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Entrainment of lactose inhalation powders: A study using laser diffraction

C.P. Watling, J.A. Elliott, R.E. Cameron*

Pfizer Institute for Pharmaceutical Materials Science, Department of Materials Science and Metallurgy, University of Cambridge, Pembroke Street, CB2 3QZ, UK

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ABSTRACT

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.

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

* Corresponding author. Tel.: +44 1223 334324.
E-mail address: rec11@cam.ac.uk (R.E. Cameron).

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Table 1
Particle shape descriptors (calculated from scanning electron microscopy images) and volume mean diameters (from dry laser diffraction in a Spraytec with an air flow of 80 l min^{-1}, calculated for equivalent volume spheres) for lactose inhalation grades and micronised fines. Elongation ratio = length/breadth, circularity = circumference of an equivalent area circle/perimeter of the particle.

Grade name	Qualitative description	Mean elongation ratio	Mean circularity	Volume median diameter/μm
LH200	Angular	1.7	0.67	66
ML001	Angular	1.6	0.64	40
SV003	Angular	1.7	0.63	56
Micronised fines	Angular	1.3	0.64	4.1

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). Respitose® 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 (predominately 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.

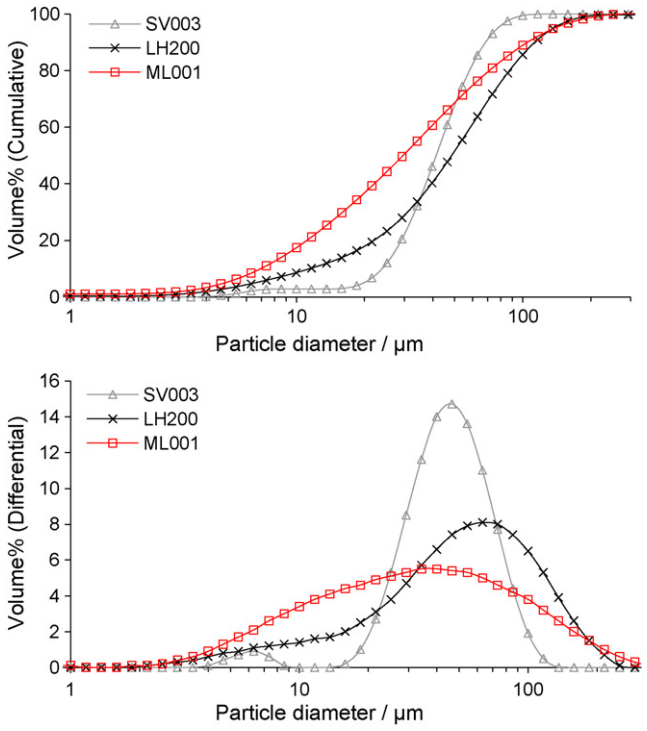

Fig. 1. Particle size distributions for lactose inhalation grades measured by dry laser diffraction in a Spraytec with an air flow of 80 l min^{-1}, calculated for equivalent volume spheres.