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Rapid characterisation of the inherent dispersibility of respirable powders using dry dispersion laser diffraction

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ABSTRACT

Understanding and controlling powder de-agglomeration is of great importance in the development of dry powder inhaler (DPI) products. Dry dispersion laser diffraction measures particle size readily under controlled dispersing conditions, but has not been exploited fully to characterise inherent powder dispersibility. The aim of the study was to utilise particle size-dispersing pressure titration curves to characterise powder cohesivity and ease of de-agglomeration. Seven inhaled drug/excipient powders (beclometasone dipropionate, budesonide, fluticasone propionate, lactohale 300, salbutamol base, salmeterol xinafoate and tofimilast) were subjected to a range of dispersing pressures (0.2–4.5 Bar) in the Sympatec HELOS/RODOS laser diffractometer and particle size measurements were recorded. Particle size-primary pressure data were used to determine the pressures required for complete de-agglomeration. The latter were employed as an index of the cohesive strength of the powder (critical primary pressure; CPP), and the curves were modelled empirically to derive the pressure required for 50% de-agglomeration (DA_{50}). The powders presented a range of CPP (1.0–3.5 Bar) and DA_{50} (0.23–1.45 Bar) which appeared to be characteristic for different mechanisms of powder de-agglomeration. This approach has utility as a rapid pre-formulation tool to measure inherent powder dispersibility, in order to direct the development strategy of DPI products.

1. Introduction

Drug deposition within the respiratory tract is dependent on the delivery of particles with an aerodynamic size of <5 μm (Shekunov et al., 2003; Usmani et al., 2005). The intrinsic cohesivity of such fine and often irregularly shaped particles means that there is a tendency for particles to agglomerate (Adi et al., 2011). Micronised drug particles are therefore often formulated with large carrier particles as a means of aiding powder dispersion (Telko and Hickey, 2005). During delivery it is essential that attractive drug–drug (cohesive) and drug–carrier (adhesive) forces are overcome and particles are restored to their primary de-agglomerated state (Telko and Hickey, 2005). Although device and patient factors affect de-agglomeration, the inherent dispersibility of the powder is a major factor dictating the ease of agglomerate dispersal and hence the delivered dose. Any imbalance of the cohesive and adhesive forces may adversely affect de-agglomeration, resulting in poor aerosolisation of the powder formulation (Begat et al., 2004b).

The ease of de-agglomeration of powders may be predicted using indirect methods that measure inter-particulate forces. These include highly technical single-particle techniques such as atomic force microscopy (AFM) (Jones et al., 2008; Begat et al., 2004a) and bulk techniques such as inverse gas chromatography (IGC) (Das et al., 2009c; Jones et al., 2012; Tong et al., 2006). AFM only measures a small proportion of the powder and provides potentially poor representation of bulk properties (Bunker et al., 2005), while IGC requires large quantities of material and long analysis times. Specially designed de-agglomeration rigs allow agglomerate break-up to be studied under controlled levels of turbulence or impaction, but need to be used in tandem with a particle size spectrometer or cascade impactor (Kurkela et al., 2008; Voss and Finlay, 2002). Impactor methods measure aerosol dispersion directly; the emitted dose provides an index of powder entrainment, and the fine particle mass is indicative of de-agglomeration efficiency (Louey et al., 2006). Although impactor methods are excellent for the quality control testing of inhalation products, the analytical procedures involved are labour-intensive and time consuming, making the methods unsuitable for rapid screening of powder formulation dispersibility during the early stages of product development (Marriott et al., 2006).

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Dry dispersion laser diffraction (LD) is increasingly used to study powder de-agglomeration. When powder is delivered to the sizer from a static bed, the powder is subjected to minimal disturbance to the powder structure and an assessment of inherent dispersibility can be made. Pressure titration, whereby size measurements are made under different levels of dispersing shear, is a requirement of method development for LD particle sizing in the dry state to define those instrument parameters that provide accuracy and precision of sizing measurements (ISO 13320: 1990). Under well-controlled dispersing conditions, changes in the measured particle size distribution (PSD) of an aerosolised plume provide an indication of agglomerate strength and degree of de-agglomeration (Adi et al., 2006; Ghoroi et al., 2012). Despite never having been substantiated in a systematic study of pharmaceutical powders, the gradient of measured particle size over a dispersion pressure/airflow range has been suggested as an indicator of powder dispersibility (Adi et al., 2006, 2008; Chiou et al., 2008; Ghoroi et al., 2012; Kaye et al., 2009). Titration experiments have been conducted for this purpose, but studies have not been validated using a wide range of sample powders nor have they involved the generation of standardised parameters for describing de-agglomeration. Where titration data have been related more fully to aerosolisation parameters (e.g. Behara et al., 2011a,b; Chiou et al., 2008) the studies have determined the particle size of the powders following actuation from either inhaler devices or dry powder dispersers, which contribute themselves to the de-agglomeration of the powder under investigation. During the early stages of inhaled product development, information is required about the fundamental dispersion behaviour of the drug powder in order to guide formulation and device designs. If dry dispersion LD were qualified as a technique for measuring particle size-dispersing pressure curves in a systematic manner, for powders delivered from a static bed, this would allow the inherent dispersibility of dry powders to be assessed reliably in the absence of device/disperser effects.

The aim of this work was to develop a rapid method to quantify the de-agglomeration of dry powders from a static bed as a measure of inherent powder dispersibility. An optimised methodology based on LD was developed, standardised and used to measure particle size-dispersing pressure titration curves for a number of inhaled drug/excipient powders. These data were used to derive parameters indicative of powder cohesivity and ease of de-agglomeration.

2. Materials and methods

2.1. Materials

The inhalation powders used in the study were beclometasone dipropionate (BDP; Pharm Dev Europe, GWRD, BN. WC60329), budesonide (Bud; LGM Pharma, USA, BN. U0015/1V040), fluticasone propionate (FP; LGM Pharma, USA, BN. 458763), Lactohale 300 (LH300; Frieslands Foods, Domo, The Netherlands, BN. 6125224/S), salbutamol base (SB; Pharm Dev Europe, GWRD, BN. WC46269), salmeterol xinafoate (SX; Vamsi Labs, India, BN. SX-0081010), and tofimilast (Tof; Pfizer Ltd, PGRD Sandwich Laboratories, UK). Cyclohexane was purchased from VWR International (France), methanol and sorbitan monooleate 80 (Span 80) were from Sigma Aldrich Ltd (UK), hexane was from Fisher Scientific (Loughborough, UK), and Span 85 and Tween 80 were from Merck (Schuchardt, Germany).

2.2. Methods

2.2.1. Particle size measurements by liquid dispersion laser diffraction

Laser diffraction particle sizing was carried out using a Malvern Mastersizer X (Malvern Instruments Ltd, UK) fitted with a 100 mm focal length lens (0.5–180 μm) and an MS7 magnetically stirred cell. Saturated solvent dispersants were prepared by sonicating for 30 min followed by overnight stirring. Approximately 1 mg of powder was added to 2 mL filtered dispersant (0.2 μm cellulose acetate syringe filter, Gema Medical S.L., Spain) and sonicated (Sonicleaner, DAWE, Ultrasonics Ltd, USA). A background reading was taken and the suspension was added to the sample cell until the obscuration was ~10–30%. Following equilibration (30–60 s), ten individual measurements were taken for $n = 3$ samples to obtain particle size measurements (D_{v10}, D_{v50}, and D_{v90}, corresponding to the particle size below which 10%, 50% and 90% of the particles by volume are smaller than, and the volume mean diameter, VMD, the volume weighted mean particle size of the sample) calculated using Fraunhofer theory. A summary of the dispersant, sonication time, stir setting, sweeps, presentation and equilibration time used to size each powder are provided in Table 1.

2.2.2. Scanning electron microscopy (SEM)

Powder samples were transferred onto glass cover-slips placed on adhesive carbon tabs (G3347N, Agar Scientific, Essex, England) which were mounted onto aluminium pin stubs (0.5 in.; G301, Agar Scientific Ltd, Essex, England). Samples were sputter coated with gold for 2 min to achieve a thickness of approx. 15–20 nm using a K550X sputter coater (Emitech, Quorum Technologies Limited, West Sussex, England). Particle morphology was viewed using a Quanta 200F field emission scanning electron microscope (FEI UK Ltd, Cambridge, England) operated at 10 kV in low vacuum mode and a working distance of 10 mm.

2.2.3. Particle size measurements by dry dispersion laser diffraction

Particle size measurements were made using a Sympatec HELOS/RODOS (Sympatec GmbH, Clausthal-Zellerfel, Germany) employing the rotary feeder and R3 lens (0.9–175 μm). Powder was hand-filled into the u-shaped groove of the rotating table to cover a length of approximately 1 cm. The sample passed under a plough scraper and roller to remove any excess and was subsequently drawn up into the dispersing line via the protruding aspiration tube from a static bed. During sample delivery the rotating table was maintained at a constant rotation setting of 20%. The measurement was set to trigger when the optical concentration (C_{opt}) exceeded 1.1% and cease when the C_{opt} fell below 1% for 5 s (or 60 s real time). The timebase was 100 ms and a forced stability of '4' was applied. The primary pressure (PP) was manually set using the adjustment valve in the range 0.2–4.5 Bar and three measurements were taken at each pressure setting using freshly loaded powder. PSDs (D_{v10}, D_{v50}, D_{v90} and VMD) were calculated using Fraunhofer theory and analysed in WINDOX 4.0 software. Particle size measurements for a complete titration curve were made on a single day.

2.2.4. Critical primary pressure

The pressure at which the particle size-primary pressure profile reached a plateau was considered to represent the pressure required to overcome the interactive forces holding agglomerates together and therefore provide a measure of the cohesivity of the powder. The critical primary pressure (CPP) was derived by calculating a difference ratio (d_r) using Eq. (1), where the D_{v50} is the geometric median diameter at a given primary pressure (mean of $n = 3$ measurements), and PP1 and PP2 are two consecutive primary pressures (PP2 > PP1). The CPP was assigned when d_r was in the range $-0.06 < d_r > 0.06$ for three consecutive measurements (the accepted coefficient of variance for D_{v50} values in particles of this