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The effects of high shear blending on α-lactose monohydrate

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Abstract

α-Lactose monohydrate is an important pharmaceutical excipient used extensively in dry powder inhaler (DPI) formulations. The ways in which a high shear blending process affect this material have been investigated and important process parameters have been identified. Total energy input (kJ/kg), blade design and the conditions in which lactose was stored prior to blending were found to have the most significant effect on the apparent particle size distribution of the processed material, which may subsequently affect the performance of DPI formulations. The power conditions used during blending, equipment temperature and humidity of the headspace above the powder were found to be less important in this respect. Additionally, it was found that high energy blending could induce changes in the water sorption characteristics of the material, although the formation of amorphous material could not be confirmed.

Keywords: Lactose; Dry powder inhaler; High shear blending

1. Introduction

Dry powder inhalers are widely-used drug delivery systems employed primarily for the treatment of respiratory diseases such as asthma. The active ingredient(s) within these systems comprise particles with aerodynamic diameters that allow deposition in the tracheobronchial regions of the airways, i.e. between 2 and 5 μm. Powders in this size range are extremely cohesive and therefore to aid flow from the inhaler device, enhance dispersion and to provide a convenient sized dose for volumetric metering, the active drug may be mixed with an excipient, commonly α-lactose monohydrate (hereafter referred to as lactose), with a larger mean geometric particle size of around 70 μm. Additionally, the lactose plays an important role in modulating the performance of the formulation. For example, it is known that the quantity of fine lactose particles that are in the same size range as the drug, influences the amount of drug that reaches the lower airways (the "drug fine particle mass", DFPM). Indeed, a number of hypotheses have been posed to explain how lactose fines produce their effects, including the possibility that they: (1) compete with drug particles for "high energy" attachment sites on the larger lactose carriers (Hersey, 1975; Staniforth, 1996), (2) form readily dispersible multiplets with drug particles (Lucas et al., 1998), (3) create mono or multilayers between the larger carrier particles and the drug, thereby reducing van der Waals forces of attraction between drug and carrier (Zeng et al., 1998) and (4) act as a lubricant in the powder systems preventing the build up of electrostatic forces that affect drug–lactose binding (Zeng et al., 1998).

Numerous studies have been carried out to investigate the nature of drug–lactose interactions and/or to examine the behaviour of the formulation after discharge from the device (e.g. Begat et al., 2004; de Boer et al., 2003; Jashnani et al., 1995; Price et al., 2002; Podczeck, 1998; Shekunov et al., 2003; Young et al., 2005; Zeng et al., 2001). However, few studies have been described that determine the effect that the secondary manufacturing process (production of the final dosage form) has on the formulation. This process comprises multiple stages, at the heart of which is a blending operation used to mix the active drug(s) and excipient (lactose). In this contribution, studies that examine the effect of *high shear* blending (a widely used industrial operation in this field) on lactose are presented. As such,

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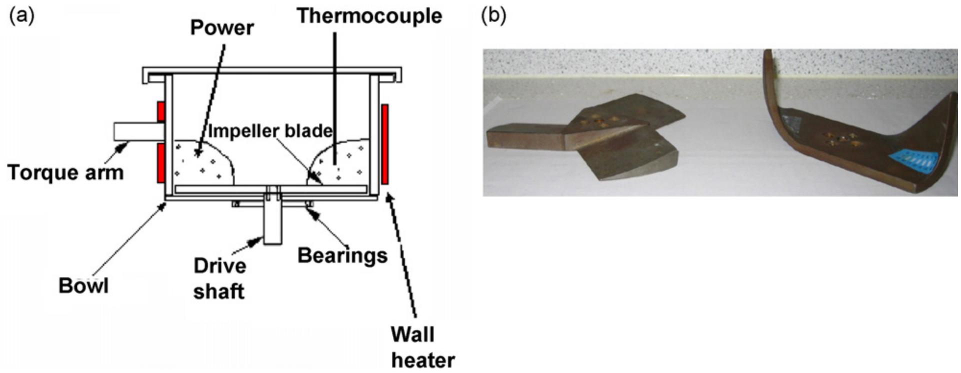

Fig. 1. (a) Schematic illustration of the high shear blender. (b) The two blades used in the study. Left—low impact, high shear, knife-edged blade. Right—high impact, twisted blade.

the mixing process used here is very different from that considered previously within the work of Podczeck (1999), Zeng et al. (2000), and Dickhoff (2006) where low shear, tumbling mixing processes were employed. In addition, in this study, the effects of storage at different relative humidities on the subsequent blend behaviour of the lactose have been investigated. No active drug has been incorporated, but as the lactose typically makes up to ∼98% of the material in the formulation, it has considerable influence on the formulation behaviour. Particular attention has been paid to monitoring the “free” lactose fines content before and after blending due to their known effect on the DFPM. Further assessment of the physicochemical properties of the material before and after blending was also carried out using dynamic vapour sorption (DVS).

2. Materials and methods

2.1. Materials

Lactose was obtained from Friesland Foods Domo, Netherlands. Aliquots of this material used throughout the study were derived from batches stored at one of the following conditions: (i) 20 °C and 40% RH in a humidity and temperature controlled cabinet (Binder, Germany), (ii) 20 °C and 70% RH also in a cabinet or (iii) “standard”, uncontrolled laboratory conditions (between 18–25 °C and 30–70% RH). In all cases, the lactose was stored within its original packaging (foil bag within cardboard box) that was open to the storage environment.

2.2. The high shear blender

A schematic illustration of the high shear blender is shown in Fig. 1 along with the two different blade designs that were used in this study. The bowl was mounted on bearings so that it would have been free to spin if it had not been prevented from doing so by a force transducer that provided a measurement of the instantaneous torque on the bowl (Knight et al., 2001). The power input, P (W) into the powder during blending could be related to this force via Eq. (1):

$$P = \frac{2\pi RFN}{60} \tag{1}$$

where R (m) is the distance from the central axis of rotation to the force transducer, F (N) the force measured by the transducer and N (rpm) is the rotational speed of the blade. The force measured was dependent upon the blade speed (N) and mass of powder in the bowl, with normally an increase in speed or mass leading to a higher force. The energy input E (J) between times t_1 and t_2 could then be found from:

$$E = \int_{t_1}^{t_2} P\,\mathrm{d}t. \tag{2}$$

2.3. Blending experiments

Blending parameters employed in this study are described in Table 1. The experiments carried out could be broadly split into three groups: (i) short blends investigating the effects of short-term (up to 4 weeks) lactose storage at either 40 or 70% RH, blade design and energy input, (ii) short blends investigating the effects of long-term storage (up to 21 weeks) at either 40 or 70% RH, blade design, energy input, bowl temperature and headspace humidity and (iii) extended blends investigating the relative importance of total shear energy input versus power, bowl temperature, headspace humidity and blade design. More detail associated with individual experiments is presented in the results and discussion section where required.

2.4. Characterisation of unblended and blended lactose

2.4.1. Particle size distribution

Particle size distributions were determined using dry powder laser light diffraction (HELOS sensor with RODOS dispersion

Table 1
Investigated blending parameters

Parameter	Description
Blender run-time	2–15 min (short blends) and extended blends
Blade rpm	200–600 rpm
Temperature of bowl	Uncontrolled or maintained at 50 °C
Humidity of headspace above powder	Uncontrolled or lowered to around 10% RH by passing a stream of dry air across the powder
Blade design	Knife-edged or twisted (Fig. 1b)
Lactose storage	Stored in high, standard or uncontrolled humidity (Section 2.1)

unit, Sympatec, Germany) at a dispersion pressure of 2 bar to give a by-volume distribution. Interest in this study centred on the lactose fines (i.e. particles around 1–5 μm), and therefore a lens that allowed measurement in the range 0.5–175 μm was employed.

2.4.2. Dynamic vapour sorption

Water sorption studies were carried out using a DVS Advantage II (Surface Measurement Systems, UK). 120 mg ± 1 mg of sample was loaded onto one side of the twin pan balance, before running the software-controlled sequence that held the sample at 0% RH (dry nitrogen) for 4 h to remove any surface moisture, followed by humidity steps from 0% RH up to 90% RH in 10% increments. The temperature throughout was 25 °C ± 0.1 °C. The sample was allowed to reach a near-equilibrium state (% $dm/dt = 0.0002\%/\text{min}$) at each humidity stage before progressing to the next.

Application of the Brunauer Emmet Teller (BET) equation to DVS adsorption data obtained using octane as a probe molecule, allowed the specific surface area of the lactose to be determined using the same instrument. For these studies, the sample was first held in a stream of dry nitrogen (no octane) for 4 h. The partial pressure was then ramped from 0 to 96% in 3% increments and this procedure was repeated three consecutive times on each sample. All other experimental details were as for the water sorption studies.

3. Results and discussion

The d_5-value (the 5th percentile of the particle size distribution) from the laser diffraction measurements was found to be a particularly sensitive indicator of free fines content in the samples (i.e. fines that retained a distinct identity during particle sizing) and as such this particle size statistic is widely reported throughout the rest of this contribution. Absolute changes in more widely-reported statistics such as d_{50} were found to be considerably smaller than the changes in d_5, indicating that blending was having the greatest influence on the fine fraction of the overall particle population.

3.1. Effect of storage conditions on the particle size distribution of unblended lactose

The d_5 of unblended lactose remained fairly constant, at around 4 μm, over the time-course of the entire study for the material stored at 40% RH. Other particle size statistics, including d_{50}, were also observed to be unchanged. In contrast, lactose stored at 70% displayed a considerable time-dependent increase in d_5, which became marked after 1–2 weeks of storage. By the end of the study the d_5 had increased to almost 7 μm. Once again however, no statistically significant change in d_{50} was seen. It is known that at relative humidities above 65–75%, condensation of moisture between gaps can lead to the formation of significant capillary forces that dominate adhesive/autoadhesive interactions (Podczeck et al., 1996; Seville et al., 1997) and that after prolonged storage crystal bridging occurs. It is hypothesised that such forces are likely to have prevented the fines from detaching from the surface of the carriers at the conditions employed during particle sizing (2 bar dispersion pressure). Of particular note however, is that the blending behaviour of the lactose was observed to change from the time point at which storage-induced changes became apparent (Section 3.2).

Results from DVS analysis of stored lactose supported the observations from laser diffraction sizing. There was a significant decrease in the specific surface area of the lactose stored at 70% RH over the 21-week storage period. Indeed the SSA fell over this time from around 1700 to 900 cm^2/g, indicating once more that some particles were losing their identity as entirely distinct elements. A depression in the water sorption isotherms was also apparent after this time, i.e. while isotherms before and after storage where the same shape, overall water adsorption was lower following storage at 70% RH. This observation could also be linked to the decrease in surface area, given that the starting material was highly crystalline and there was no evidence in the DVS data of a recrystallisation event. These humidity-induced effects were not readily reversible, in that they were still evident despite exposure to the drying phase incorporated into the DVS methodology (4 h at 0% RH followed by continued exposure at 0% RH until equilibrium, as defined in the method, had been reached). Indeed, previous work suggests that the subsequent removal of condensed water by evaporation from hydrophilic surfaces may in fact increase adhesive forces due to the formation of solid bridges that originate from material previously dissolved in liquid bridges (Padmadisastra et al., 1994).

3.2. Effect of energy input on lactose stored at different conditions

Particle size analysis of some of the first blends to be carried out in this study (short blends using lactose stored at 40% RH for up to 4 weeks), showed that there was an emerging trend for d_5 to increase as the energy input increased. Due to the presence of other variables within these experiments (power, blade type, blade speed, etc.) some degree of scatter was observed. Therefore, extended blends in which all other variables were controlled were carried out to explore this relationship further. The results of these are shown in Fig. 2 and confirm that an energy-dependent loss of free fines was taking place during blending.

Although active material was not included in this study, it is proposed that these blending-induced, energy-dependent changes may affect the DFPM associated with drug-containing preparations. For example, a loss of free fines could reduce lubrication effects and the extent of multiplet formation, both of which may be expected to reduce DFPM. Alternatively, drug particles may simply be affected by blending in the same way as the equivalently sized lactose, i.e. as energy input increases a greater number of them become tightly attached to the surface of the larger lactose carriers. Again, this may reduce DFPM. If however lactose fines were more susceptible to the effects of blending than the active, then their increased occupation of strong binding sites with energy input could increase DFPM.

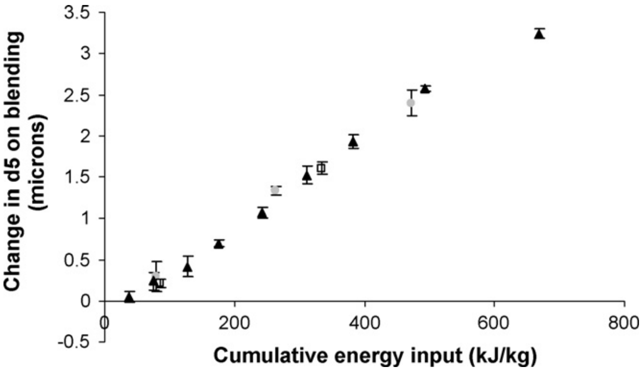

Fig. 2. Relationship between energy input and fines content of blended lactose. Lactose used in these experiments was from a newly opened batch stored at laboratory conditions. Results are from three independent blending runs using the knife-edged blade. Each point represents the mean ± one standard deviation of at least three sizing measurements.

Given the wide-ranging physicochemical nature of actives used in this field and the potentially important role of factors such as surface roughness (e.g. Ganderton, 1992; Podczeck, 1999; Flament et al., 2004; Dickhoff et al., 2005) and electrostatics (Byron et al., 1997), it would be naïve to think that such explanations for any observed changes in DFPM are complete. However, the impact of altering the free fines content should be given serious consideration when selecting a blending strategy or deciding on appropriate process parameters. More specifically, results such as those shown here could allow for the more rational design of specific "pre-conditioning" strategies whereby the strong binding sites on the large lactose carriers are pre-saturated with fines by high shear blending before subsequently blending with drug and, if necessary, additional lactose fines.

For lactose stored at 70% RH, completely different blend outcomes were observed and no obvious trend between energy input and d_5 emerged when blending this material. Instead, storage effects were seen to dominate so that, irrespective of blend regime, a decrease in d_5, relative to the starting material, was observed for all cases where lactose had been stored at 70% RH for longer than 2 weeks. It therefore appeared that the humidity-induced agglomeration described above was being partially reversed by blending, releasing some of the finer material.

3.3. The relative importance of power and powder temperature

It can be hypothesised that the observed, energy-dependent decrease in free fines content shown in Fig. 2 is due to agglomeration that results from particle collisional events, the number of which might be expected to be proportional to the total (non-thermal) energy input. These collisions lead to small particles becoming more tightly attached to the surface of the larger ones and being swept into crevices. Following this hypothesis, for any given total energy input, the extent of total agglomeration would be the same, irrespective of the rate at which the energy is added to the system, as is approximately the case in high-shear mixer agglomeration, provided that breakage is not a major factor (Bardin et al., 2004). To test this hypothesis, extended runs with different power regimens were compared (Fig. 3). The profiles (change in d_5 versus energy input) for different power inputs were seen to be similar, i.e. total energy was indeed found to have a greater impact on free fines content than the rate at which that energy was introduced.

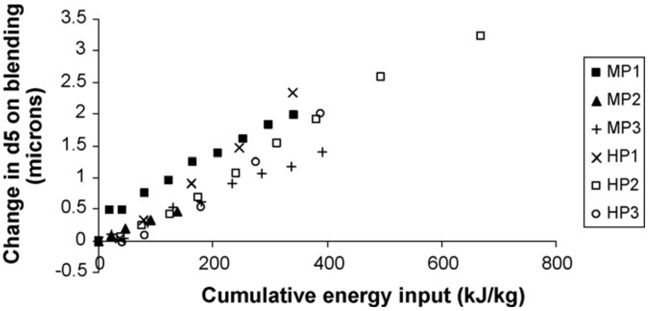

Fig. 3. Relationship between cumulative energy input and changes in d_5 for lactose blended with the knife-edged blade at either "medium" power (MP, 356 rpm) or "high" power (HP, 600 rpm). Each set of data points is derived from an independent experiment. Lactose had been stored in standard laboratory conditions and both bowl temperature and head space humidity were uncontrolled (as described in Table 1).

It should also be noted that the temperature profiles within the bowl varied considerably with different power inputs, i.e. high power runs produced greater temperature rises than low power ones. For example, during typical high power runs such as those shown in Fig. 3, the powder temperature reached ∼55 °C after an energy input of 400 kJ/kg compared to ∼40 °C in the medium power equivalents. Indirectly therefore, these results also show that temperature profiles are unimportant with respect to changes in particle size distribution (at least within this range). Similarly, the outcomes for neither short (Fig. 4a) nor extended (Fig. 5) blend experiments during which the wall of the bowl was heated appeared to be significantly different from the unheated comparisons. However, when considering systems in which an active agent is present, the importance of this parameter should not be dismissed; temperature-dependent changes in %RH could influence the interaction between drug and carrier for example by changing the electrostatics of the system.

3.4. Effect of blade design

Blade design was not found to have a statistically significant effect on blending outcome when the results obtained from short blends were combined as shown in Fig. 4b. The large standard deviations seen in this figure result from the effects of combining experimental data from experiments in which other variables were also changing. However, subsequent extended blends, in which all other variables were controlled did reveal a substantially different profile (Fig. 6). Such differences are consistent with the fact that the modes of energy input are different for each of the blades—largely frictional in the case of the knife-edged blade and inertial for the blunt, twisted blade (Knight et al., 2001). The flatter profile associated with the twisted blade may therefore be a result of an equilibrium between breakage and agglomeration.

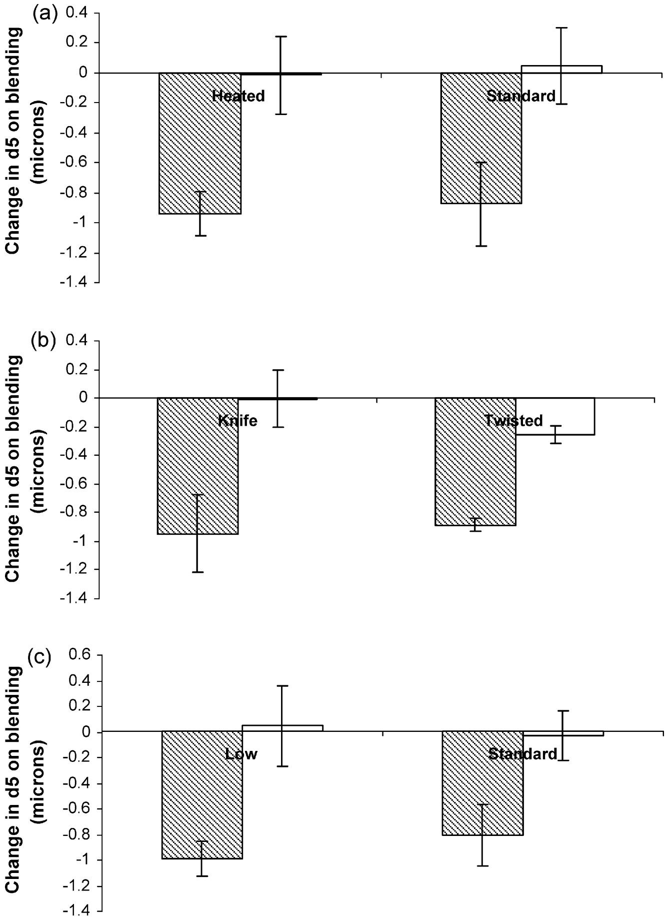

Fig. 4. Results for short blends showing the effects of (a) bowl heating, (b) blade type and (c) headspace humidity on lactose that had been subject to long-term storage at either 40% RH (clear bars) or 70% RH (hatched bars). Each bar represents the overall mean of between 3 and 7 experiments ± S.D of the mean. In addition to the highlighted variable under comparison, each set of results comprises combined data from experiments spanning different energy inputs, blade types, humidity and temperatures conditions.

When blending lactose that had been had been stored at 70% RH, a decrease in d_5 was always seen, irrespective of blade design; this illustrates once more the profound effect of different storage conditions (Fig. 4b).

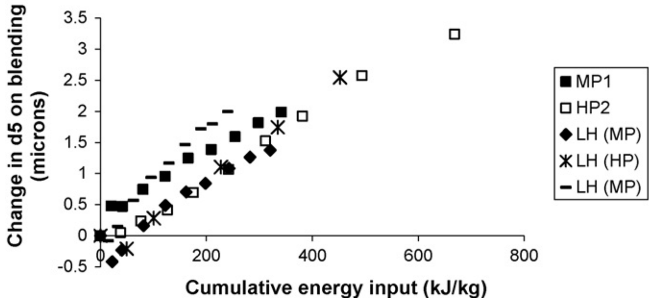

Fig. 5. Relationship between cumulative energy input and changes in d_5 for lactose blended at lowered head-space humidity (LH) in a heated bowl at “medium” (MP) or “high” (HP) power. As typical comparisons, MP1 and HP2 from Fig. 3 are also shown (uncontrolled temperature and humidity). Lactose had been stored in standard laboratory conditions and was blended with the knife-edged blade. Each set of data points is derived from an independent experiment.

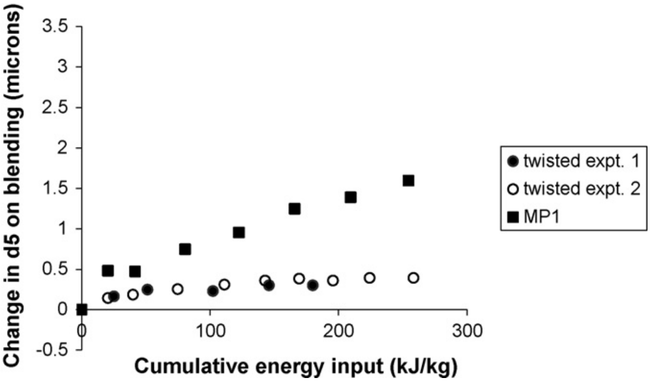

Fig. 6. Relationship between cumulative energy input and changes in d_5 for two independent blending experiments (black circles and clear circles) carried out with the twisted blade at a medium power setting (356 rpm). As a typical comparison, MP1 from Fig. 3 is also shown (knife-edged blade). Lactose had been stored in standard laboratory conditions and both bowl temperature and head space humidity were uncontrolled.

3.5. *Effect of headspace humidity*

In their analysis of powder blending (lactose and salicylic acid) using a V-blender for solid dosage form production, El-Hagrasy et al. (2006) found that humidity of the blend environment affected the particle size distribution of the investigated powders. Their mean particle size was found to be greater after blending at 20% RH than after blending at 60% RH. It was proposed that a build up of static charge was responsible for the effects seen at the lower %RH and that softening of particles, leading to an increased susceptibility to attrition were responsible for those seen at the higher %RH. Comparisons with the work described in this contribution are not entirely valid, due to the vastly different energy inputs involved in the two types of blending, and indeed the findings of our work do differ. Here, lowering the humidity did not seem to influence the blending outcome greatly with respect to changes in the d_5 particle size distribution. Figs. 4c and 5 show the results of short blends and extended blends, respectively. In the case of Fig. 5, the results are from experiments in which both temperature and humidity effects were simultaneously under investigation. It has already been argued that temperature does not affect the d_5 of lactose, so any difference seen in these experiments could be attributed to the humidity. It can be seen that although the majority of each profile for the lower humidity blends is comparable with that from standard, uncontrolled humidity blends, there is a drop in d_5 in the early stages of blending before the familiar increase. It is possible therefore that the lower humidity environment initially promotes fines release, possibly through a drying mechanism, before the agglomeration effects take over.

3.6. *Blending-induced changes in surface properties*

It is well known that high energy processing of pharmaceutical material can induce surface changes, e.g. the introduction of amorphous material. Fig. 7 shows how the lactose in this study was typically affected by high energy blending. The data for the top profile were collected immediately after blending.

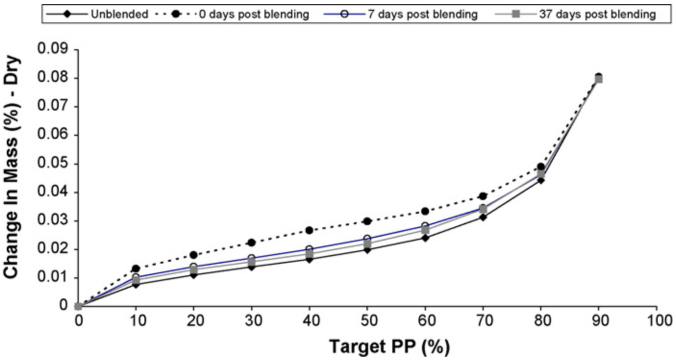

Fig. 7. Moisture sorption profiles of lactose before and at various time intervals after blending. Total energy input 200 kJ/kg.

A sample of the blended lactose was also retained, and stored at 20 °C/40% RH, for further analysis at subsequent time intervals. It can be seen that the moisture sorption capacity of the material immediately post blending is considerably higher than that of the original, unblended material. In combination with the observed change in inflection points, it appears that the surface of the lactose had been altered in some, currently unknown, way by blending. Mackin et al. (2002) showed a similar isotherm for xemilofiban that had been subjected to high energy milling. In their work, these apparent surface changes were those that had persisted after the recrystallisation of amorphous material, the presence of which was clearly identifiable by a typical "amorphous collapse" in preceding isotherms. In our work, no such collapses were ever observed, i.e. when examining data showing change in mass as a function of increasing %RH, no (sudden) mass loss was seen. It is not yet known whether this is because any amorphous material recrystallised very rapidly before DVS analysis, or if such material had never in fact been formed. Irrespective of the origins of the surface changes, they were seen to reverse over time.

4. Conclusions

To ensure patient safety and guarantee efficacy, drug products must possess well-defined quality attributes. Whether or not a batch of product passes all necessary quality assessments is often a result of events occurring during the manufacturing processes that make them. It is therefore important to add understanding to processes so that they can be controlled with confidence, resulting in high quality products. As part of this, variability in ingredients must be accommodated. This work contributes towards a better understanding of how high shear blending might be better controlled to ensure consistent quality and functionality of dry powder inhalable products. Although much work remains, the authors conclude the following with respect to the processing of lactose:

(1) Storage of the materials prior to blending should be considered as part of the process and as such should be carefully controlled and monitored.
(2) In relation to the particle size distribution of the samples, the most important parameter to control and monitor during blending is the total energy input. The temperature of the bowl and humidity of the blending environment (within the investigated limits) are secondary to, and may be unimportant, compared with energy input.
(3) With respect to blender design, attention should be paid to blade design to ensure not only that the powders will be well-mixed, but that the effects on primary particle interactions are fully understood.

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