Novel Dual-Chamber Dry Powder Inhaler for Combination Therapy

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INTRODUCTION

- For long-term treatment of patients with moderate to severe asthma, combination inhalation therapy simultaneously delivering an inhaled corticosteroid (ICS) with a long-acting β2–agonist (LABA), is the accepted standard of care. In particular, the ADVAIR Diskus® (fluticasone/salmeterol; GlaxoSmithKline) has achieved blockbuster status, with annual sales well in excess of $1 billion. However, despite the commercial success of combination therapy inhalers, overall drug delivery remains low, with published studies reporting between 10 – 25% of the nominal dose found to be respirable *in vitro* [1 – 3].

- The objective of this study was to develop an inhaler for combination therapy based on Respira's drug-engine technology using large drug-coated, low-density polystyrene beads. A prototype inhaler was designed that incorporated dual dispersion chambers in parallel, thereby providing a moderately low resistance device that enabled two drug-coated beads (each coated with a distinct API) to be actuated simultaneously during inhalation. Additionally, the use of two beads allowed each drug to be processed and loaded separately. The *in vitro* aerosol performance of the prototype inhaler was then compared directly against the ADVAIR Diskus® at multiple inhalation flow rates.

MATERIALS AND METHODS

- **Materials:** Fluticasone propionate and salmeterol xinafoate (Kemprotec Ltd., UK) were micronized using a high energy jet mill (Fluid Energy, PA, USA). The ADVAIR Diskus®(250 mcg Fluticasone Propionate/50 mcg Salmeterol; Lot: 1ZP7529; GlaxoSmithKline, NC, USA) was purchased from a local pharmacy. Low-density polystyrene beads were generously provided by Nova Chemicals Corp. (Canada).

- **Inhaler Prototype**: A dual-chamber DPI was designed to allow two drug-coated polystyrene beads to be actuated simultaneously in parallel, where each bead is coated with pure micronized powder of either fluticasone propionate or salmeterol xinafoate. The dual-chamber DPI was designed using CAD software and developed via rapid prototyping (Harvest Technologies, TX, USA). The inhaler was designed such that the device resistance was comparable to that of the ADVAIR Diskus®. To evaluate the resistance of the ADVAIR Diskus® and the dual chamber prototype, the pressure drop (cmH_2O) across the Handihaler at multiple volumetric flow rates was measured using a digital manometer (SPER Scientific; AZ, USA). The device resistance was determined according to the method described by Clark and Hollingworth [4].

- **Drug Coating:** Micronized drug powder (2 mg) and 5.2 mm polystyrene beads were placed in vials, which were then 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.

- ***In vitro* Aerosol Performance:** Each actuation was comprised of either one dose from the ADVAIR Diskus®, or two drug-coated polystyrene beads (one coated with fluticasone propionate, the other with salmeterol xinafoate) actuated simultaneously through the prototype dual-chamber DPI. Aerosol performance was assessed using a Next Generation Impactor (NGI; MSP Corp., USA) at flow rates corresponding to a 4, 2, and 1 kPa pressure drop across each device, with actuation times adjusted to allow 4 L of air to flow through the inhaler. Deposited drug was collected by rinsing each experimental component with a mobile phase comprised of a 75:25 mixture of methanol and 0.8% (w/v) ammonium acetate buffer (pH = 5.5); drug content was analyzed via HPLC at 228 nm [1]. The FPF(emitted) is provided as the percent ratio of the drug mass depositing on stages 2 – 8 of the NGI over the total dose (at the corresponding 4 and 2 kPa flow rates) and stages 3 – 8 at the 1 kPa flow rate.

RESULTS

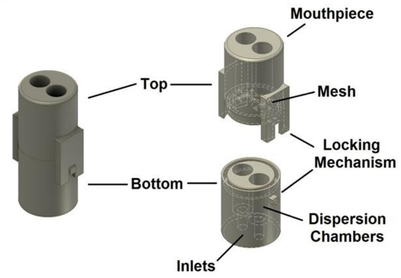

Fig. 1. Prototype inhaler for combination therapy includes dual dispersion chambers located in parallel to enable simultaneous actuation of two drug-coated beads.

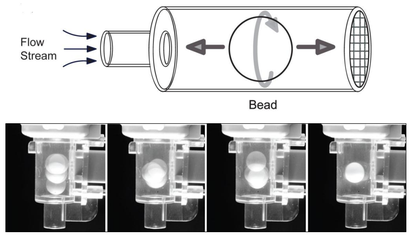

Fig 2. (Top) Illustration depicting the relative motion of a drug-coated bead within a dispersion chamber of the prototype inhaler. (Bottom) The images depict the oscillating motion of an uncoated, polystyrene bead in the dispersion chamber of the Handihaler at 30 L min^{-1}. The images were captured with a 1/8 second exposure using a strobe flash for the solitary light source firing five times at a rate of 199 Hz, depicting the bead motion during a single 4-second actuation.

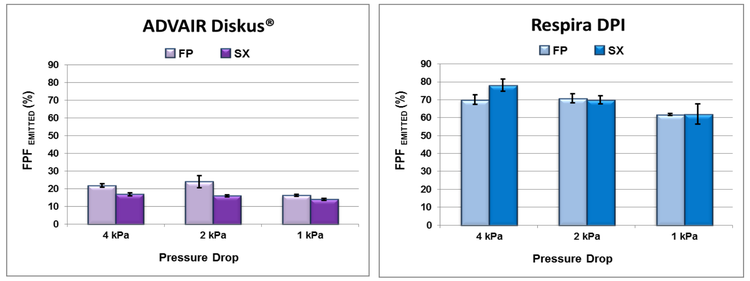

Fig. 3. *In vitro* aerosol performance, as measured by the fine particle fraction of the emitted dose ($FPF_{Emitted}$) for the ADVAIR Diskus® and Respira's dual-chamber prototype inhaler delivering fluticasone propionate (FP) and salmeterol xinafoate (SX) actuated at flow rates corresponding to a 4, 2, or 1 kPa pressure drop across the DPI. The values are presented as mean (± standard deviation) for N = 3 replicates.

ADVAIR DISKUS® (250/50)

Pressure Drop	Fluticasone Propionate				Salmeterol			
	EF (%)	*FPF (%)*	*RF (%)*	*FPD (mcg)*	*EF (%)*	*FPF (%)*	*RF (%)*	*FPD (mcg)*
4 kPa	100.2 (1.5)	21.8 (0.9)	21.8 (0.8)	54.6 (2.0)	108.1 (5.1)	16.7 (0.9)	18.0 (0.5)	9.0 (0.3)
2 kPa	94.2 (8.8)	23.8 (3.4)	22.3 (0.9)	55.6 (2.4)	108.2 (2.7)	15.9 (0.6)	17.2 (1.1)	8.6 (0.5)
1 kPa	97.7 (5.0)	16.2 (0.6)	15.8 (0.8)	39.5 (2.0)	111.7 (6.3)	13.8 (0.6)	15.4 (1.5)	8.4 (0.6)

RESPIRA INHALER (150/35)

Pressure Drop	Fluticasone Propionate				Salmeterol			
	EF (%)	*FPF (%)*	*RF (%)*	*FPD (mcg)*	*EF (%)*	*FPF (%)*	*RF (%)*	*FPD (mcg)*
4 kPa	65.2 (1.6)	70.0 (2.7)	45.7 (2.6)	69.1 (6.6)	56.6 (3.5)	78.2 (3.4)	45.5 (3.0)	16.6 (1.7)
2 kPa	56.5 (0.3)	70.8 (2.5)	40.0 (1.4)	66.2 (6.1)	56.6 (4.3)	72.1 (3.2)	40.8 (4.2)	15.0 (3.4)
1 kPa	48.1 (2.9)	61.7 (0.6)	29.7 (1.6)	46.7 (2.5)	42.9 (4.6)	62.1 (5.6)	26.5 (0.3)	9.1 (1.5)

Table 1. Emitted fraction (EF), fine particle fraction (FPF), respirable fraction (RF) and fine particle dose (FPD) values determined *in vitro* for the ADVAIR Diskus® and dual-chamber prototype inhaler. For the ADVAIR Diskus®, EF and RF are provided as the percentage of the labeled dose. All values are presented as mean (± standard deviation) for N = 3 replicates.

DISCUSSION

- A simple, two-piece prototype inhaler was developed, incorporating dual dispersion chambers placed in parallel to enable two drug-coated beads to be actuated simultaneously (Fig. 1). The top part of the device contained a mesh in each dispersion channel to prevent the bead from exiting the device during inhalation. The overall resistance of the dual-chamber device was comparable to that measured through the ADVAIR Diskus®, allowing performance to be evaluated at similar flow rates.

- The ADVAIR Diskus® exhibited excellent drug emission. However, detachment of the drug particles from the carrier lactose appeared to be largely incomplete, as the majority of the dose was collected from the induction port and pre-separator, resulting in a low fine particle fraction value and low overall drug delivery (RF values = 15 - 22%).

- By comparison, despite the lower overall emitted fraction from the dual-chamber DPI, the effective powder dispersion yielded high fine particle fractions at all tested inhalation flow rates, with FPF values in excess of 60% at the corresponding 1 kPa flow rate and ranging up to 71% and 78% for fluticasone and salmeterol respectively at the higher flow rates (Fig. 3).

- The excellent powder dispersion from the dual-chamber prototype resulted in salmeterol RF values approximately 70 – 150% greater than those observed from the commercial DPI. For fluticasone, the RF values were roughly twice that of the Diskus®, such that while only approximately 150 mcg of fluticasone propionate was coated onto each bead (compared with 250 mcg fluticasone/dose in the ADVAIR Diskus®), a greater fine particle dose was still achieved across all tested flow rates (Table 1).

CONCLUSIONS

- The development of a combination therapy prototype inhaler, incorporating dual parallel dispersion chambers for pulmonary delivery via Respira's drug-coated bead technology, demonstrated excellent powder dispersion performance coupled with greater overall performance *in vitro* relative to the ADVAIR Diskus®.

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