Aerosol Performance of Large Drug-Coated Beads across Multiple Inhalation Flow Rates

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INTRODUCTION

- Dry powder inhaler (DPI) formulations are generally binary mixtures of micronized API (1 - 5 μm) and a population of coarse (~ 50 – 100 μm) lactose particles comprising the bulk of the formulation. The larger lactose carrier particles assist in dose metering and entrainment by the flow stream during inhalation, but detachment of drug from the carriers remains inefficient, and generally < 30% of the nominal dose reaches the deep lung [1 - 3].
- To improve the efficiency of pulmonary drug delivery, a novel powder dispersion mechanism was developed incorporating a single, large (> 1 mm) carrier particle coated with pure micronized API. For these studies, the large carrier particle was a low-density polystyrene bead approximately 5.2 mm in diameter. When placed in the dispersion chamber of the Handihaler®, the drug-coated polystyrene beads oscillate rapidly, (Fig. 1), generating detachment forces that are sufficient in magnitude to liberate the drug from the bead surface and emit it from the device.
- The purpose of the present study was to assess the performance of drug-coated polystyrene beads at multiple inhalation flow rates and compare the results against traditional binary blends prepared with lactose carrier particles.

MATERIALS AND METHODS

- **Materials:** Budesonide and salbutamol were purchased in bulk (Jinhuo Chemical Co., China) and micronized using a high energy jet mill (Fluid Energy, PA, USA). Inhalation-grade lactose (Respitose® ML006) was generously provided by DMV-Fonterra (NJ, USA). Size-3 gelatin capsules were provided by Capsugel (NJ, USA). Low-density (ρ = 0.027 g/cc) polystyrene beads were obtained from Fairfield Processing Corp. (CT, USA).
- **Preparation of Binary Blends:** Micronized budesonide and salbutamol were each blended at 2% (w/w) with ML006 lactose in a Turbula® orbital mixer (Glen Mills, USA). For the polystyrene beads, 2 mg of micronized drug powder and 5.2 mm polystyrene beads were placed in vials and partially submerged in a sonicating water bath, producing a sustained aerosol plume enveloping the bead throughout the duration of the coating period. This method resulted in drug particles adhering to the bead via van der Waals interactions.
- **Imaging and Acoustic Characterization:** Images of the beads during device actuation were shot at f/22 with a 1/8 second exposure using a strobe flash (Canon Speedlite 500EX) for the solitary light source firing five times at a rate of 199 Hz. Long exposure photographs were captured at f/14 and 4 s to allow the imaging of both the beads and the capsules over the course of a normal inhalation profile. To assess the frequency of the oscillating polystyrene beads, the audible feedback signal of the bead in the Handihaler at a given flow rate was recorded and the waveform of the collected audio data visualized to measure the distance (in time) from one peak (an audio event) to the next, determining the average frequency of an audio event.
- ***In vitro* Aerosol Performance:** For each actuation, either 20 (± 1) mg of lactose binary blend, or a single drug-coated polystyrene bead was dispersed through a Handihaler® DPI, and aerosol performance was assessed using a Next Generation Impactor (NGI; MSP Corp., USA) at 15, 30, and 45 L min^{-1} . Deposited drug was collected, and drug content was analyzed with a UV-VIS spectrometer at 230 nm and 244 for salbutamol and budesonide, respectively. The respirable fraction (RF) is shown as the percent ratio of the drug mass depositing on stages 3 – 8 of the NGI over the total dose (at 30 and 45 L min^{-1}) and stages 4 – 8 (plus filter) at 15 L min^{-1}. At 15 L min^{-1} a pre-separator was not employed for the lactose formulations, and an external filter was connected downstream of the MOC [4].

RESULTS AND DISCUSSION

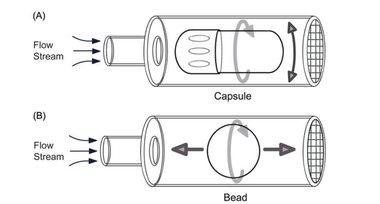

Fig. 1. Illustration depicting relative capsule and bead motions in the Handihaler. The polystyrene bead oscillates rapidly near the center of the dispersion chamber, with infrequent contact against the inner walls of the DPI. Though only a single arrow is provided depicting the rotation of the polystyrene carrier, during actuation the bead spins three dimensionally.

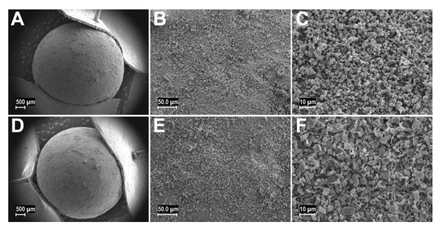

Fig 2. SEM micrographs of polystyrene beads following 2-minutes of piezo-assisted coating with either micronized (A - C) budesonide or (D – F) salbutamol. As seen in figures A and D, the double-sided tape was folded against opposite sides of the polystyrene bead and transfixed to provide adequate conduction for imaging.

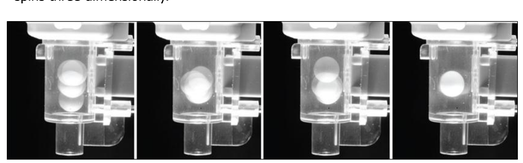

Fig 3. Image series of polystyrene bead oscillations. The images depict the oscillating motion of an uncoated, polystyrene bead in the dispersion chamber of the Handihaler at 30 L min^{-1}. The images were captured with a 1/8 second exposure using a strobe flash for the solitary light source firing five times at a rate of 199 Hz. The strobe captured the position of the polystyrene bead at five distinct locations (ca. 5 milliseconds between flashes) within the inhaler during actuation. The above images were all captured during a single, 8-second actuation period.

	Flow Rate (L min-1)		
	15	30	45
Bead Oscillations (Hz)	55	95	112

Table 1. During actuation the polystyrene beads generate a strong audible signal in the form of a loud 'rattle.' The acoustic profiles at different flow rates were measured and analyzed to assess the time between 'rattles' (the audio events) and obtain the frequency at which the beads oscillate. One audio event was assumed to represent one virtual impaction, with two impactions occurring in one full bead oscillation cycle.

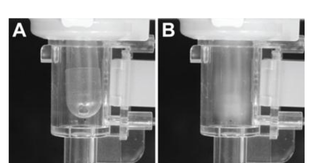

Fig. 4. Long exposure photographs of capsule and bead motion. At 15 L min^{-1} the image of the capsule (A) is not blurred because it remained stationary throughout the 4 second exposure. By contrast, the capsule at 30 L min^{-1} (B) produced a blurred image as it vibrated rapidly in the dispersion chamber. The polystyrene beads oscillated at both 15 L min^{-1} (C) and 30 L min^{-1} (D), though their respective frequencies and amplitudes differed.

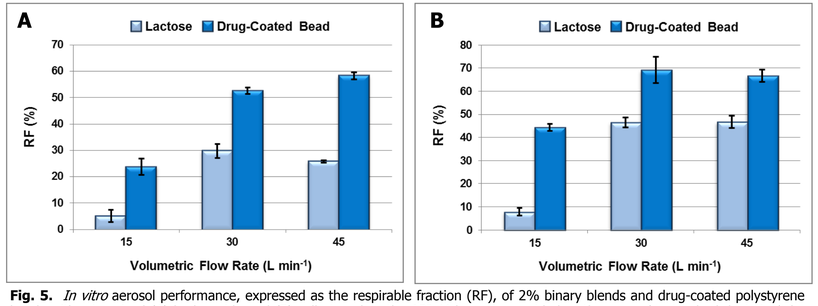

Fig. 5. *In vitro* aerosol performance, expressed as the respirable fraction (RF), of 2% binary blends and drug-coated polystyrene beads with micronized (A) budesonide and (B) salbutamol as the API. Values are provided as the mean (± standard deviation) for N = 3 replicates.

Flow Rate (L min^{-1})	Lactose Formulation			Drug-Coated Bead		
	EF (%)	*FPF (%)*	*RF (%)*	*EF (%)*	*FPF (%)*	*RF (%)*
Budesonide						
15	8.9 (4.1)	52.7 (4.3)	5.2 (2.3)	44.8 (4.6)	55.3 (1.9)	23.8 (3.0)
30	84.4 (1.9)	35.3 (4.0)	29.7 (2.7)	78.9 (2.1)	66.7 (1.6)	52.6 (1.2)
45	84.1 (2.6)	30.7 (1.4)	25.8 (0.4)	85.9 (1.5)	67.8 (2.0)	58.2 (1.3)
Salbutamol						
15	15.1 (3.8)	52.4 (7.9)	7.8 (1.6)	65.4 (2.5)	68.2 (2.7)	44.4 (1.5)
30	87.6 (1.5)	53.0 (1.7)	46.5 (2.2)	84.9 (4.1)	81.4 (2.9)	69.2 (5.7)
45	90.4 (0.4)	51.7 (2.7)	46.7 (2.6)	89.4 (3.2)	74.6 (1.3)	66.7 (2.6)

Table 2. Emitted fraction (EF), fine particle fraction (FPF) and respirable fraction (RF) of 2% lactose-based binary formulations and 5.1 mm drug-coated polystyrene beads. EF, FPF, and RF values are provided as the mean (± standard deviation) for N = 3 replicates.

- Micronized drug particles were coated onto the surface of the polystyrene beads as multiple layers comprised of loose aggregates of primary particles (Fig. 2). By coating the drug particles onto the beads via this method the formation of stable drug agglomerates is minimized, resulting in excellent FPF and RF values for both APIs at 30 and 45 L min^{-1} (Table 2).
- When a drug-coated polystyrene bead was actuated, the resistance of the Handihaler (0.144 (cmH$_2$O)$^{0.5}$ / L min^{-1}) was lower relative to the value measured when a capsule occupied the dispersion chamber (0.173 (cmH$_2$O)$^{0.5}$ / L min^{-1}).
- The bead oscillations are largely confined to the center of the dispersion chamber, exhibiting minimal physical collisions with the inhaler (Fig. 3). Accordingly, minimal contact between the drug-coated bead surface and the inner walls of the inhaler produces high EF values at 30 and 45 L min^{-1} (Table 2).
- At 15 L min^{-1}, the flow rate is insufficient to induce the capsule to vibrate, resulting in very low emission and < 10% overall deposition (Fig. 4). By contrast, the polystyrene bead oscillates with an average frequency of 55 Hz at this very low flow rate (Table 1), such that the drug-coated polystyrene beads exhibit performance comparable to the binary lactose formulations at 30 and 45 L min^{-1}.

CONCLUSIONS

- The drug-coated polystyrene beads significantly outperformed lactose-based binary formulations at all tested flow rates for both budesonide and salbutamol. The low mass of the beads allowed them to oscillate rapidly during actuation, even at flow rates where traditional lactose-based binary blends delivered from capsules ceased to be effective.

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