glass cover slide. Samples were scanned over the range 5–50° 2θ at a rate of 1° 2θ/min using a copper Kα radiation source of wavelength 1.542 Å with 1 mm slits. The performance of the diffractometer was assessed using a carborundum standard.

2.2.7. Dynamic vapour sorption (DVS)

Moisture sorption isotherms were determined using a microprocessor controlled automated IGAsorp moisture sorption analyser (IGA*SORP*, Hiden Isochema Ltd., Warrington, UK). Measurements were performed using 30–50 mg of starting material and micronised samples at 25 °C, under a continuous nitrogen flow of 250 ml/min in the range 0–95% RH. Relative humidity was held at each point until equilibrium was achieved with the sample mass represented as a percentage of the initial mass. The balance was calibrated using a range of calibration weights of 20 mg, 50 mg and 100 mg (KERN and Sohn GmbH, Germany). Humidity conformance was established using lithium bromide and lithium chloride humidity standards (Rotronic AG, Switzerland). Calibration was performed using 10%, 50% and 80% sodium chloride salt solutions. In this study, the finer grade of lactose monohydrate L-Dcrit (D50 = 13.93 μm) was considered to be the crystalline standard, with freeze-dried samples produced from 10% aqueous lactose monohydrate solutions considered to be the amorphous standard. The degree of crystallinity of processed samples was classified relative to the crystalline standard. The calibration curve was determined using a mixture of crystalline and amorphous samples (50:50, 75:25, 90:10, 95:5, 97:3, 99:1) at 40% RH. Percentage crystallinity of micronised samples relative to the crystalline standard was determined using the equation of the line of best fit for percentage of moisture uptake at 40% RH against percentage crystallinity.

Table 3
Median particle size (D50) and polydispersity for micronised batches of SV003, SV010 and L-Dcrit.

Samples and values of processing conditions	SV010		SV003		L-Dcrit	
	D50 (μm) (±SD)	PDI (±SD)	D50 (μm) (±SD)	PDI (±SD)	D50 (μm) (±SD)	PDI (±SD)
Starting material	102.79 (0.90)	1.46 (0.02)	52.06 (0.37)	1.38 (0.00)	13.93 (0.63)	1.78 (0.23)
– – –	4.44 (0.15)	2.07 (0.07)	91.30 (12.56)	3.95 (0.65)	3.22 (0.03)	1.77 (0.08)
+ – –	N/A	N/A	2.93 (0.04)	1.63 (0.28)	N/A	N/A
– + –	6.88 (0.07)	2.29 (0.03)	3.80 (0.23)	2.23 (0.03)	3.24 (0.05)	1.52 (0.32)
+ + –	13.73 (1.29)	7.69 (0.21)	3.87 (0.07)	1.76 (0.11)	N/A	N/A
– – +	52.11 (0.62)	3.55 (1.22)	12.07 (1.05)	4.43 (0.08)	4.75 (0.25)	2.39 (0.27)
+ – +	11.77 (2.00)	8.00 (0.34)	6.59 (0.11)	3.67 (0.02)	N/A	N/A
– + +	55.80 (1.27)	9.88 (1.40)	8.69 (0.24)	4.32 (0.09)	2.95 (0.30)	2.97 (0.41)
+ + +	10.23 (1.15)	9.87 (0.89)	5.31 (0.83)	18.0 (1.28)	2.27 (0.02)	1.93 (0.28)
Average	22.13	6.19	16.82	5.00	3.29	2.12

N/A – Micronisation was not possible due to ejection of particles from the chamber under these processing conditions. Value in parenthesis indicates standard deviation.

2.2.8. Inverse gas chromatography (IGC)

IGC measurements were carried out using an automated Perkin Elmer gas chromatograph (Perkin Elmer, USA) equipped with a flame ionization detector (FID). Nitrogen was used as the carrier gas with hydrogen and compressed air employed for the FID. The flow rate of carrier gas at the column outlet (N_{flo}) was measured using the bubble flow meter. The IGC method used in this study was previously reported by Saxena (2007). Adsorption measurements were performed at 30 °C and 0% RH at infinite probe dilution. Hexane, heptane. octane and nonane were used as non-polar probes and acetone, ethylacetate, chloroform and THF were used as polar probes in this study. The dispersive component of surface free energy and specific surface free energy were determined using the method described by Schultz and Lavielle (1989).

2.2.9. Andersen cascade impactor

Lactose monohydrate particles in the 1–3 μm size range were isolated using an Andersen Cascade Impactor (ACI) fitted with a pre-separator and a standard USP metal throat. The ACI was connected to a dry powder inhaler and a vacuum pump (all equipment Copley scientific limited, Nottingham, UK). The ACI was washed with methanol and dried before use. As powder particles were required in the dry state in this study, impactor plates were not coated with silicon spray. 10 mg of lactose monohydrate (SV010 below 20 μm) was filled into hard gelatin capsules (size 3) (Capsugel, UK). Ten doses of lactose monohydrate were discharged into the apparatus using the Aerolizer™ device (Novartis, Switzerland) at a flow rate of 60 L/min for 5 s. After discharging all doses, the material deposited on stages 3 to stage 5 was collected using a small brush and analysed by TGA and DSC.

2.2.10. Sieving

A range of sieve fractions (<20 μm, 20–38 μm, 38–45 μm, 75–90 μm, 90–120 μm, 120–150 μm and 150–180 μm) were generated in this study to evaluate powders with different size distributions. Particles in the 1–3 μm size range were obtained using the ACI, as discussed in Section 2.2.9 owing to difficulties in separating this size fraction by sieving. Bulk powders were screened individually through sieves of different mesh size to achieve particles in the desired range.

3. Results and discussion

3.1. Particle size distribution

Particle size distribution data shown in Table 3 demonstrates that a range of median sizes and polydispersity was achieved using each of the three grades of lactose monohydrate, across the range of process parameters. Table 3 also shows that batches micronised from L-Dcrit showed lowest average median size (D50) and polydispersity compared to batches micronised from the other two coarser grades of lactose monohydrate. However it was still possible to produce ultrafine material even from the coarser feed stock (Fig. 2) by manipulating the process conditions.

Laser diffraction data (Table 3) show that it was possible to micronise lactose monohydrate to sizes below the reported brittle–ductile transition (23.7 μm) (Roberts, 1991). Size reduction occurs for small particles through attrition forces rather than brittle fracture, which predominates at the edges and corners of particles (Meier et al., 2009), with shearing and abrasion leading to the production of ultrafine powders. The results of this study suggest that the particle size of starting materials markedly affects the degree of particle size reduction for the three grades of lactose monohydrate (Fig. 3). Using similar processing conditions (GP = 8 bar, IP = 8 bar and FR = high), it was possible to produce the powders with lowest D50 from the finest grade of starting material (L-Dcrit).

Although the lowest D50 was achieved from the finer grade starting material, a 10 fold reduction ratio (ratio of initial median particle size to the micronised median particle size) was obtained for coarser grade starting materials SV010 and SV003 (Table 3) when using similar processing conditions (GP = 8 bar, IP = 8 bar and FR = high). This suggests that coarse particles have greater propensity for particle size reduction although finer grade starting materials facilitate production of the lowest median particle size. Vogel and Peukert (2003) observed that when applying a similar level of energy, smaller particles exhibited a smaller breakage probability due to the smaller circumference of the particles and the reduced contact area with fewer crystallographic flaws providing reduced potential for particle fracture.

The results from this study suggest that the effects of processing conditions are dependent on the size of the starting material. The magnitude of the effect for all process conditions was evaluated by calculating the difference between average particle sizes for

Table 4
Percentage crystallinity for micronised batches of SV010, SV003 and L-Dcrit (value in bracket indicate range of data, $n = 2$).

Experiment	SV010 (%crystalline)	SV003 (%crystalline)	L-Dcrit (%crystalline)
– – –	94.0 (1.6)	99.8 (0.1)	99.7 (0.1)
+ – –	97.9 (0.1)	91.1 (1.0)	99.8 (0.1)
– + –	92.5 (3.0)	98.2 (0.1)	99.6 (0.1)
+ + –	96.6 (0.6)	99.0 (0.5)	99.2 (0.5)
– – +	96.7 (0.7)	99.4 (0.1)	99.7 (0.1)
+ – +	97.1 (0.1)	98.7 (0.9)	99.8 (0.1)
– + +	97.6 (0.3)	98.2 (1.2)	99.4 (0.3)
+ + +	96.1 (0.9)	98.0 (1.4)	99.7 (0.1)

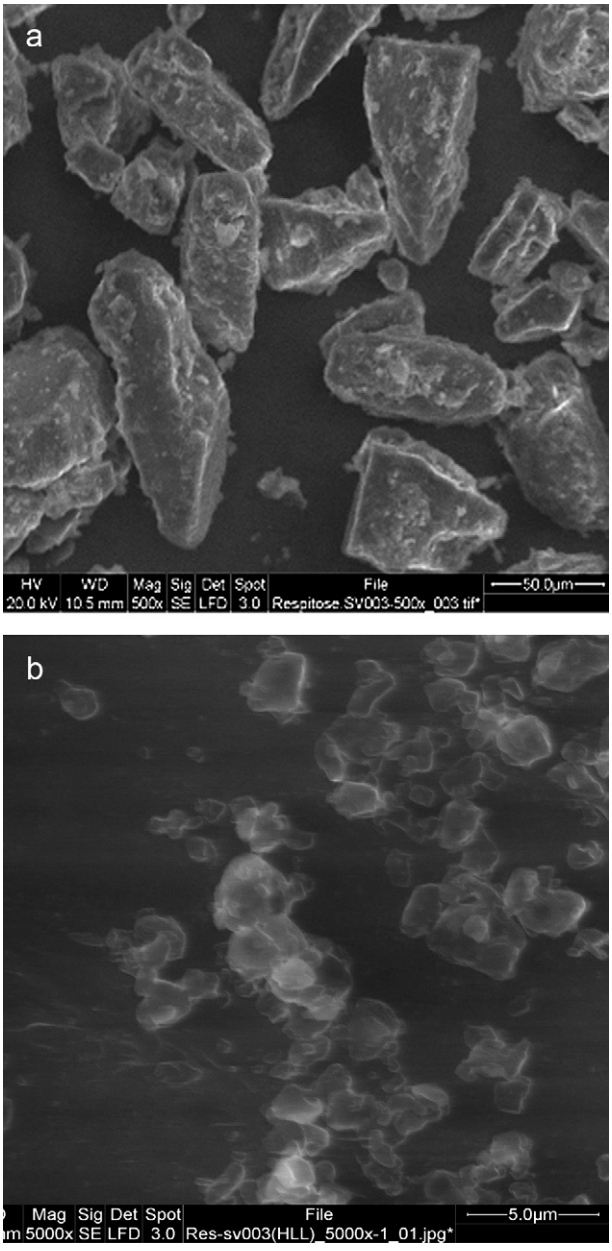

Fig. 2. Scanning electron micrographs of (a) SV003 (Mag. = 500×. Scale = 50.0 μm) and (b) SV003 (+ − −) Mag. = 2600×. Scale = 10.0 μm.

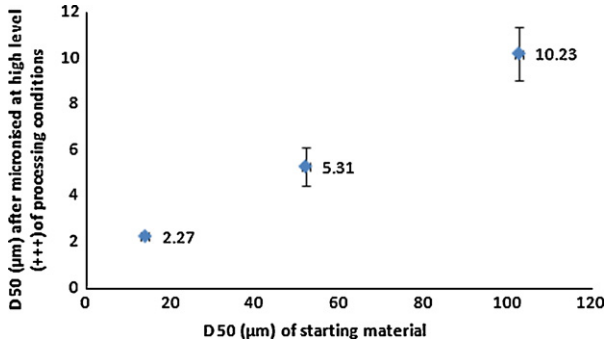

Fig. 3. Effects of starting material particle size on median paticle size (D50) for micronised batches of SV010, SV003 and L-Dcrit.

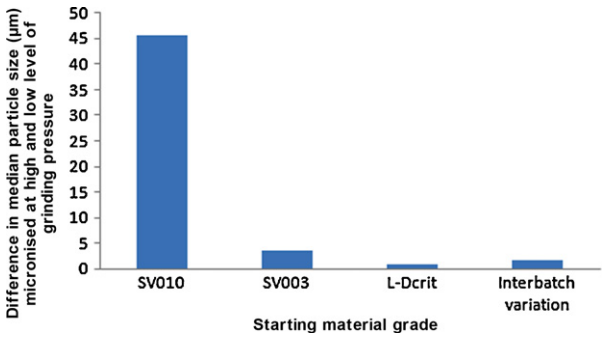

Fig. 4. Effect of grinding pressure on median paticle size (D50) for micronised batches of SV010, SV003 and L-Dcrit.

all batches manufactured at high and low levels of those parameters. The effect of all process parameters on median particle size of three grades of lactose monohydrate was also compared with interbatch variation which was considered to be the standard deviation calculated for several micronised batches processed under identical processing conditions. The effect of each process parameter was considered relevant if it exceeded the interbatch variation. The pareto chart in Fig. 4 shows that grinding pressure (GP) markedly affected the median particle size of micronised batches of SV010. Batches micronised from SV003 and L-Dcrit however showed limited sensitivity for particle size reduction at increased grinding pressure. Size reduction of coarse particles probably occur via brittle fracture, whereby increases in grinding pressure result in improved crack propagation and fragmentation. For finer grade starting materials, particle size reduction is more likely to occur through shearing and abrasion, where increases in grinding pressure therefore may have limited effect on size reduction. Injector pressure and feed rate showed no marked effect on the particle size distribution of three grades of lactose monohydrate compared to interbatch variation.

3.2. Thermal and structural analysis

DSC data showed that an endothermic transition occurred for all samples in the temperature range 140–145 °C, which corresponds to the dehydration of the incorporated crystalline water (Berlin et al., 1971). Melting and decomposition of lactose monohydrate occurred at temperatures in the range 214–217 °C as reported by de Matas (1997). In addition to the endothermic events, exothermic transitions were observed for several micronised batches of SV010 and SV003 at temperatures in the range 170–175 °C with broad

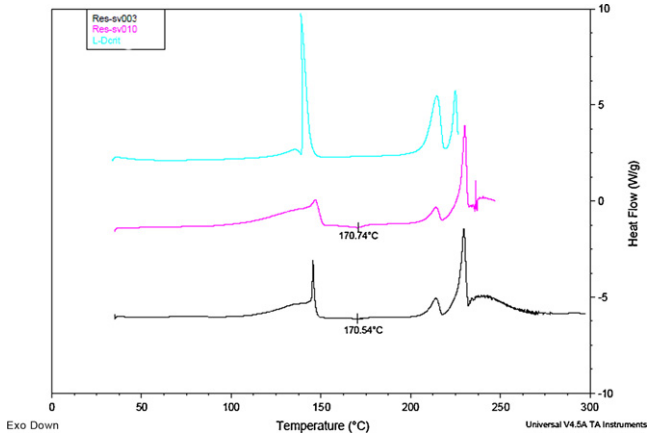

Fig. 5. DSC data showing thermal characteristics for the micronised batches of L-Dcrit, SV010 and SV003 manufactured at (− + −) processing condition.

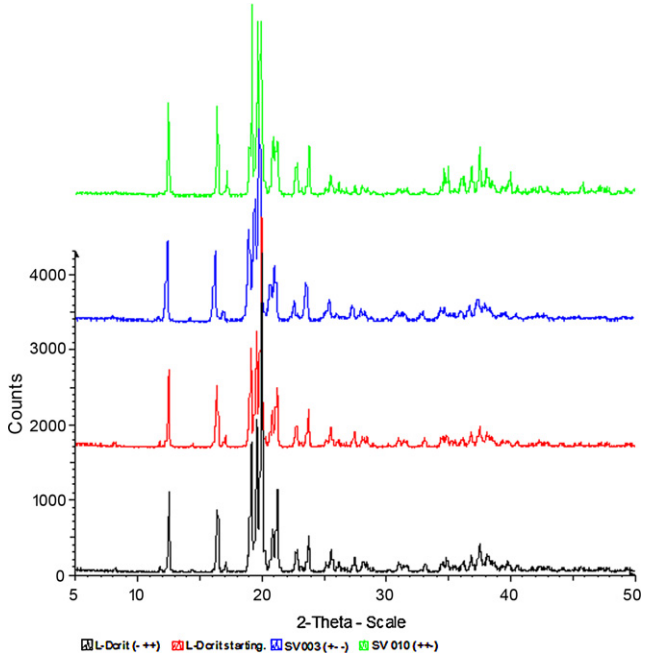

Fig. 6. PXRD data showing no physical form transformation for the micronised batches of SV010, SV003, L-Dcrit and starting L-Dcrit material.

dehydration endotherms observed at 140–145 °C (Fig. 5). This phenomenon is attributed to the recrystallisation of amorphous lactose monohydrate (Elamin et al., 1995), suggesting that disruption of crystal structure has occurred during micronisation particularly for the coarser grade starting material (Fig. 5). Micronised batches of L-Dcrit, however showed no exothermic events (Fig. 5), which suggests that reduced numbers of fracture events were experienced by these samples compared to the coarser starting materials.

PXRD data (Fig. 6) however indicated that no detectable physical form transformation had occurred during micronisation for any of the batches, although the presence of two dehydration peaks was evident for several micronised batches of SV010 and SV003 shown by DSC (Fig. 7). All micronised batches of L-Dcrit and the L-Dcrit starting material also showed the presence of this double endotherm in the DSC profiles, which is probably related to the presence of both 'fines' (< 5 μm) and larger particles (>40 μm) in the micronised powders and L-Dcrit feedstock. DSC thermal profiles for batches demonstrating the two dehydration endotherms (see Fig. 7) were characterised by an initial broad peak with onset 119-

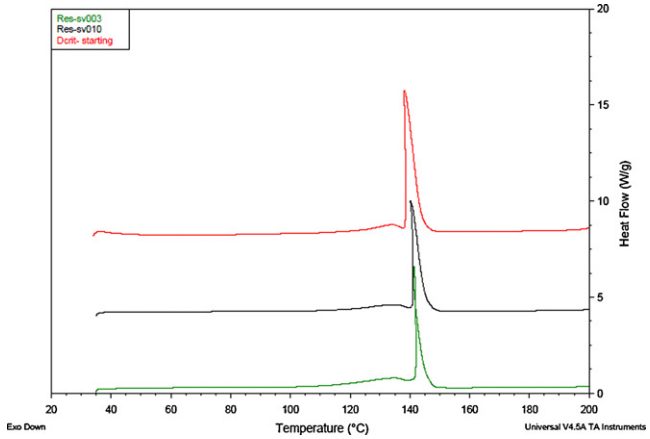

Fig. 7. DSC data showing the double endothermic event for selected batches of SV010, SV003 and starting L-Dcrit.

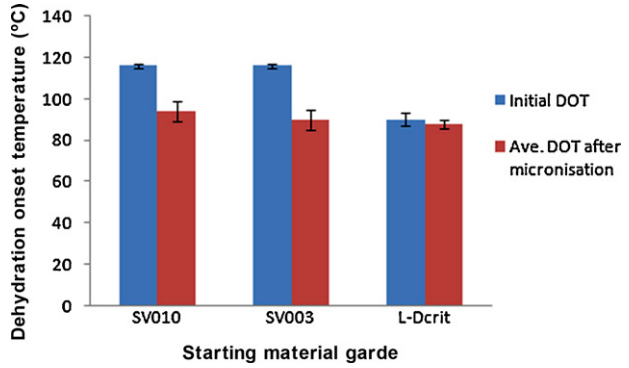

Fig. 8. Dehydration onset data for starting material and micronised batches of SV010, SV003 and L-Dcrit determined by TGA.

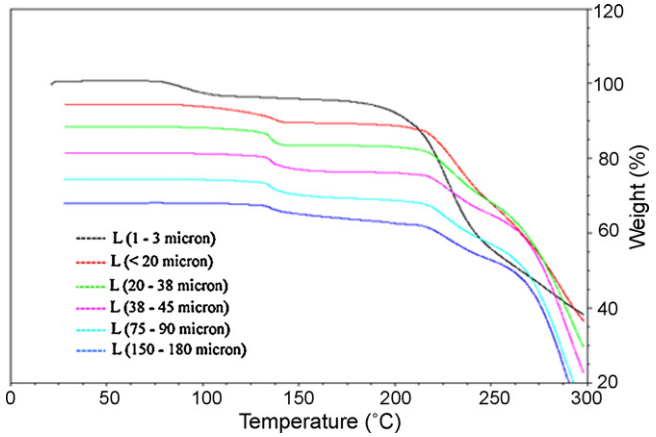

Fig. 9. TGA data showing the effect of particle size fraction on dehydration onset temperature for SV010.

121 °C and a peak temperature at approximately 134 °C followed by a sharp endothermic transition with peak temperature at approximately 143 °C. It is clear that a marked reduction in dehydration onset temperature (DOT) occurred for both SV010 and SV003 after micronisation while for the finer L-Dcrit a similar dehydration onset temperature (DOT) was observed both for starting material and micronised batches (Fig. 8).

To evaluate this relationship further, dehydration behaviour was determined for different sieve size fractions of SV010 with the sieve cuts of particle diameters in the ranges 1–3 μm, 1–20 μm, 20–38 μm, 38–45 μm, 75–90 μm, 90–120 μm, 120–150 μm and 150–180 μm (see Section 2.2.10). TGA data (Fig. 9) shows that dehydration onset temperature of lactose monohydrate is a particle size dependent phenomenon and decreases as the particle size is reduced. Figs. 10 and 11 show that dehydration onset and peak temperatures measured by TGA and DSC were diminished for smaller

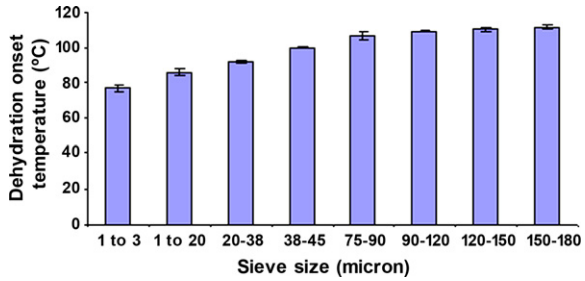

Fig. 10. Relationship between particle size (sieve fraction of SV010) and dehydration onset temperature determined by TGA.

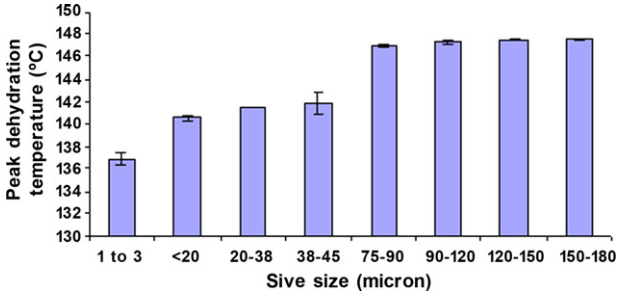

Fig. 11. Relationship between particle size (sieve fraction of SV010) and dehydration peak temperature determined by DSC.

sieve size fractions. Owing to difficulties in achieving classification of particles in the range 1–3 μm using conventional sieve analysis, particles were obtained by retrieval of aerosolised samples from the ACI (see Section 2.2.9). A plateau in behaviour was reached at 75 μm (Figs. 10 and 11), with similar dehydration temperatures for all samples above this particle size.

Vromans et al. (1986) reported that the speed of dehydration of lactose monohydrate was dependent on both the powder surface area and temperature. Results of the relevant study suggest that the dehydration mechanism of lactose monohydrate is a particle size dependent phenomenon, with particles below 75 μm showing marked reduction in dehydration onset temperature. Process variables however showed no marked effect on dehydration onset temperature of three grades of lactose monohydrate relative to interbatch variation.

3.3. Dynamic vapour sorption (DVS)

Data for degree of crystallinity determined by DVS (Table 4 and Fig. 12) showed that batches micronised from L-Dcrit (<20 μm) were typically more crystalline than batches processed from SV003 (D50 = 65 μm) and in particular SV010 (D50 = 102 μm). Batches micronised from SV003 were marginally more crystalline than those processed from SV010. It is likely that less energy input was required during micronisation to reduce the size of finer materials, resulting in less mechanical activation of surfaces. Buckton (1997) has suggested that fluid energy milling may induce more than 7% amorphous material in micronised samples of lactose monohydrate. Relatively high amorphous content (7–9%) was also observed for some batches of SV010 (− + −) and SV003 (+ − −) (Table 4).

The degree of crystallinity of micronised products was calculated at 40% RH using a calibration curve (Fig. 13) constructed from the mixture of freeze dried amorphous standard and L-Dcrit crystalline starting material. The relative crystallinity of micronised batches of three grades of lactose monohydrate was markedly

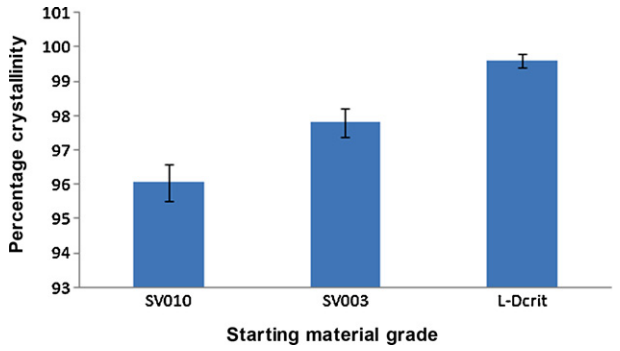

Fig. 12. Average percentage crystallinity for micronised batches of SV010, SV003 and L-Dcrit.

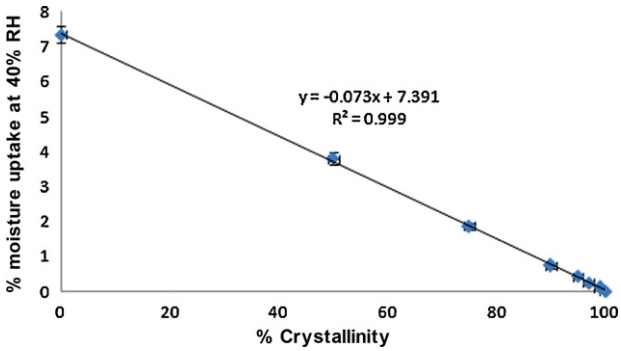

Fig. 13. Calibration curve used to calculate the percentage crystallinity for micronised batches of SV010, SV003 and L-Dcrit.

dependent upon the median size of the starting material (Fig. 12). This is probably due to difference in duration of milling, where batches micronised from finer grade lactose monohydrate experienced shorter milling times thus exhibiting highly crystalline characteristics.

In addition to the impact of particle size on relative crystallinity of micronised samples, grinding pressure was also shown to influence the integrity of the crystal structure (Fig. 14). These data suggest that increases of grinding pressure markedly impacts crystallinity for SV010, although no marked effect was observed for the micronised batches of SV003 and L-Dcrit when compared to interbatch variation. It is probable that grinding pressure becomes important for coarse starting material, which experience greater forces during processing.

3.4. Inverse gas chromatography (IGC)

IGC data (Table 5) shows that there is no marked difference in dispersive surface energy for the starting materials and their respective micronised batches of lactose monohydrate. It was however shown that the dispersive and specific surface energies of finer grade starting material (L-Dcrit) and its consequent micronised batches were comparatively lower than those determined for coarse starting materials SV010 and SV003 (Table 5). This relatively low surface energy of micronised L-Dcrit is attributed to decreased duration of milling for finer grade starting materials, which reduces the potential for disruption of crystals and leads to fewer defects on particulate surfaces. The specific surface energy measured using tetrahydrofuran (THF) as a basic probe, increased for the micronised batches of SV010 and SV003. This finding suggests that the surface of lactose monohydrate has become more acidic, which is most probably linked to an increased exposure of hydroxyl groups at the surface of particles post micronisation.

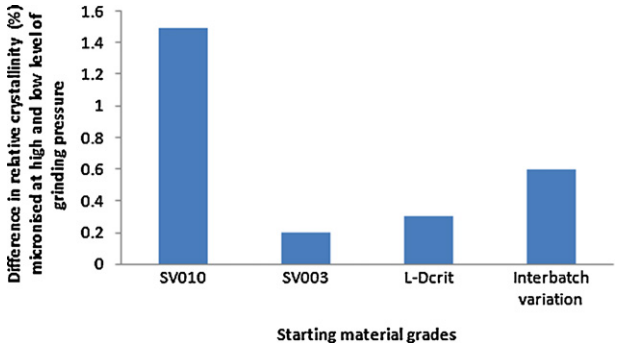

Fig. 14. Effect of grinding pressure (GP) on percentage crystallinity for micronised batches of SV010, SV003 and L-Dcrit.

Table 5
Dispersive and specific surface free energy for starting and micronised batches of three grades of lactose monohydrate (value in brackets indicates range of data, $n = 2$).

Lactose Grade	Batch	Dispersive surface energy, (mJ/m^2)	Specific Surface energy in tetrahydrofuran, (kJ/mol)	Specific Surface energy in chloroform, (kJ/mol)	Specific Surface energy in ethyl acetate, (kJ/mol)	Specific Surface energy in acetone, (kJ/mol)
SV010	Starting	44.2 (0.6)	6.19 (0.02)	1.99 (0.01)	7.45 (0.12)	7.75 (0.02)
	Average value of micronised batches	44.3 (2.2)	7.31 (0.35)	1.83 (0.12)	8.58 (0.51)	8.84 (0.48)
SV003	Starting	46.3 (1.1)	6.69 (0.11)	2.01 (0.15)	7.94 (0.08)	8.46 (0.01)
	Average value of micronised batches	43.6 (3.3)	7.03 (0.17)	1.75 (0.11)	8.39 (0.26)	8.68 (0.33)
L-Dcrit	Starting	41.4 (0.5)	5.05 (1.09)	1.53 (0.01)	5.09 (0.41)	5.75 (0.60)
	Average value of micronised batches	42.7 (2.0)	5.45 (0.38)	1.85 (0.17)	6.83 (0.32)	7.11 (0.65)

Ticehurst (1995) observed that the dispersive surface free energy of unmilled and milled lactose monohydrate was similar, while hydroxyl groups which are the predominant functional moiety of lactose, were exposed to a greater extent at surfaces after milling. This surface rich in hydroxyl groups is more acidic, with an increased interaction of basic polar probes (especially THF). However, micronised batches of finer grade lactose material, L-Dcrit (<20 μm) showed increased specific interactions with the amphoteric probe acetone rather than with acidic chloroform ($CHCl_3$) or basic THF (Table 5). This result suggests that both strong electron donor and electron acceptor interactions occur at the surface of micronised batches of L-Dcrit probably due to greater increases in surface area to volume ratio compared to batches micronised from the coarse starting materials SV010 and SV003.

The median particle size of the starting material was shown to have an effect on the specific surface energy determined from THF for micronised batches of SV010, SV003 and L-Dcrit (Fig. 15). It suggests that batches micronised from coarse grade starting material showed high specific surface free energy for THF, possibly due to increased numbers of fracture events. This phenomenon probably increases the exposure of acidic hydroxyl groups at the surface of powder particles, maximising the interactions with the basic probe THF. This result supports the findings observed from the moisture sorption studies, where samples produced from SV010 showed greatest levels of moisture uptake supporting the increased exposure of hydroxyl groups at particle surfaces.

Process variables showed no marked effects on the dispersive surface free energy for the batches micronised from SV010, SV003 and L-Dcrit. Process conditions were however found to have an effect on the specific surface energy determined using the tetrahydrofuran (THF) probe. Fig. 16 indicates that increases of GP markedly affected the specific surface energy measured using THF for the micronised batches of SV010, while GP has only demonstrated a marginal effect for the batches micronised from SV003 and L-Dcrit when compared to interbatch variation.

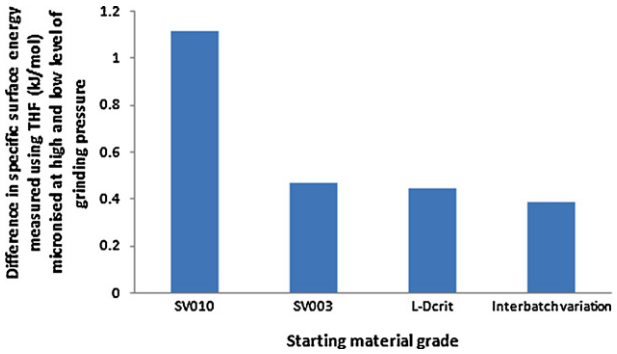

Fig. 16. Effect of grinding pressure (GP) on specific surface free energy measured using THF for micronised batches of SV010, SV003 and L-Dcrit.

Fig. 17 shows that increased injector pressure affects specific surface energy (THF) for the micronised batches of SV010 compared to interbatch variation. However increased injector pressure showed no marked effect on specific surface energy (THF) for batches micronised from SV003 and L-Dcrit. These results suggest that the impact of proccessing conditions was dependent on the size of starting material with larger particle being subject to a greater degree of size reduction than their finer counterparts. Feed rate showed no marked effect on the specific surface energy (THF) for the batches micronised from any of the starting materials. It is therefore clear that the propensity of micronisation is markedly dictated by the particulate properties of the feedstock for lactose monohydrate with consequences for the attributes of the size reduced materials.

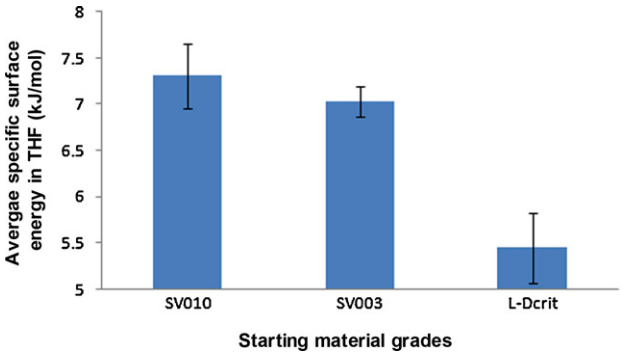

Fig. 15. Effect of starting material median particle size on average specific surface free energy measured using THF for the micronised batches of SV010, SV003 and L-Dcrit.

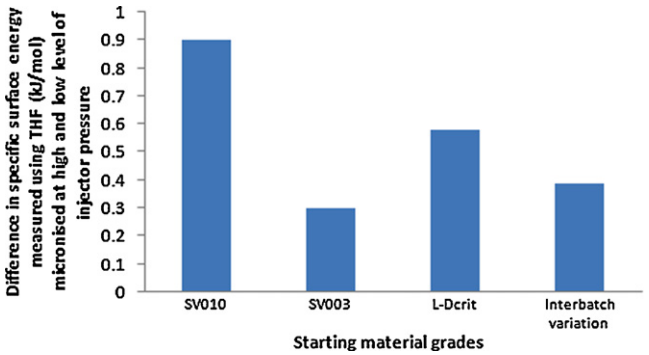

Fig. 17. Effect of Injector pressure (IP) on specific surface free energy measured using THF for micronised batches of SV010, SV003 and L-Dcrit.

4. Conclusion

The results suggest that the impact of processing conditions was dependent on the size of three grades of lactose monohydrate, which influenced the characteristics of the micronised product. TGA and DSC data showed that changes in dehydration behaviour of lactose monohydrate samples was dependent on particle size, with ultrafine materials showing more facile loss of water of crystallisation. This phenomenon was observed for particles below 75 μm, while particles above this size showed no marked difference in dehydration behaviour. It was possible to micronise lactose monohydrate to sizes below the brittle–ductile transition (23.7 μm), which is probably due to changes in particle size reduction mechanism from brittle fracture to shearing. The degree of disorder induced in the micronised material was dependent on the particle size of the feedstock and the levels at which the process conditions were set. From the findings and analysis reported, it is proposed that lactose monohydrate be micronised from finer grade starting material (L-Dcrit) to achieve ultrafine materials. In order to achieve similar effect for materials with similar mechanical properties to lactose monohydrate, finer grade starting materials should be used even at sizes below the brittle–ductile transition. Further work however needs to be undertaken to optimise the process conditions for this material.

References

Berlin, E., Kliman, P.G., Anderson, B.A., Pallansch, M.J., 1971. Calorimetric measurement of the heat of desorption of water vapour from amorphous and crystalline lactose. Thermochim. Acta 2, 143.

Buckton, G., 1997. Characterisation of small changes in the physical properties of powders of significance for dry powder inhaler formulations. Adv. Drug Deliv. Rev. 26, 17–27.

Chen, Y., Ding, Y., Papadopoulos, D.G., Ghadiri, M., 2004. Energy-based analysis of milling alpha-lactose monohydrate. J. Pharm. Sci. 93, 886–895.

Chow, A.H.L., Henry, H.Y., Tong Chattopadhyay, P., Shekunov, B.Y., 2007. Particle engineering for pulmonary drug delivery. Pharm. Res. 24, 411–437.

de Matas, M., 1997. The phase metamorphoses of caffeine and lactose. PhD Thesis, University of Bradford, UK.

Elamin, A.A., Sebhatu, T., Ahlneck, C., 1995. The use of amorphous model substances to study mechanically activated materials in the solid state. Int. J. Pharm. 119, 25–36.

Garnier, S., Petit, S., Mallet, F., Petit, M.N., Lemarchand, D., Coste, S., Lefebvre, L., Coquerel, G., 2008. Influence of ageing, grinding and preheating on the thermal behaviour of α-lactose monohydrate. Int. J. Pharm. 361, 131–140.

Gommeren, H.J.C., Heitzmann, D.A., Moolenaar, J.A.C., Scarlett, B., 2000. Modelling and control of a jet mill plant. Powder Technol. 108, 147–154.

Huttenrauch, R., 1978. Molecular pharmaceutics as the basis of modern formulation. Acta Pharm. Technol. 6, 55–127.

Kwan, C.C., Chen, Y.Q., Ding, Y.L., Papadopoulus, D.G., Bentham, A.C., Ghadiri, M., 2004. Development of a novel approach towards predicting the milling behaviour of pharmaceutical powders. Eur. J. Pharm. Sci. 23, 327–336.

Meier, M., John, E., Wieckhusen, D., Wirth, W., Peukert, W., 2009. Influence of mechanical properties on impact fracture: prediction of milling behaviour of pharmaceutical powders by nanoindentation. Powder Technol. 188, 301–313.

Newell, H.E., Buckton, G., Butler, D.A., Thielmann, F., Williams, D.R., 2001. The use of inverse gas chromatography to measure the surface energy of crystalline, amorphous and recently milled lactose. Pharm. Res. 18, 662–666.

Patel, R.P., Baria, A.H., Patel, N.A., 2008. An overview of size reduction technologies in the field of pharmaceutical manufacturing. Asian J. Pharm. 2, 216–220.

Price, R., Young, P.M., 2004. Visualization of the crystallisation of lactose from the amorphous state. J. Pharm. Sci. 93, 155–164.

Pritchard, J.N., 2001. The influence of lung deposition on clinical response. J Aerosol Med. 14, S19–S26.

Roberts R.J., 1991. The elasticity, ductility and fracture toughness of pharmaceutical powders. PhD Thesis, University of Bradford, UK.

Saxena, A., 2007. A comparative study of the surface energetics of pharmaceutical excipients by inverse gas chromatography and molecular modelling. PhD Thesis, University of Bradford, UK.

Schultz, J., Lavielle, L., 1989. Interfacial properties of carbon fiber-epoxy matrix composites. In: Lloyds, D.R., Ward, T.C., ans Schreiber, H.P. (Eds.), Inverse gas chromatography ACS Symposium Series 391. Washington, pp. 185–202.

Ticehurst M.D., 1995. Characterisation of surface energetics of pharmaceutical powders by inverse gas chromatography. PhD Thesis, University of Bradford, UK.

Ticehurst, M.D., Basford, P.A., Dallman, C.I., Lukas, T.M., Marshall, P.V., Nichols, G., Smith, D., 2000. Characterisation of the influence of micronisation on the crystallinity and physical stability of revatropate hydrobromide. Int. J. Pharm. 193, 247–259.

Vogel, L., Peukert, W., 2003. Breakage behaviour of different materials-construction of a mastercurve for the breakage probability. Powder Technol. 129, 101–110.

Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D., 1986. Studies on tableting; properties of lactose; the effect of initial particle size on binding properties and dehydration characteristics of lactose monohydrate. Drug Dev. Ind. Pharm. 12, 1715–1730.

Young, P.M., Chan, H.K., Chiou, H., Edge, S., Tee, T.H.S., Traini, D., 2007. The influence of mechanical processing of dry powder inhaler carriers on drug aerosolization performance. J. Pharm. Sci. 96, 1331–1341.