Entrainment of lactose inhalation powders: A study using laser diffraction
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A R T I C L E   I N F O
Article history:
Received 14 December 2009
Received in revised form 18 March 2010
Accepted 17 April 2010
Available online 24 April 2010

Keywords:
Lactose
Dry powder inhalation
Entrainment
Fluidisation
Laser diffraction
Fracture
Erosion
Flowability

A B S T R A C T
We have investigated the mechanism of entrainment of lactose inhalation blends released from a dry powder inhaler using a diffraction particle size analyser (Malvern Spraytec). Whether a powder blend entrains as a constant stream of powder (the “erosion” mechanism) or as a few coarse plugs (the “fracture” mechanism) was found by comparing transmission data with particle size information. This technique was then applied to a lactose grade with 0, 5 and 10 wt% added fine particles. As the wt% fines increased, the entrainment mechanism was found to change from a mild fracture, consisting of multiple small plugs, to more severe fracture with fewer plugs. The most severe fracture mechanism consisted of either the powder reservoir emptying as a single plug, or of the reservoir emptying after a delay of the order of 0.1 s due to the powder sticking to its surroundings. Further to this, three different inhalation grades were compared, and the severity of the fracture was found to be inversely proportional to the flowability of the powder (measured using an annular ring shear tester). By considering the volume of aerosolised fine particles in different blends it was determined that the greater the volume of fines added to a powder, the smaller the fraction of fines that were aerosolised. This was attributed to different behaviour when fines disperse from carrier particles compared with when they disperse from agglomerates of fines. In summary, this paper demonstrates how laser diffraction can provide a more detailed analysis of an inhalation powder than just its size distribution.

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1. Introduction
1.1. Lactose inhalation blends

Dry powder inhalers (DPIs) are devices for delivering drug particles to the lung. The drug particles must have an aerodynamic diameter of 1–5 μm to be deposited in the correct part of the lung (Newman and Clarke, 1983). However, in this size range, particles are highly cohesive resulting in agglomeration and poor flowability properties, which in turn can result in inaccurate measurement of doses (Podczeck, 1998, 1999; Young et al., 2005). If the drug particles are mixed with coarse (median size 20–100 μm), inert carrier particles (usually lactose, in typical weight ratio 67.5:1: carrier:drug), processing properties are improved since the drug particles adhere to the carrier particle surfaces. However, DPIs employing these binary blends have a low dose efficiency, believed to be a result of poor drug-carrier separation (Podczeck, 1998; Young et al., 2005; Islam and Gladki, 2008). This is in part caused by natural surface asperities on milled lactose particles which shield the drug particles from the air flow and prevent de-agglomeration (de Boer et al., 2003; Kawashima et al., 1998; Zeng et al., 2000). The inhaled fine particle fraction has been increased using a ternary component such as fine lactose particles (micronised to have an aerodynamic diameter of 1–5 μm) to “valley fill” the gaps between asperities before the addition of the drug, so that drug particles are no longer shielded from the air flow (Iida et al., 2005; Zeng et al., 1998, 2001b; Iida et al., 2004; Huber and Wirth, 2003).

1.2. Entrainment mechanisms

When a patient actuates a DPI, the flow of air both lifts the powder out of the inhaler (fluidisation) and causes the separation of drug from carrier (de-agglomeration). Shear fluidisation occurs when the air passes over the powder, generating a pressure differential across the bed (Zeng et al., 2001a). At low air flow rates, the pressure drop across the powder bed increases linearly with air flow rate (Shur et al., 2008). This pressure drop causes a vertical lift force which will fluidise the powder if sufficient to overcome the weight of the particles and the interparticulate forces between particle layers. Using high-speed photography, Tuley et al. (2008) observed that lactose becomes fluidised by a “fracture” mechanism in which the powder bed is emptied as several large “plugs” rather than layer-by-layer in a constant stream. Due to the cohesive nature of lactose, the lift force acting on the top layer of particles must be...
great enough to lift several layers of particles until the powder bed cracks along a line of weakness. The plug is then carried away by the air and breaks up to form an aerosol cloud. This process was found to be independent of the powder reservoir geometries or pressure drop gradients tested.

However, Shur et al. (2008) found that only highly cohesive lactose powders, such as those containing high proportions of fine lactose, resulted in fracture fluidisation. Coarser, less cohesive, lactose blends showed continuous layer-by-layer entrainment from the surface of the powder bed, termed “erosion”. Tuley et al. (2008) found that a lactose powder with 16% fines (where % fines refers in this example to the mass fraction of particles smaller than 15 μm) exhibited a clear fracture mechanism, whereas lactose with only 6% fines showed a “milder” fracture mechanism in which the powder entrained as a greater number of smaller plugs than those observed for lactose with 16% fines. Cohesive powders that entrained by the fracture mechanism produced a greater fine particle fraction than slowly eroded powders, since when plugs of lactose are aerosolised the density of particles in the air is greater, leading to a greater number of interparticle collisions that can aid de-agglomeration. It is thus desirable to know how a particular lactose inhalation blend in a particular DPI is entrained, but high-speed photography is not always available. This paper demonstrates how a laser diffraction particle size analyser can be used to characterise the entrainment of lactose inhalation blends, and further how it can be used to assess how effectively an inhalation blend releases micronised particles.

2. Materials and methods

2.1. Lactose inhalation grades

Lactohale® LH200 (milled α-lactose monohydrate) was obtained from Friesland Foods Domo (The Netherlands). Repsitose® SV003 (sieved α-lactose monohydrate) and ML001 (milled α-lactose monohydrate) were obtained from DMV-Fonterra Excipients (The Netherlands). These grades are designated “inhalation grades” and have similar shapes and volume median diameters (Table 1), but LH200 and ML001 have a broad particle size distribution (PSD) (coarse carrier particles and fines) whereas SV003 has a narrow PSD (predominantly coarse carrier particles, but with surface fine particles that detach at high air flow rates, giving a bimodal distribution) (Fig. 1). Micronised (fine) lactose particles were obtained from Pfizer (UK). Micronised fines have a volume median diameter of 4.1 μm and are less elongated than the inhalation grade particles (Table 1).

Throughout this article “fine particles” are defined as those with equivalent sphere diameters under 5 μm, and “coarse particles” are defined as those suitable for use as carrier particles (20–100 μm).

2.2. Mixing lactose blends

Commercially available inhalation grades were used as supplied, and also blended with fine lactose. To prepare blends, the fine lactose was added to the coarse grades in a glass container such that the final proportions of the fines were 1.0, 5.0 and 10.0 wt%.

Blends were mixed using a spinner-rotator (Turbula T2F, Willy A Bachofen AG, Basel, Switzerland) at 46 rpm for 30 min.

2.3. Inhaler

A purpose-built single-dose DPI was used to deliver the powder. After re-distributing the powder in the spinner-rotator to promote homogeneity, approximately 25 mg of lactose was filled into a powder reservoir, such that the top of the powder reservoir was in line with the air flow channel. The DPI emptied by shear fluidisation.

2.4. Laser diffraction particle size analysis

Entrainment observations and particle size measurements of lactose inhalation blends were obtained using dry laser diffraction (Spraytec with Inhalation Cell, Malvern Instruments, Malvern, UK) with a 300 mm lens (which is able to measure particles in the size range 0.1–900 μm, although the sizing of sub-micron particles is inaccurate since their scattering becomes increasingly isotropic (Washington, 1992)). Mie theory was used to calculate the particle size distribution (PSD) from the scattered laser light. The particles were assumed to be spherical.

<table>
<thead>
<tr>
<th>Grade name</th>
<th>Qualitative description</th>
<th>Mean elongation ratio</th>
<th>Mean circularity</th>
<th>Volume median diameter/μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH200</td>
<td>Angular</td>
<td>1.7</td>
<td>0.67</td>
<td>66</td>
</tr>
<tr>
<td>ML001</td>
<td>Angular</td>
<td>1.6</td>
<td>0.64</td>
<td>40</td>
</tr>
<tr>
<td>SV003</td>
<td>Angular</td>
<td>1.7</td>
<td>0.63</td>
<td>56</td>
</tr>
<tr>
<td>Micronised fines</td>
<td>Angular</td>
<td>1.3</td>
<td>0.64</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Fig. 1. Particle size distributions for lactose inhalation grades measured by dry laser diffraction in a Spraytec with an air flow of 801 min⁻¹, calculated for equivalent volume spheres.
The overall set-up consisted of a DPI inserted into an airtight rubber mouthpiece connected to a USP throat. Powder entrained in the DPI was sucked through the USP throat, through the inhalation cell of the Spraytec and into a dose collector. A Copley vacuum pump was used to generate the air flow (Copley Scientific Limited, Nottingham, UK). In addition to this pump, a Copley TPK 2000 critical flow controller was used to obtain a reproducible, constant air flow. A 4.0 kPa pressure drop was achieved using an air flow rate of 80 l min$^{-1}$, and 41 of air was drawn through the inhaler in 3 s. The reservoirs were completely emptied of powder on every occasion at this air flow rate, which gave transmission minima of 65–85%, and sonic flow was achieved. Light scattering data was collected when the transmission was below 98%.

2.5. Shear cell flowability test

Flowability measurements were carried out using an RST-XS Annular Ring Shear Tester (Dietmar Schulze Schüttgutmesstechnik, Wolfenbüttel, Germany). Approximately 25 g of lactose was filled into the annular shear cell without applying any downward force to the top surface. The powder was pre-sheared with a normal stress of 6000 Pa, and a yield locus was constructed for each powder by measuring the shear stress required to cause the powder to fail under five normal stresses (1200, 2100, 3000, 3900 and 4800 Pa). At least three independent measurements were made to check for consistency.

A Testo 625 humidity/temperature measuring instrument (Testo Limited, Hampshire, UK) was used to monitor environmental conditions. All laser diffraction and shear cell tests were carried out at 20 ± 2 °C and 40 ± 5% relative humidity.

3. Results and discussion

3.1. Interpretation of an inhalation profile

Fig. 2 is a plot of laser transmission against time for the entrainment of a single-dose of a milled lactose blend, LH200 (5 wt% fines). Also plotted are the “Dv(10)”, “Dv(50)” and “Dv(90)” against time. “Dv(X)” is an equivalent sphere particle diameter, where X% of the volume of the powder has a diameter below this value. This LH200 (5 wt% fines) sample was selected as the baseline for comparison to others in the following sections, and the characteristic features described before (Malvern, 2001) and is interpreted to mean that a large volume fraction of coarse particles is detected during the transmission trough and a small volume fraction of coarse particles is detected before and after the trough. Similarly the Dv(10) was low (<10 μm) before the transmission trough and increased during the first trough (to a maximum of 20 μm). However, the Dv(10) curve dropped back to below 10 μm during the second trough, and remained this low throughout the remainder of the experiment.

We can distinguish between these explanations by considering the PSD during the two troughs. If both troughs correspond to the same sized particles then option 2 is more likely, and if the troughs correspond to different sizes then option 1 is more likely. The dashed lines and thin solid line on Fig. 2 show the Dv(90), Dv(50) and Dv(10). We observed that the Dv(50) and Dv(90) were large during the periods of low transmission (approximately 80 μm and 160 μm, respectively) but lower than this before and after. This characteristic “step” shape for the Dv(50) and Dv(90) has been described before (Malvern, 2001) and is interpreted to mean that a large volume fraction of coarse particles is detected during the transmission trough and a small volume fraction of coarse particles is detected before and after the trough. Similarly the Dv(10) was low (<10 μm) before the transmission trough and increased during the first trough (to a maximum of 20 μm). However, the Dv(10) curve dropped back to below 10 μm during the second trough, and remained this low throughout the remainder of the experiment.

So, before the first dip in transmission we saw mostly fine particles (since fine particles accelerate more quickly than coarse particles due to their lower mass), and during the first dip in transmission we saw mostly coarse particles. The second dip corresponds to the detection of both coarse and fine particles, and then after this mostly fine particles were detected (a layer of fine lactose particles adheres to the insides of the USP throat and other airway tubes; with continuous air flow some fine particles may detach from the walls, but after a noticeable delay). The fact that both dips in transmission contain coarse particles suggests that the powder is entrained by the fracture mechanism—the most likely explanation for detecting coarse particles at two different times is because they have left the reservoir at different times.
In summary, provided that a step shape is seen in the Dv(50) and Dv(90) corresponding to the trough seen in the transmission curve, the shape of the trough and the number of times it splits will correspond to the number of plugs that the powder has entrained with. This means that the shape of the transmission curve can be used to determine the method of entrainment.

3.2. How volume of fine particles affects aerosolisation

With this knowledge we can determine how the entrainment and PSD of a carrier particle grade changes with the addition of fine lactose particles.

Fig. 3 shows the transmission profiles for three LH200 blends. LH200 (5 wt% fines) entrains in two stages (there are two troughs in the transmission) whereas LH200 and LH200 (10 wt% fines) entrain in a single stage. This was consistent for three independent repeated measurements. Each specimen showed a step shape in the Dv(50) and Dv(90) corresponding to the transmission trough. The main difference between the troughs for LH200 and LH200 (10 wt% fines) is that the LH200 trough is much broader and shallower; the powder was aerosolised at a slower rate over a longer period of time.

We determined from Fig. 2 that LH200 (5 wt% fines) entrains by the fracture mechanism, and therefore we would expect LH200 (10 wt% fines) to entrain by fracture also, since the addition of fines increases cohesivity (Shur et al., 2008). Tuley et al. (2008) found that entrainment by fracture emptied the reservoir more quickly than by erosion when exposed to the same air flow rate. Considering the transmission curves of LH200 (5 wt% fines), each plug of powder is aerosolised in ~0.1 s. If the LH200 (10 wt% fines) powder was entrained as a single plug then it would take ~0.1 s to aerosolise. It does, which implies that when lifted from above, the powder is sufficiently cohesive to support the weight of the entire reservoir contents. LH200 (5 wt% fines) is slightly less cohesive, and so when the top of the powder is lifted, it fractures and the powder mass splits into two such that it entrains as two plugs. LH200, however, shows a significantly broader single trough. Although the least cohesive powder, LH200 still has some stickiness to it; it is not free-flowing. It may be entraining by the erosion mechanism, which would explain the broadness of the trough, or it may be entraining by a fracture mechanism consisting of multiple smaller plugs; the fracture mechanism tends to the erosion mechanism in the limit where each plug is only a single layer of particles.

In summary, we can determine from comparison of laser diffraction measurements that the addition of increasing wt% of micronised lactose to the LH200 carrier blend causes the powder to entrain by a more severe fracture mechanism. This is considered to be desirable since the powder aerosolises in denser clouds which increases collision frequency, aiding the de-agglomeration of drug particles. So, considering the entrainment mechanism alone, a powder with a transmission profile such as that seen for LH200 (10 wt% fines) is likely to release drug particles more efficiently than a powder with a profile such as LH200.

As discussed in Section 1.1, micronised lactose fines are manufactured to be the same size as micronised drug particles so that they occupy the same sites on the carrier particles. By observing how lactose fines de-aggregate from the carrier particles then we can, by analogy, predict how efficiently the drug particles would de-aggregate from the same carrier particles. We will now attempt to do this using PSD data for the same LH200 blends. Fig. 4 shows the PSDs averaged over the entire aerosolisation. We can see that the greater the volume of fine material in the blend, the greater the volume of aerosolised fine material. The addition of 10 wt% fines to LH200 decreased the Dv(10) by ~8 μm averaged over the entire aerosolisation. However, to determine the precise relationship between added fines and aerosolised fines, the PSD data has been averaged over the three repeats in Fig. 5. These plots of aerosolised “vol% < 5 μm” and “vol% < 10 μm” against “wt% fines in the blend” are not linear, but have a decreasing gradient. This means that when extra fines are added to the carrier particles, not all of these fines will be detected during the aerosolisation. Although LH200 (10 wt% fines) releases the greatest volume of fine particles, it is the least efficient at releasing fine particles. So, if 1 wt% fines are added to LH200, then these particles loosely attach to the carrier surface and are easily de-agglomerated upon aerosolisation. However, when 5 wt% or more fines are added, a smaller proportion becomes de-agglomerated. Although the addition of fines will lead to more collisions during entrainment, it appears that the additional fine particles are more strongly bound so that it is harder for them to de-agglomerate. At first this would appear to disagree with the data of Zeng et al. (2001a) who found that when fines are added to a carrier the high-energy, strongest bonding sites on the surface of the carrier particles are filled first. However, when fine particles are added to a blend, in addition to attaching to the carrier particle surfaces, they form agglomerates of fines which, if they do not break apart when aerosolised, will not be
In this section, three different lactose grades (LH200, ML001 and SV003) are assessed for their potential as carrier particles using the same techniques described above. The transmission profiles with time are given in Fig. 6 and the flowabilities of the lactose grades are given in Table 2. Table 2 also gives the variation of aerosolised “vol% < 5 μm” with an increasing proportion of fine particles in the blend, which will be used to determine how efficiently micronised particles de-aggregate from the carriers.

In Fig. 6, each transmission profile shows a step shape in the Dv(50) and Dv(90) corresponding to the trough seen in the transmission curve, allowing us to determine the method of entrainment as discussed in Section 3.1. The steps are subtle for SV003 (with only a 20 μm difference between high and low) since this grade has a narrow PSD, and thus all the particles are of a similar size. Additionally, the Dv(50) and Dv(90) for SV003 start high because there are no de-aggregated fines. When 10 wt% fines are added to SV003, the Dv(10) is initially high (30 μm), but then drops to 10 μm for the second half of the transmission trough. This is because when the first fines are added they “valley fill” the SV003 particles, and thus they do not de-aggregate easily during the aerosolisation.

We have already discussed that LH200 entrains via a mild fracture tendency to erosion mechanism. Pure SV003 powder shows a similar transmission curve and since it contains a low fraction of fines and has a high flowability, the single shallow, broad trough is likely to represent the erosion mechanism. Pure ML001, however, has an extremely broad trough with three minima that take in total ∼0.3 s to entrain. Since ML001 has the highest vol% of fine material (Fig. 1 and Table 2), which will give it a high cohesivity due to strong interparticulate forces (and hence the poorest flowability), we would expect this powder to entrain by the fracture mechanism. The presence of three minima suggests that three plugs are entrained, and the broadeness of the trough is likely to be due to the powder sticking to the sides of the powder reservoir, delaying its release.

When 10 wt% fines are added to the carrier particles, for every example the entrainment becomes a more severe fracture mechanism due to increased powder cohesivity (Fig. 6). LH200 changes from erosion/multiple small plugs to entrainment as a single plug. SV003 changes from erosion/multiple small plugs to fracture as two plugs. ML001 changes from fracture with three plugs to fracture with two plugs. Since LH200 (10 wt% fines) entrains as a single plug it is the most cohesive powder. Both SV003 and ML001 take a greater amount of time to entrain when 10 wt% fines are added because the secondary plugs adhere to the insides and bottom of the powder reservoir, which delays their entrainment. Whether a cohesive powder entrains as a single plug or as two plugs with a delay may depend upon the relative forces of powder cohesion and adhesion with the pocket.

If we compare the “vol% < 5 μm” before the addition of fines in Table 2, we see that the most fines are aerosolised from ML001.
Fig. 6. Time profiles for LH200, ML001, SV003, and the same grades with 10 wt% fines, showing transmission, Dv(10), Dv(50) and Dv(90).
then LH200, then SV003. This is in agreement with the volume of fines that make up the powder blend (Fig. 1). With added fines the “vol% < 5 μm” increased by 5% for LH200, whereas it only increased by half that for ML001. This result would suggest that when additional fine particles are added to LH200, they are more freely available to be aerosolised than those added to ML001. We noted above that fine particles in the form of agglomerates are less likely to disperse than fine particles attached to carrier particles. So, if lactose fines can be considered analogous to fine drug particles, to allow the release of a greater volume of micronised drug we do not want agglomerates in the blend, and thus LH200 is a better blend for inhalation properties than ML001. If we now look at the data in Table 2 for SV003, a grade with no loose fine particles and therefore no fine particle agglomerates, we see that this grade too shows a greater increase in “vol% < 5 μm” than ML001 when 10 wt% fines are added. This is further evidence that fine particle agglomerates have a negative effect on the release of micronised particles from an inhalation blend.

4. Conclusions

In conclusion, we have shown how data obtained from a laser diffraction particle size analyser can be used to provide information about the entrainment mechanism of an inhalation powder. Applied to specific example formulations, we have seen that as the wt% of fines in a carrier particle grade (whether added to make a ternary blend or fines already in the carrier grade) increases, the transmission profile shows a series of large plugs rather than a single broad trough, due to the fracture mechanism becoming more severe. Ultimately, at high fine particle concentrations, the powder may entrain in <0.1 s as a single plug. Alternatively, the powder may stick to the sides and bottom of the powder container, which will delay its release. Although a more severe fracture mechanism is desirable to increase the likelihood of interparticulate collisions, this comes at the cost of poorer powder handleability and a decreasing efficiency in the release of fine particles, potentially because fines are released more easily from carrier particle surfaces than from agglomerates of fine particles.

Acknowledgements

The authors are grateful to Patrick McGarry for conducting the shear cell experiments, and to Pfizer Inc. for financial support. They would also like to acknowledge helpful discussions with Claire Scruton, Valerie Diart and Imogen Gill.

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