Novel High Efficiency Inhaler For PDE5i Lung Delivery

James Hannon[1], Martin Donovan[1], Aileen Gibbons[1], Zhen Xu[1], Robert Curtis[1], Hugh Smyth[1,2], and Andy Clark[1]

[1] Respira Therapeutics, Inc., Albuquerque, NM, USA

[2] College of Pharmacy, Division of Pharmaceutics, The University of Texas at Austin, Austin, TX, USA

INTRODUCTION

- Several dry powder inhalers (DPI) have been successfully commercialized for the treatment of asthma and chronic obstructive pulmonary disease (COPD). These devices suitable for the original intended drug product, often have poor aerosol performance when used for other drugs and diseases.
- Our hypothesis was that using the Respira Axial Oscillating Sphere (AOS) technology as a supplemental dispersion mechanism, would enhance the aerosol performance of off the shelf inhalers to deliver various inhaled drug formulations, this device would be suitable for delivery and development of a phosphodiesterase 5 inhibitor (PDE5i) formulation.
- A small "dispersion engine" that can be easily coupled to existing inhalers or dose containment systems was developed as illustrated in **Figure 1**. We tested this dispersion engine using commercial devices and formulations, and also using commercial devices with a PDE5i formulation.

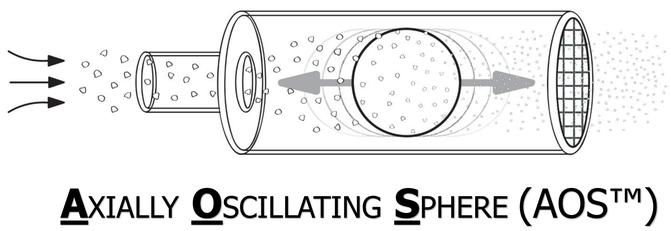

Fig. 1. A schematic of the dispersion engine known as an axially oscillating sphere (AOS™) system, image not to scale.

MATERIALS AND METHODS

- Designs of a small dispersion engine were developed based on previous generations of an inhaler containing an axially oscillating sphere (AOS).[1]
- AOS dispersion engine consisted of a specially designed chamber and a spherical 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
- Aerosol testing using a Next Generation Impactor (NGI) was performed initially using commercial device and product (Flovent Diskus®) with and without AOS dispersion engine, shown in **Figure 2.**
- The AOS dispersion engine was added to the outlet of inhalers HandiHaler® & Plastiape RS01 inhalers as shown in **Figure 2** & **Figure 3**.

MATERIALS AND METHODS

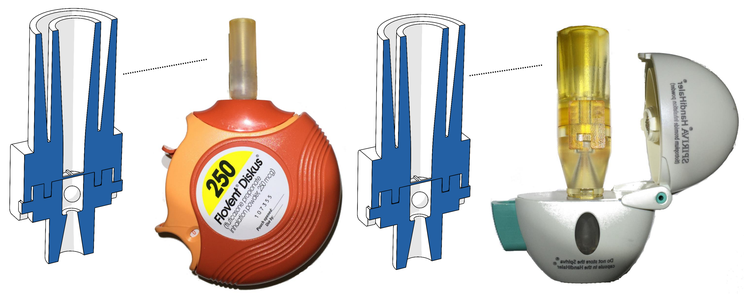

Fig. 2. Cross section view of the rapid prototyped adaptor (far left) used to couple the AOS engine to the commercial Diskus device (left) and Handihaler (far far right). The AOS was coupled to the outlet of the mouthpiece of the Diskus and capsule chamber of the Handihaler.

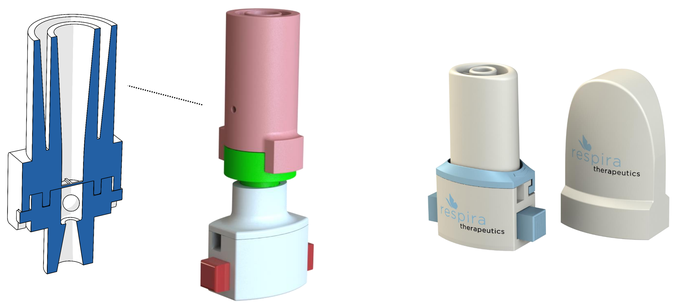

Fig. 3. Cross section view of the rapid prototyped adaptor (far left) used to couple the AOS engine as a replacement mouthpiece for the Plastiape RS01 device (right). Proposed commercial device design (far right) illustrating the size savings of an integrated AOS over lab prototype (left).

RESULTS

- AOS dispersion engine increased the Fine Particle Dose (FPD<3µm) of commercial Flovent formulation from the Diskus blister DPI by 2.2 times using the same pressure drop (4kPa) during NGI testing.
- Using the Handihaler capsule DPI device, the addition of the AOS increased the (FPD<3µm) of a high API dose of the PDE5i formulation (4000µg) by 2.6 times.
- Addition of the AOS to the RS01 DPI increased the (FPD<3µm) of commercial Foradil formulation by 1.5 times and a high dose (4000µg) PDE5i formulation by 1.7 times. Additional studies showed that FPD did not change when reducing the testing pressure drop from 4kPa to 2kPa.

RESULTS

Device	API/ Product	Dose (µg)	FPD<3µm² (µg)	AOS FPD Enhancement
Diskus	Flovent	250	30	2.2X
Diskus+AOS			*67*	
HH	PDE5i	4000	632	2.6X
HH+AOS			*1633*	
RS01	Foradil	12	1.8	1.5X
RS01+AOS			*2.7*	
RS01	PDE5i	4000	1254	1.7X
RS01+AOS			*2136*	

Table 1. Dispersion enhancement at 4 kPa (N=3) 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.

CONCLUSIONS

- Initial proof of concept studies showed that an axially oscillating sphere (AOS) based dispersion engine enabled highly efficient powder deaggregation from a commercial DPI product (Flovent Diskus).
- AOS dispersion engine was then adapted to two different capsule based devices (Handihaler, Plastiape RS01) for the testing of a high dose PDE5i formulation. Similarly, these data demonstrated the effectiveness of the AOS dispersion engine to improve the performance of off-the-shelf devices.
- The AOS dispersion engine was shown to be easily integrated within a commercial DPI device envelope.

ACKNOWLEDGEMENTS

- We acknowledge Plastiape S.p.A. for providing the RS01 devices for testing.

REFERENCES

1. Donovan, M, Gibbons, A, Pappo, J, Smyth, HD: Novel low resistance DPI for high efficiency delivery in a broad range of drug classes. In *Respiratory Drug Delivery 2012. Volume 3.* Edited by Dalby, RN, Byron, PR, Peart, J, Suman, JD, Farr, SJ, Young, PM. DHI Publishing; River Grove, IL: 2012: 717-20.
2. Newman, SP, Chan, HK, 2008. In vitro/in vivo comparisons in pulmonary drug delivery. J Aerosol Med Pulm Drug Deliv 21(1), 77-94