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Effect of carrier particle shape on dry powder inhaler performance

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ABSTRACT

The aim of this study was to characterise the aerosolisation properties of salbutamol sulphate (SS) from dry powder inhaler (DPI) formulations containing different carrier products. The difference in the elongation ratio (ER) of the different carriers was highlighted. Different set of carriers, namely commercial mannitol (CM), commercial lactose (CL), cooling crystallised mannitol (CCM), acetone crystallised mannitol (ACM) and ethanol crystallised mannitol (ECM) were used and inspected in terms of size, shape, density, crystal form, flowability, and *in vitro* aerosolisation performance using Multi Stage Liquid Impinger (MSLI) and Aerolizer® inhaler device. Solid-state and morphological characterization showed that CM product was in pure β-form having particles with smaller ER (CM: ER = 1.62 ± 0.04) whereas ACM and ECM mannitol particles were in pure α form with higher ER (ACM: ER = 4.83 ± 0.18, ECM: ER = 5.89 ± 0.19). CCM product crystallised as mixtures of β-form and δ-form and showed the largest variability in terms of particle shape, size, and DPI performance. Linear relationships were established showing that carrier products with higher ER have smaller bulk density (D_b), smaller tap density (D_t), higher porosity (P), and poorer flow properties. *In vitro* aerosolisation assessments showed that the higher the ER of the carrier particles the greater the amounts of SS delivered to lower airway regions indicating enhanced DPI performance. Yet, DPI performance enhancement by increasing carrier ER reached a "limit" as increasing carrier ER from 4.83 ± 0.18 (ACM) to 5.89 ± 0.19 (ECM) did not significantly alter fine particle fraction (FPF) of SS. Also, carrier particles with higher ER were disadvantageous in terms of higher amounts of SS remained in inhaler device (drug loss) and deposited on throat. Linear relationship was established (r^2 = 0.87) showing that the higher the carrier ER the lower the drug emission (EM) upon inhalation. Moreover, poorer flowability for carrier products with higher ER is disadvantageous in terms of DPI formulation dose metering and processing on handling scale. In conclusion, despite that using carrier particles with higher ER can considerably increase the amounts of drug delivered to lower airway regions; this enhancement is restricted to certain point. Also, other limitations should be taken into account including higher drug loss and poorer flowability.

1. Introduction

Efficient drug delivery to the lungs through dry powder inhalers (DPIs) is dependent on several factors including inhaler device, formulation, and inhalation manoeuvre. Preparing ideal DPI formulations requires control overall formulation characteristics at particulate and bulk level to ensure the drug delivery to lower airway regions (Malcolmson and Embleton, 1998; Heyder et al., 1986). In DPI formulations, it is customary to blend micronized drug particles (less than 5 μn in size) with larger carrier particles to address flowability and dose variability issues (Telko and Hickey, 2005; Feeley et al., 1998). The typical concentration of drug in drug–carrier DPI formulations is low (e.g. 1 drug: 67.5 carrier) (Timsina et al., 1994) as in the case of Ventolin Rotocaps® (Glaxo) and cyclohaler® (Pharbita). Therefore, during drug–carrier mixing, drug particles will preferably adhere to the active binding sites (more adhesive areas (Hersey, 1975)) on the carrier surface and expected to separate from carrier surface upon inhalation. Drug re-dispersion is considered most important for getting drug particles into deep lung airway regions (Zeng et al., 2000). Usually, only small amounts of drug reaches the lower airway regions due to strong drug–carrier adhesion (Young et al., 2005). Indeed, drug re-dispersion is a function of balance between cohesive forces (between the drug particles) and the adhesive forces (between drug and carrier particles) (Frijlink and De Boer, 2004). In order to aerosolise drug particles, patient inspiratory force should overcome drug–carrier adhesive forces which are dependent on physicochemical properties of both drug

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particles and carrier particles (Prime et al., 1997; Berard et al., 2002; Ferron, 1994). Consequently, the characteristics of carrier particles must be well-controlled in terms of size, morphology, crystal form, surface energy, etc. It has been reported that the differences in carrier particle size is likely to have significant impact on DPI aerosolisation performance (Steckel and Müller, 1997). The presence of fine particles on carrier surface may decrease the drug–carrier contact area and consequently drug–carrier adhesion forces leading to improved DPI performance (Louey et al., 2003). Better aerosolisation performance was observed when the carrier tap density was higher (Kaialy et al., 2011a), whereas no correlation was found between carrier flowability and DPI performance (Kaialy et al., 2011b; Louey and Stewart, 2002). Carriers with reduced dispersive surface energy produced higher fine particle fraction (FPF) of the drug upon aerosolisation (Sethuraman and Hickey, 2002). Carrier particles with higher elongation ratio (Hamishehkar et al., 2010) or increased surface roughness (Kaialy et al., in press) showed favorable inhalation properties.

In this paper, in order to improve the understanding of the effect of carrier physical properties on DPI performance, the influence of using carrier particles with considerably different morphologies on the content uniformity and inhalation behaviour of a model drug (salbutamol sulphate) from Aerolizer® DPI inhaler device were investigated.

2. Materials and methods

2.1. Materials

Micronized Salbutamol Sulphate (LB Bohle, Germany) was employed as a model drug ($d_{50\%}$ = 1.8 ± 0.3 μm). Mannitol, acetone, and absolute ethanol were supplied from Fisher Scientific, UK. Lactose was obtained from DMV International, Netherlands.

2.2. Preparing of different carrier products

Five different carrier powders were investigated including commercial mannitol (CM), commercial lactose (CL), cooling crystallised mannitol (CCM), acetone crystallised mannitol (ACM) and ethanol crystallised mannitol (ECM). CM and CL and were used as received from suppliers. CCM product was prepared as follows: 5 g of mannitol was dissolved in 25 mL deionised water to prepare 20% saturated solution of mannitol under heating (40 °C) and stirring (250 rpm). Once prepared, mannitol saturated solution was removed from heating and left uncovered in ambient conditions (22 °C, 50% RH) for 96 h. After that, CCM particles were collected by spatula and transferred to watch glass for further drying. The watch glass containing CCM particles were left to dry in drying oven for 24 h at 80 °C after which they were transferred to glass vials and sealed until required. The yield was 97.60% for this sample. ACM (Kaialy et al., 2010a) and ECM (Kaialy et al., 2010b) were prepared using the published methods. DSC traces showed that no water was associated with mannitol crystallised samples after drying (figures not shown).

The reproducibility of the crystallization technique for crystallised mannitol powder was tested by making 3 batches. Analysis on each specific batch demonstrated that, when stored at ambient conditions (22 °C, 50% RH); solid state, size, and aerosolisation performance was not significantly influenced.

2.3. Sieving

In order to limit the effect of carrier particle size, all carrier powders were sieved to separate particles in geometric size fractions of 63–90 μm (Bell et al., 2006; Byron and Jashnam, 1990; Steckel et al., 2004). These size fractions were obtained after mechanical sieving by pouring each carrier powder onto the top of 90 μm sieve which was placed above 63 μm sieve. The sieve shaker (Retsch® Gmbh Test Sieve, Germany) was then operated for 15 min. After the sieving process was complete, the particles retained on the 63 μm sieve were collected and stored in sealed glass vials until required for further investigation. All investigations described below on carriers were performed on the 63–90 μm size fractions.

2.4. Image analysis using optical microscopy

Dynamic shape analysis was employed to assess particle shape of different carriers using image analysis software (designed in-house at King's College, London) installed on an Archimedes computer attached to an optical microscope (Nikon Labophot, Tokyo, Japan) via a miniature video camera). For each carrier sample, a micro-spatula was used to sample about 20 mg of powder and then finger tapped until the powder was homogeneously scattered onto a microscopic slide. For each sample, one hundred particles were selected from different positions and measured. Particle elongation ratio (ER) and roundness (RO) were calculated using Eqs. (1) and (2) respectively:

$$\mathrm{ER} = \frac{\text{Maximum feret diameter}}{\text{Minimum feret diameter}} \quad (1)$$

$$RO = \frac{(\text{Perimeter})^2}{4 \times \pi \times \text{area}} \quad (2)$$

where the minimum and maximum Feret diameters were calculated from 16 calliper measurements at 6° intervals around the particle and "area" in Eq. (2) is the area occupied by particle images.

2.5. Scanning electron microscope (SEM)

Electron micrographs of all carrier samples were obtained using a scanning electron microscope (Philips XL 20, Eindhoven, Netherlands) operated at 15 kV. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation.

2.6. Particle size measurements

Particle size analyses were conducted by Sympatec laser diffraction particle size analyser (Clausthal-Zellerfeld, Germany) as described in details elsewhere (Kaialy et al., 2010b).

2.7. True density assessments

Ultrapycnometer 1000 (Quantachrom, USA) was employed to assess true density of salbutamol sulphate and all carrier samples under helium gas. The input gas pressure was 19 psi and the equilibrium time was 1 min.

2.8. Powder flow and porosity assessment

Bulk density (D_b) and tap density (D_t) of all carrier powders were measured as descriptors of bulk powder cohesive properties. Each carrier powder was filled in 5 mL measuring cylinder and then after recording the volume (bulk volume) the cylinder was tapped 100 times and the new volume was recorded (tapped volume). A preliminary experiment showed that 100 taps (n = 100) was sufficient to attain the maximum reduction in the volume of powder bed. D_b and D_t were calculated as powder weight over powder bulk volume (n = 0) and tap volume (n = 100) respectively. Flowability of each carrier powder was estimated by Carr's compressibility index (CI) and Hausner ratio (H) calculated using Eqs. (3) and (4) (Carr,