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Novel alternatives to reduce powder retention in the dry powder inhaler during aerosolization

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ABSTRACT

Dry powder inhalers (DPIs) are used predominantly for the treatment of pulmonary diseases by delivering drugs directly into the lungs. The drug delivery efficiency is typically low and there is significant drug retention inside the DPI. An innovative 'green' initiative aimed at minimizing drug wastage via channeling the residual drug into the useful inhaled therapeutic fraction was pioneered. Drug retention could be minimized via coating the drug capsule and delivery device with pharmaceutically acceptable force-control agents. This coating reduces the adhesion between the drug particles and the internal surfaces of the DPI, which in turn increases the fine particle dose by as much as 300%.

1. Introduction

Many global pharmaceutical companies today are encouraged to adopt 'green' initiatives into their research and development (R&D) and manufacturing activities (Butters et al., 2006; Jimenez-Gonzalez et al., 2011). This is driven by the need to not only lower costs and improve productivity, quality and control, but also to create an overall awareness of sustainability to the manufacturing process. The key aim is to deliver medicines to the patient with minimal environmental impact (Jimenez-Gonzalez et al., 2011).

Although the ubiquitous dry powder inhaler (DPI) is a much greener alternative over the metered dose inhaler (MDI) in terms of stability and avoidance of ozone-depleting and global warming propellants (Fischer et al., 1989; Ibiapina et al., 2004; Leach, 2005), its delivery efficiency is not high and in some cases, only 10% of the inhaled dose reaches the lung (Timsina et al., 1994). Therefore, there is a growing need to enhance and improve upon the performance of today's devices and formulations (Smith et al., 2010; Weers et al., 2010) from both an efficacy and cost-containment standpoint (i.e. drug wastage leads to economic loss (Fasola et al., 2008; Gillerman and Browning, 2000; Herold and Hieke, 2003)).

Capsule-based DPIs can be limited by powder retention in the capsule and device, which leads to a reduction in the emitted dose (Steckel and Muller, 1997; Vidgren et al., 1988). Although the fraction of drug remaining in the mouthpiece is generally between 13–20% (determined via in vitro aerosolization tests), in some inhalers, it could be nearly 30–50% (Hu et al., 2008; Kwok et al., 2011; Steckel and Muller, 1997; Tajber et al., 2009). In an in vivo setting (Vidgren et al., 1988), inhaler retention of around 15–60% of the administered drug had been reported.

As the pharmaceutical industry embraces nanotechnology (Chan and Kwok, 2011; Chiou et al., 2008; Chow et al., 2007; Heng et al., 2008a,b, 2011, 2009; Kwok et al., 2011; Tsapis et al., 2002) to improve drug delivery and bioavailability, novel developments or inroads have to be made to adequately exploit the full benefits of nanomedicine to inhalation aerosol therapy. Currently, there are publications indicating inhaler retention as a significant barrier towards more effective utilization of nanoparticles (Hu et al.,

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2008; Kwok et al., 2011). Capsule and device retention of as high as 40–50% were previously reported for budesonide (Hu et al., 2008) and lysozyme nanoagglomerates (Kwok et al., 2011). Furthermore, in an age of increasing combination therapy development (Chan et al., 2012; Kumon et al., 2010; Lee et al., 2012; Tajber et al., 2009; Traini et al., 2012; Wertheimer and Morrison, 2002), drug retention at the inhaler continues to be a factor plaguing the performance of these novel inhalers (Tajber et al., 2009; Traini et al., 2012). A high inhaler retention of ≥58% was previously reported for an asthma combination formulation (Tajber et al., 2009; Traini et al., 2012).

In view of the wide-ranging deficiencies, this work seeks to explore 'greener' solutions by minimizing drug wastage, and to channel the residual drug into the useful inhaled therapeutic fraction. This would aid the performance enhancement of DPIs, as the device had previously been shown to be a key limiting factor in optimization studies (Heng et al., 2012). Currently, there has been a lot of 'downstream' work focused on improving dispersion and deaggregation of drug powders via carriers and/or fines (Tee et al., 2000; Zeng et al., 2000, 1998) with little attention paid to the 'upstream' mechanics. This work seeks to improve drug retention at the inhaler device and capsule region.

It is well-known that force control agents (e.g. fatty acid derivatives such as magnesium stearate, amino acids such as leucine and phospholipids such as lecithin) (Begat et al., 2008), traditionally used only as surface coatings for powders, would help to improve aerosol dispersion (Tay et al., 2010). These force control agents typically exhibit anti-adherent and/or anti-friction properties (Begat et al., 2008) and had previously been applied to the coating of lactose carriers (Guchardi et al., 2008; Kumon et al., 2008, 2006; Young et al., 2002) and active pharmaceutical ingredients (API) (Boraey et al., 2012; Lahde et al., 2008; Raula et al., 2008, 2009; Swaminathan and Kildsig, 2002; Zhou et al., 2010).

In this work, magnesium stearate (MgSt), a commonly-used force control agent, was innovatively applied to the surfaces of the DPI device and capsule to minimize drug retention and increase the therapeutic fraction entering the lungs. The extent of powder emptying from an inhaler is closely related to the emitted dose (Behara et al., 2011). Turbulent skin friction drag reduction by 'additives' (Bushnell and Moore, 1991; Roy and Larson, 2005) (e.g. bubbles, polymers, lubricants, surfactants, slag powder) has potential applications in the throughput enhancements of oil and natural resource processing pipelines (Abdul Bari et al., 2012, 2009), in increased aircraft, ship or surfboard speeds (Bushnell and Moore, 1991) and in fire fighting (Chen et al., 1998). In the natural world, this phenomenon is evident in the movement of Avians and Nektons (i.e. fliers and swimmers) in fluids (Bushnell and Moore, 1991). For example, drag-reducing surfactants (e.g. lipids, phospholipids, lipoproteins) are known to be a constituent of fish slime (Bushnell and Moore, 1991).

In the present work, spray-dried lysozyme was used as the model adhesive protein powder (Kwok et al., 2011). Two model capsule-based DPIs: the Rotahaler® – low efficiency and low resistance (GlaxoSmithKline, UK) and the Aerolizer® – high efficiency and medium/low resistance (Novartis, Switzerland) (Clark and Hollingworth, 1993), with different mechanisms of powder emptying (rattling/oscillating and spinning respectively) (Behara et al., 2011) and flow patterns (Coates et al., 2004), were investigated.

2. Materials and methods

2.1. Materials

The Aerolizer® and Rotahaler® dry powder inhalers were manufactured by Novartis® and GlaxoSmithKline® respectively. Lyophilized hen-egg white lysozyme and magnesium stearate were purchased from Sigma–Aldrich Co. LLC (Louis, MO, USA). Ultrapure water was used in the experiments.

Table 1
Spray drying parameters.

Parameters	
Spray mesh size (μm)	5.5
Feed concentration (w/v %)	0.75
Nitrogen flow rate (L/min)	120
Relative spray rate (mL/h)	4
Inlet Temperature (°C)	120
Outlet Temperature (°C)	40–45
Yield (%)	70–80

2.2. Preparation of spray-dried powder

Lysozyme powder was obtained by spray drying an aqueous solution of the protein on a B-90 Nano Spray Dryer (Büchi Labortechnik AG, Flawil, Switzerland) (Heng et al., 2011; Lee et al., 2011) with operating parameters as detailed in Table 1. All solutions were filtered through a 0.45 μm syringe filter (Millipore, Bedford, MA, USA) prior to spray-drying to minimize blockage due to any undissolved particles at the spray mesh. The spray-dried powder was collected from the particle collecting electrode using a particle scraper and then stored in a desiccator at room temperature for further characterization.

2.3. Scanning electron microscope (SEM) imaging

Powder samples were mounted onto metal sample stubs and coated with gold. The samples were then examined under a high resolution field emission scanning electron microscope (Jeol JSM 6700, Japan) at 10 kV.

2.4. Energy dispersive X-ray (EDX) spectroscopy

EDX analysis was carried out at 20 kV on a high resolution field emission scanning electron microscope (Jeol JSM 6700, Japan) coupled with an energy dispersive X-ray detector (Oxford Instruments, UK).

2.5. Particle size determination

The particle size distribution of spray-dried lysozyme was measured by laser diffraction on the Malvern Mastersizer 2000 (Malvern Instruments, UK) using the Scirocco dry dispersion unit. The powders were dispersed in triplicates at 3 bars of pressure using refractive index (RI) of 1.445 for lysozyme.

2.6. Coating methodology

The inhalers and capsules were coated with ethanol-based magnesium stearate suspensions (0.05–0.3 g/ml) via painting and dipping respectively and left to dry in a desiccator at room temperature for at least an hour before usage.

2.7. Dispersion methodology

Dispersion behaviour of the powder was assessed using either a Rotahaler® (GlaxoSmithKline, UK) or an Aerolizer® (Novartis, Switzerland) coupled through a USP stainless steel throat to a multi-stage liquid impinger (MSLI, Copley, UK), operating at 60 L/min. Approximately 15 mg of powder was filled into a hydroxypropyl methylcellulose (HPMC) capsule (size 3, Capsugel®, USA), loaded into the inhaler and then dispersed through the in vitro testing system. The test was performed in triplicate to obtain