An Add-on to Dry Powder Inhaler Device that Can Improve Dose Delivery to the Lungs

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INTRODUCTION

A dry powder inhaler (DPI) is a device that delivers medication to the lungs in the form of a dry powder. Most DPIs rely on the force of patient inhalation to entrain powder from the device and subsequently break-up the powder into particles that are small enough to reach the lungs [1]. Over the past 50 years, numerous DPI devices have been developed and marketed, and there has been a steady evolution in improvement of inhaler characteristics [2]. The challenge for formulation scientists and device engineers is to provide a DPI product capable of simply and quickly adapting aerosol generation to the needs of each medication and the particulars of a given user. In this work, a novel powder dispersion add-on device, the Axial Oscillating Sphere (AOS™, Respira Therapeutics Inc.), is used in conjunction with a commercially available DPI device, the RS01 (Plastiape,SpA), to optimize the powder dispersion of a formulation containing a force control agent (FCA). The function of AOS is to add a secondary deagglomeration step (the oscillation of the sphere during inhalation flow) in the mouthpiece of a DPI device promoting the formation of fine aerosol particles. The aim of this study was to present the performance of AOS accessory/add-on device compared with normal RS01 device before modification, using a consistent preclinical batch of DPI formulation containing magnesium stearate FCA. Previous work for the two types of devices was evaluated at different flow rates using a formulation without FCA (Foradil Aerolizer capsules), which demonstrated the performance of the AOS device is less dependent on the inspiratory effort (pressure drop) [3]. In this study, we used a standard 90 L/min for APSD to compare the upper limit performance of the devices.

MATERIALS AND METHODS

RS01 devices were obtained from Plastiape. For the comparator device, the RS01 mouthpiece was shortened and a small spherical bead was introduced. Oscillation of the bead in the cylindrical chamber (Figure 1) promotes additional powder dispersion [3].

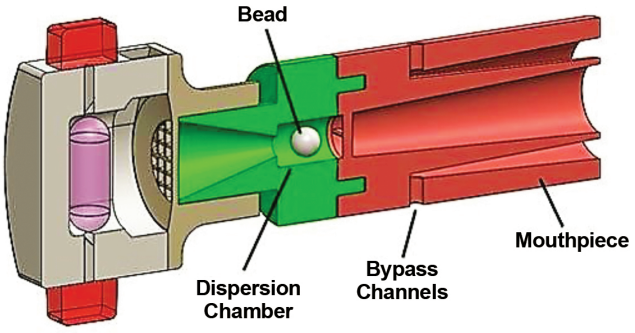

Figure 1. **Schematic showing a longitudinal section of RS01-AOS device. Upon inhalation, the small sphere in the AOS dispersion chamber axially oscillates freely within in the chamber. A parallel flow path (bypass channel) was included in the AOS to reduce overall device resistance. The overall length of the accessorized device is 8 cm and the diameter of the mouthpiece is 2 cm.**

The performance of both unmodified RS01 and RS01-AOS devices were evaluated using a preclinical lot of formulated dry powder. Size 3 capsules were manually filled with 25 mg of formulation, nominally containing 50 μg of API. The formulation of the dry powder contains active pharmaceutical drug (Dv50 is 1.3 μm from Sympatec HELOS laser diffraction data) which is suitable in the treatment of chronic obstructive pulmonary disease (COPD), blended with a carrier which contains lactose and magnesium stearate FCA. Aerodynamic particle size distribution (APSD) and delivered dose (DD) tests were performed with a Next Generation Impactor (NGI) and Dosage Unit Sampling Apparatus (DUSA) tubes, respectively (both from Copley Scientific Ltd., Nottingham,UK). The pre-separator and impactor stages were coated with silicon oil to prevent particle bounce. The DD was assessed at the same pressure drop (4 kPa) and inhaled volume (4 L) for the two devices. For APSD testing, the two devices were assessed at a constant flow rate (90 L/min) and inhaled volume (4 L). Quantification of the drug was determined by high performance liquid chromotography (HPLC) method for DD and APSD. Precision and accuracy was previously validated for the method.

RESULTS AND DISCUSSIONS

Similar DD values were obtained for the RS01 and RS01-AOS devices at a 4kPa pressure drop (n = 3 replicates) (Table 1).

It should be noted that modification of the RS01 device to include the AOS results in an increase in device resistance. This is reflected in the different flow rates achieved at the 4 kPa pressure drop. Under the same standard test condition, the RS01-AOS produced more consistent delivery as compared to the RS01 without the AOS.

Table 1.

Delivery dose results for RS01-AOS and normal RS01 device.

Device	P_1 (kPa)	Flow (L/min)	Duration Time (s)	Mean DD (μg)	%RSD (n=3)
RS01-AOS	4.0	59.12	4.1	38.5	4.13
RS01	4.0	109.53	2.4	38.9	6.87

For APSD testing, the RS01-AOS device shows a better performance on promoting the formation of fine aerosol particles, thus a larger FPF (Table 2, Figure 2).

Table 2.

Effect of DPI device on the formulation aerosolization (values are mean ± SD, n=3).

Device	ED (%)	$FPF_{\leq 5\mu m}$ (%)	$FPF_{S4\text{-}F}$ (%)	MMAD (μm)
RS01-AOS	82.9 (1.6)	79.7 (1.1)	67.7 (0.6)	1.4
RS01	87.5 (0.6)	62.5 (4.0)	48.2 (3.4)	1.7

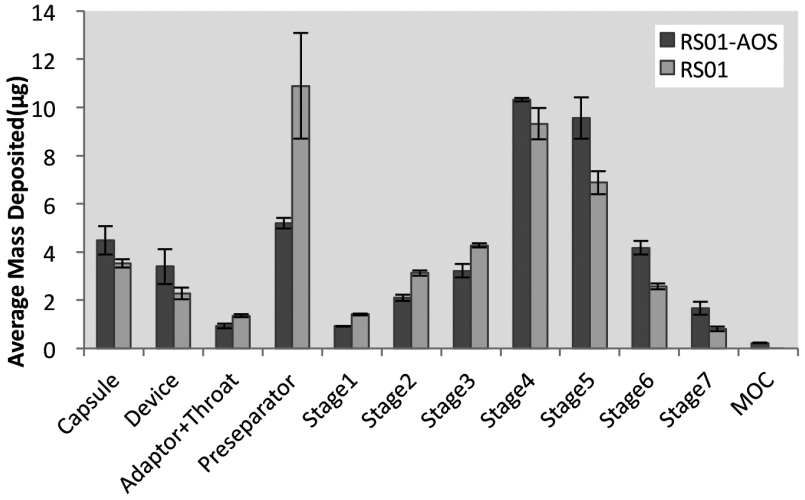

Figure 2. Deposition profile of the two devices.

The emitted dose (ED) was the percentage of the total drug deposition from the throat to MOC divided by total drug recovered. The result of ED% shows RS01-AOS device delivers a slightly less amount of drug compared with RS01 device.

The $FPF_{<5\mu m}$, a traditional measure of the respirable fraction of a pharmaceutical aerosol [4], was calculated using Copley CITDAS software (Table 2). The results are expressed as a percentage of the ED. Results show that the fine particle fraction (<5μm) delivered from the RS01-AOS

can be increased to nearly 80% of respirable fraction. By adding the AOS to the RS01 DPI device, its $FPF_{<5\mu m}$ performance at the standard 90L/min tested improved by 18%..We believe that the AOS contributes to the adhesive and cohesive detachment of the formulation. The mass median aerodynamic diameter (MMAD) results also demonstrate the improved powder dispersion of the RS01-AOS device, with a decrease in MMAD from 1.7 μm for the RS01 to 1.4 μm for the RS01-AOS.This latter value is very close to the mass median volume diameter (Dv_{50}) of micronized API tested by laser diffraction. Hence, it is likely that the AOS is effective at dispersing drug that bypasses deposition in the device, throat and preseparator back to its primary size.

By analyzing the NGI data by grouping the deposition on stage 4 to MOC, the RS01-AOS showed a FPF below 2.3 μm of 68% of ED, which demonstrate the possible use of this modified device to target deep lung deposition. Reductions in variability in the APSDs were also observed for the RS01-AOS device.

CONCLUSIONS

The addition of an axial oscillating sphere to the RS01 DPI leads to dramatic improvements in powder dispersion of a lactose blend containing micronized API and a force control agent. Given that most commercial DPI products have a total lung dose between 30% to 60% [5], the AOS add-on has shown to improve the performance of a lactose blend to reach what can usually only be obtained by particle engineering (80% of FPF). The aerodynamic particle size distribution was also shifted to smaller sizes, and improvements in consistency in drug delivery were noted.

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