Novel High Efficiency Inhaler for PDE5i Lung Delivery

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INTRODUCTION

Several dry powder inhalers have been successfully commercialized for the treatment of asthma and chronic obstructive pulmonary disease (COPD). These devices, perhaps suitable for the original intended drug product, often have poor performance when used for other drugs and diseases. In these studies, our hypothesis was that using an additional dispersion mechanism, coupled to existing off-the-shelf inhalers, we could enhance performance and therefore, this device would be suitable for delivery and development of a phosphodiesterase 5 inhibitor formulation. Specifically, a small "dispersion engine" that can be easily coupled to existing inhalers or dose containment systems was developed as exemplified in Figure 1. We tested this dispersion engine using commercial products themselves, and also using commercial devices with PDE5i formulations.

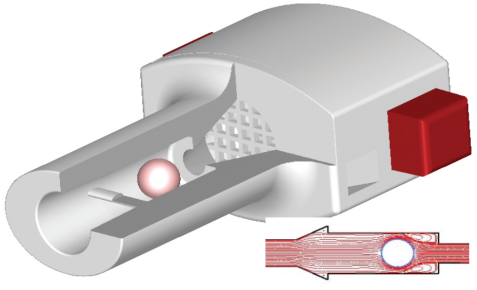

Figure 1. **A schematic of the dispersion engine known as an axially oscillating sphere (AOS™) system, coupled to a commercial inhaler.**

METHODS

Designs of a small dispersion engine were developed based on previous generations of an inhaler containing an axially oscillating bead [1]. The dispersion engine consisted simply of a chamber and a bead that could be coupled to the mouthpiece of different readily available commercial dry powder inhalers. These designs were rapid prototyped (W.M. Keck Center for 3D Innovation, El Paso, TX) and airflow resistance characterized using standard methods. Aerosol testing using a next generation impactor (NGI) was performed initially using commercial formulations and a commercial device (Flovent® Diskus®). In these initial studies, the dispersion engine was simply added to the outlet of the device as shown in Figure 2.

Subsequently, the dispersion engine was coupled to the capsule piercing and dispersion system of the HandiHaler® (HH) as shown in Figure 2. Lastly, a re-designed mouthpiece to the Plastiape RS-01 inhaler was fabricated and tested with formulations containing the PDE5i drug (Figure 3). Aerosol performance was assessed using standard pharmacopoeial method (USP) cascade impactor studies quantifying fine particle fraction ((FPF), both as a function of emitted and loaded/labeled dose), fine particle dose (FPD), and emitted dose (ED). The flow conditions were controlled and performed at 2 and 4 kPa pressure drop.

Figure 2. **Schematic view of the internal design of the rapid prototyped adaptor (left) used to couple the AOS™ engine to the commercial Diskus® device (left) and HandiHaler® (right). The device was coupled to the outlet of the mouthpiece of the Diskus and capsule chamber of the HandiHaler.**

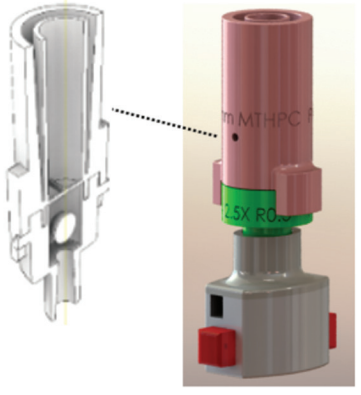

Figure 3. **Schematic view of the internal design of the rapid prototyped adaptor (left) used to couple the AOS™ engine as a replacement mouthpiece for the Plastiape RS01 device (right).**

RESULTS

The axially oscillating sphere (AOS) dispersion engine increased the fine particle dose of commercial Flovent formulations in from the Diskus blister DPI by 2.2 times using the same pressure drop during NGI testing. Using the Handihaler capsule DPI device, the addition of the AOS dispersion engine increased the fine particle dose of a high API dose of the PDE5i formulation (4000µg) by 2.6 times. Similarly, the addition of the AOS to the RS01 DPI increased the FPD of high dose (4000µg) PDE5i formulation in by 1.7 times. Additional studies showed that FPD did not change when reducing the testing pressure drop from 4kPa to 2kPa.

Table 1.

Dispersion enhancement at 4 kPa pressure drop using the AOS coupled to the Flovent® Diskus®, HandiHaler® with high dose PDE5i formulation, Plastiape RS01 with both Foradil® and high dose PDE5i formulation.

Device	API/Product	Dose (µg)	FPD <3µm (µg)	AOS FPD Enhancement
Diskus	Flovent	250	30	2.2 X
Diskus+ AOS			*67*	
HH	PDE5i	4000	632	2.6 X
HH+AOS			*1633*	
RS01	Foradil	12	1.8	1.5 X
RS01+AOS			*2.7*	
RS01	PDE5i	4000	1254	1.7 X
RS01+AOS			*2136*	

CONCLUSIONS

Initial proof of concept studies showed that an oscillating sphere based dispersion engine enabled highly efficient powder deaggregation from a commercial DPI product (Flovent Diskus). This dispersion engine was then adapted to two different capsule-based devices for the testing of a high dose PDE5i formulation. Similarly, these data demonstrated the utility of the dispersion engine to improve the performance of off-the-shelf devices. Moreover, the engine was shown to be easily integrated within a commercial DPI device envelope.

ACKNOWLEDGEMENT

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REFERENCE

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