Accessorized DPI: A Shortcut Towards Flexibility and Patient Adaptability in Dry Powder Inhalation

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Summary

In this work, a novel powder dispersion add-on device, the AOS (Axial Oscillating Sphere), was studied in conjunction with commercially available DPI devices to investigate the improvement of powder dispersion and to minimize the dependence of the device performance on the inspiratory effort. An ordered mixture of formoterol fumarate and lactose was selected. We studied the emission and dispersion of the drug at different flow rates, paying particular attention to a number of metrics of Fine Particle Dose (FPD).

Two novel findings emerged from the data collected: the aerosol quality, measured as fine particle dose, was increased by adding the accessory promoting the formulation deagglomeration and the flow dependence of the aerosol formation was reduced [1].

Increasing inhaler performance can be achieved using an add-on accessory that enhances aerosol dispersion and minimizes flow rate dependency.

Introduction

Drug delivery and intrinsic lung deposition from a dry powder inhaler (DPI) are influenced by the inspiratory flow produced by the patient, the resistance of the inhaler and formulation characteristics.

It has been reported that clinical efficacy is related to the inhalation flow rates achieved through a DPI [2, 3]. Delivery of drug to the lung has been shown to be lower in children than in Chronic Obstructive Pulmonary Disease (COPD) patients, whereas adults with asthma produce the greatest dependency on inhalation flow rates [4].Therefore, the inspiratory profile of the patient is an issue that must be addressed for an efficient DPI performance.

Lung deposition differences between patients using DPIs underline the need of technologic expedients that are capable of minimizing flow rate and interpatient variability. One novel concept translated into product form has been the design of the accessory named AOS (Axial Oscillating Sphere, Respira Therapeutics Inc.), which is to be used in conjunction with dry powder devices to optimize the aerosol formation. The objective of this study was to evaluate the AOS as an accessory to different DPI devices, assessing its impact on drug aerosol dispersion and its ability to promote the formation of extra-fine aerosol particles while taking into account the impact of device resistance. The concept of using the AOS as a simple "upgrading accessory" to enhance inhalation performance has been reported previously [5].

The aim of this research was to study the performance of the AOS accessory in connection with RS01 DPI device (Plastiape SpA), a capsule based reservoir device, using RS01 DPI versions with two different intrinsic airflow resistances. In order to conduct the study a commercial drug product consisting of an ordered mixture of formoterol fumarate and lactose for inhalation was selected. We studied the emission and dispersion of the drug at different flow rates, paying attention not only to the fine particle dose (< 5 µm), but in particular to the extra-fine particle dose (< 3µm).

Materials and Methods

The drug product employed was formoterol fumarate lactose blend (Foradil Aerolizer, Novartis – inhalation powder in hard gelatine capsules) purchased from a local pharmacy. Each capsule is filled with 12 µg of formoterol fumarate blended with 25 mg of lactose.

All chemicals used were of analytical grade and water was purified by ElixEssential (Merck Millipore, MA, USA). The device used in the study was RS01 (Plastiape Spa, Osnago LC, Italy), available in two different versions: medium and low resistance, coded as RS01_MR and RS01_LR respectively. The AOS accessory uses a small spherical bead oscillating in a cylindrical chamber to promote powder dispersion, as reported by Hannon *et al* [5].

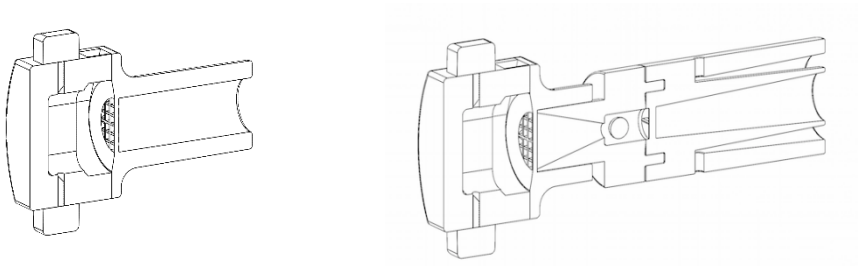


Figure 1 - Schematic cross-sections of RS01+AOS with the modified mouthpiece and added AOS dispersion chamber. The small bead in the AOS chamber primarily oscillates along the axis of the cylindrical chamber. A parallel flow path was included in the RS01-AOS to reduce overall device resistance.

The aerodynamic assessment was performed using the Next Generation Impactor (NGI) (Copley Scientific, Nottingham, UK). The methodology followed the USP36 guidelines for dry powder inhalers (Apparatus 5, United States Pharmacopoeia, Chapter 601). The flow rate used during each test was adjusted with a Critical Flow Controller TPK (Copley Scientific, Nottingham, UK) in order to produce a pressure drop of 2 kPa or 4 kPa across the inhalers. The resistance of the tested devices is reported in Table 1.

Table 1 - Resistance values for RS01 inhalers in the different configuration tested.

Inhaler	R ($kPa^{0.5}$/LPM)
RS01-MR	0.033
RS01-MR AOS	0.038
RS01-LR	0.019
RS01-LR AOS	0.036

The metered dose (MD), the mass of drug recovered, was quantified by HPLC by summing the drug recovered from the device and capsule and the impactor (induction port, pre-separator, stages 1 to 7 and MOC). The Emitted Dose (ED) was calculated as the amount of drug leaving the device, *i.e*. reaching the impactor (induction port, pre-separator, stages 1 to 7 and MOC). The mass median aerodynamic diameter (MMAD) was determined as indicated by USP 36. The Fine Particle Dose (FPD) was defined in two different ways: (i) mass of drug < 5 µm (calculated from log-probability plots), (ii) mass of drug < 3 µm (calculated from log-probability plots).

Results and Discussion

The emitted dose for all the cases studied was higher than 75% with no significant difference observed between the standard RS01 devices and those with the AOS attached. Figure 2 shows the two categories of fine particle dose, *i.e*., less than 5 µm and less than 3 µm. A similar trend is presented for both. The mass of drug < 5 µm, with or without the AOS accessory, depended on the flow rate (pressure drop). An increase of FPD to approx. 3.5 µg for air flow rates > 60 L/min was observed for the RS01 without accessory. When the AOS was connected to the device, the FPD values improved compared to the values without AOS at the same flow rate. The oscillating sphere of AOS enhanced the detachment of the drug particles from the lactose carriers, allowing the use of the DPI at lower flow rates while maintaining delivery performance.

For the mass of drug < 3 µm, the values with AOS accessory were also consistently higher compared to those generated without AOS.

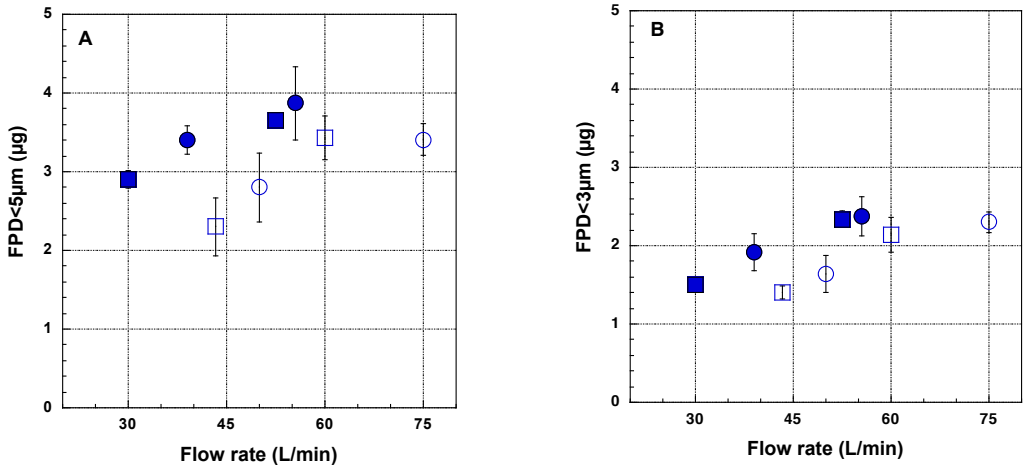
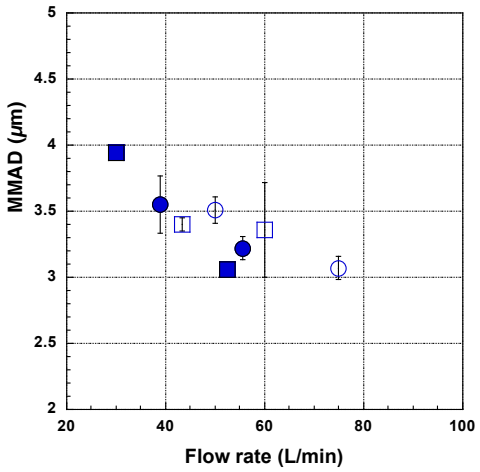


Figure 2 - Fine Particle Dose of formoterol fumarate < 5 µm and < 3µm (circle: RS01-LR; square: RS01-MR. Empty symbols: without AOS; full symbols: with AOS).

Another value examined was the Mass Median Aerodynamic Diameter for both the two types of RS01 with or without AOS. An inverse relationship between MMAD and the airflow rate was observed with and without the AOS device with the MMAD of the aerosol generated by the AOS equipped devices showing and asymptote to that of



the micronized drug powder (Figure 3).

Figure 3 - MMAD and flow rate for the RS01 devices with and without AOS (circle: RS01-LR; square: RS01-MR. Empty symbols: without AOS; full symbols: with AOS).

The fraction of an inhaled aerosol reaching, and depositing in, the lungs is dependent upon the filtering that takes place in the mouth and oropharynx. Traditionally, FPD is defined as the fraction of particles under 5 µm aerodynamic diameter. It is known that the best way to compare the performance of dry powder inhalers is to compare them at equal pressure drops. Therefore, the low resistance devices have to be tested at high flow rates, while, on the other hand, high resistance devices at low flow rates. Since the deposition within the airways is controlled by flow rate and particle size, not pressure, this underlines that ideally the size fraction considered to be "respirable" has to change with the device resistance, *i.e*. test flow rate.

Over the past few decades, numerous definitions of "Fine Particle Dose" or "Respirable Fraction" have been employed. The principle behind all of these definitions is to estimate through *in vitro* tests the dose likely to deposit in the lungs of patients *in vivo*. In general, a respirable fraction of < 5 µm cut-off has been used; this is derived from the size distribution data obtained from multistage impaction instruments by plotting the size distribution and interpolating. More recently, studies using a compilation of published scintigraphy studies have shown that a more appropriate cut-off size is < 3 µm. This definition of FPD produces a 1:1 correspondence with lung deposition, albeit with a rather large scatter about the mean [6].

For this report we chose not to try and correct for the influence of flow rate on the definition of FPD, but rather to concentrate on two different fixed cut-off diameters (< 5 µm and < 3 µm) to compare the respirable dose emitted from the devices we investigated.

Conclusion

The presence of the AOS increased the deposition of the drug on the lower stages of the impactor (*i.e*. with smaller cut-offs diameters) at all flow rate and showed better dispersion, compared to the standard RS01 devices using both definitions of FPD. The oscillating sphere of AOS contributes to the detachment of drug particles from the carrier and their subsequent dispersion[1]. This was particularly evident at the lower test flow rates. Thus, the use of an AOS accessorized DPI enhances the dispersion and deagglomeration of the tested ordered blend and, as a consequence of its better performance at lower flow rates, makes the DPI performance less dependent on the inspiratory effort of the patient (pressure drop).

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