Breathing Simulators: One step closer to representative deposition profiles?

Maria Palha[1], Sofia Silva[1], Isabel S. Lopes[1] & Eunice Costa[1]

[1]Hovione FarmaCiencia SA, Sete Casas, 2674-506 Loures, Portugal

Summary

Cascade impactors are widely used for aerodynamic performance testing of dry powder inhalers (DPIs). Impactors are useful and efficient tools for quality control of inhalation products as well as for formulation development as a simple *in vitro* assessment of the deposition of the drug in the respiratory tract. However, the current USP pharmacopeia method considers a non-physiological representation of the human mouth-throat, the induction port, and a constant flow during testing. The flow achieves a 4 kPa pressure drop and an inhalation volume of 4 L, which does not account for the variability inherent in the patient population when evaluating product performance [1].

The main goal of this work was to compare the recently developed breathing pattern simulator and the Alberta Idealized Throat (AIT) [2], with the current pharmacopeia standard in the aerodynamic performance assessment. Three different setups operating under pharmacopoeia conditions, mimicking a square wave breathing profile, were tested: Fast Screening Impactor (FSI) + Induction Port (IP); FSI + AIT; FSI + AIT + Breathing Simulator (BRS). The two parameters evaluated, Emitted Dose (ED) and Fine Particle Dose (FPD), were relatively insensitive to test conditions when comparing the three setups, with the FSI + AIT + BRS improving reproducibility. In addition, three different breathing patterns were evaluated: medium, strong and weak, as defined in the literature [1]. These patterns represent inhalation profiles derived from patient measurements and capture different target patient populations. It was observed that BRS reduced method variability and that the square and medium profiles yielded the same results. In relation to the weak profile, a reduced FPD was observed, most probably due to insufficient powder dispersion. In relation to the strong inhalation profile, the ED was higher but no differences were observed in terms of the FPD in comparison to the medium and square waves profiles.

Introduction

The aerodynamic particle size distribution (APSD) of dry powder inhalers is typically measured via cascade impaction techniques. These apparatus fractionate the product into discrete aerodynamic size ranges, providing information on the potential product deposition in the respiratory tract. These methodologies rely on the fact that a an average adult generates approximately 4 kPa pressure drop across a given forced inhalation and inhales a total volume of 4 L of air. These parameters are used to define a constant test flow and duration and give origin to a square wave profile that is applied during dose uniformity and cascade impactor testing [3]. In addition, the actual acceleration of the flow from the inhalation manoeuvre is lower than the acceleration of the flow provided by a vacuum pump; hence, most patients may not be able to achieve the inhalation volume of 4 L [1].

The performance assessment of DPIs, as per the USP method, is not, therefore, representative of some of the patient populations. Patients with lower inspiratory capacity or with severely impaired lung function may not be able to generate a 4 kPa pressure drop upon device actuation, especially geriatric and paediatric users. On the other hand, healthy patients who may have been using DPIs for systemic treatments (rather than for the treatment of pulmonary disease) might have a much higher inspiratory capacity. In addition, there are also those patients that operate the device itself incorrectly (sub-standard manoeuvre technique) and that have sub-standard deposition profiles. This leads to differences observed between the products' particle deposition prediction (*in vitro* results) and the real particle deposition results (*in vivo* results), amongst other factors such as lung anatomy and physiology [1].

Based on this, there is the need to test DPIs under conditions that mimic the breathing pattern of the target patient population. In recent years researchers have been developing breathing simulators in order to test the products with more representative inhalation profiles, mimicking the variable lung functions of certain patient groups [1, 4]. Additionally, and after recognizing that the standard Induction Port does not provide accurate data on the deposition in the upper respiratory tract, the Alberta Idealized Throat (AIT) was developed based on typical patient population geometries provided by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans [3], enabling a better simulation of both the aerosol deposition and the flow across the human mouth-throat [3]. There has also been development work to adjust models to the different types of patients and their respective anatomy (neonates, infants, adolescents and adults).

The current work compares results obtained using the standard pharmacopoeia test conditions while using different breathing patterns and the AIT to evaluate the product performance and prediction of delivered lung doses. This assessment was performed using a composite particle formulation, with a commercially available device and an abbreviated impactor measurement (AIM) method, the Fast Screening Impactor (FSI), in order to determine Emitted Dose and Fine Particle Dose parameters (the key properties to evaluate the formulation's performance).

Experimental methods

The characterized material comprises 80% w/w Trehalose and 20% w/w Leucine and was produced by spray drying as described in [5]. The PSD of the obtained powder was Dv10 = 0.49 μm; Dv50 = 1.49 μm and Dv90 = 3.97 μm (the complete powder characterization can be found in [5]). The obtained product was characterized in terms of aerodynamic performance using one commercially available capsule based device: Plastiape, model RS01 operating at 60 L/min at 4 kPa. HPMC size #3 capsules were filled using a MG2 FlexaLab capsule filler unit, with a target fill weight of 17 mg per capsule.

The product performance was evaluated by gravimetric FSI, where the weight changes detected in the capsule, device and filter stage were determined by an analytical balance with an accuracy of ±0.01mg. The ED parameter corresponds to the fraction that exits both the capsule and device; and the FPD parameter corresponds to the fraction that is collected with a cut-off diameter of 5 μm.

- **Aerodynamic product performance by AIM**
  - **Standard pharmacopoeia set up: Induction Port + FSI**

The ED and FPD were determined by FSI coupled with the Induction Port (USP throat) using a gravimetric method. A total of 3 replicates were carried out. The total inhalation volume considered was 4 L and the total inhalation time was 4 s [6].

  - **AIT + FSI**

The ED and FPD were determined by FSI coupled with the AIT using a gravimetric method coupled. A total of 3 replicates were carried out. The total inhalation volume considered was 4 L and the total inhalation time was 4 s.

  - **BRS + AIT + FSI**

The ED and FPD were determined by FSI, using a gravimetric method, coupled with a mixing inlet and the AIT and applying different breathing patterns using a BRS. The patterns evaluated were: i) square wave pattern and ii) three user defined patterns taking into account real inhalation profiles described in the literature (where a different device was evaluated but presenting the same airflow resistance as the Plastiape device) [1] that represent the 10^{th}, 50^{th} and 90^{th} percentiles of a patient population (mimicking weak, medium and strong inhalation profiles) [1]. A weak inhalation profile represents the impaired population lung function and additionally may represent paediatric and geriatric patients (who either have lower inhalation capacity or might have an incorrect inhalation manoeuvre). A strong inhalation profile represents healthy patients that use inhalation products for the delivery of systemic therapies. A total of 3 replicates were carried out for each pattern. The total inhalation volume and time considered for the medium, weak and strong profiles were 1.4 L and 2.2 s, 1.8 L and 5.5 s, 2.3 L and 2.6 s, respectively.

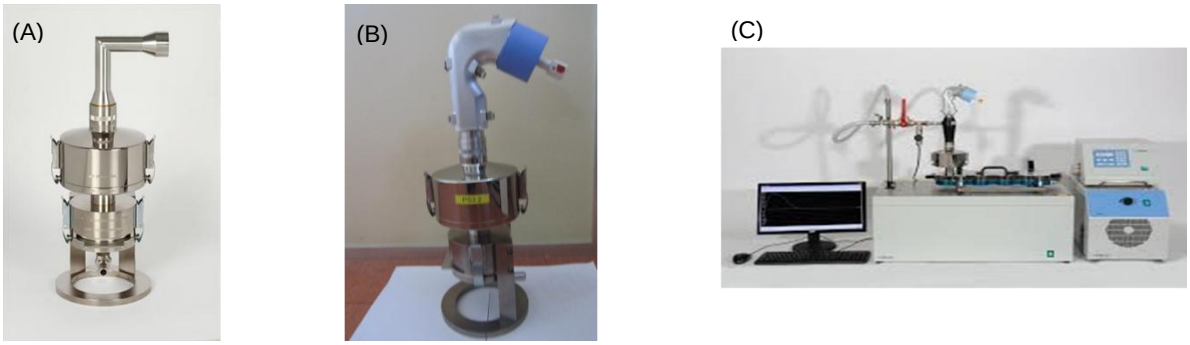

Figure 1 – Set up equipment used during the course of this work: (A) – IP + FSI (image from Copley Scientific website), (B) AIT + FSI, (C) – BRS + AIT + FSI (image from Copley Scientific website)

Results and Discussion

The key properties of the product performance were compared in two different stages, one where the pharmacopoeia testing conditions were maintained and the comparison was performed using the standard equipment and the state of the art tools (AIT and BRS); another where only AIT and BRS were used applying different breathing patterns.

- **Pharmacopoeial testing conditions**

Three set ups were tested: FSI coupled with IP, FSI coupled with AIT (mimicking a human like upper airway geometry) and FSI coupled with AIT and BRS (also generating a square wave profile). The ED and FPD results are presented in Figure 1.

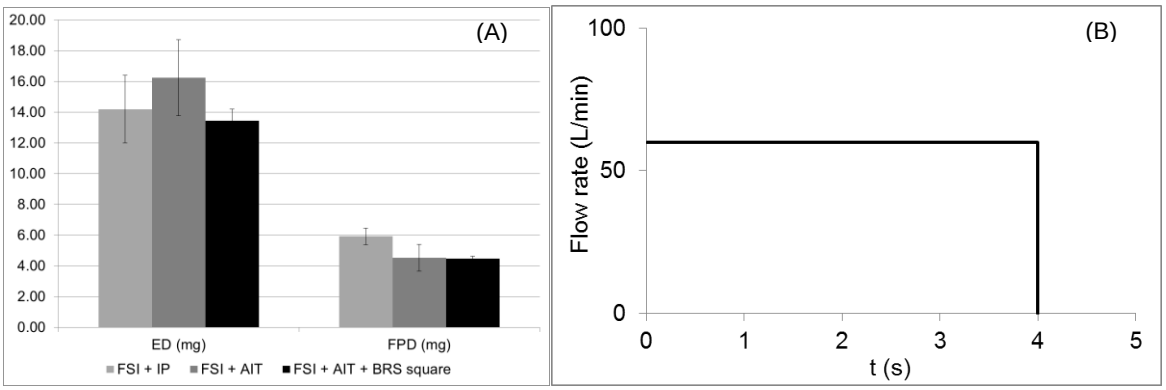

Figure 2 - (A) ED and FPD results obtained by gravimetric FSI with the Plastiape device, where the error bars correspond to one standard deviation; (B) Square wave profile (representative of a vacuum profile).

In terms of ED, the FSI + AIT setup yields similar aerodynamic performance as the conventional apparatus. Although slightly higher values of ED are observed for the FSI + AIT set up, the high variability presented does not enable definitive conclusions. FSI + AIT + BRS set up reduces the variability observed, which can be explained by the fact that the BRS (and adjacent mixing inlet) allows steady state conditions during testing and that a turbulence-free mixing of the sample air stream occurs before the sample enters the impactor [3].

In terms of FPD, it is observed that the introduction of the AIT leads to a reduced FPD, which is in accordance with expectations [3]. As the AIT was designed to represent a more physiological airway geometry, it is expected that this design leads to a higher entrapment of the particles. It has been recognized that the standard Induction Port tends to overestimate the lung deposition [3]. Once again, the steady state conditions promoted by the BRS lead to a lower variability in the FPD obtained. The results demonstrate that the FSI + AIT + BRS setup can be used in replacement of the standard equipment.

- **Breathing profiles**

Three different breathing patterns were tested and compared with the square wave profile using BRS. The ED and FPD results are presented in Figure 3.

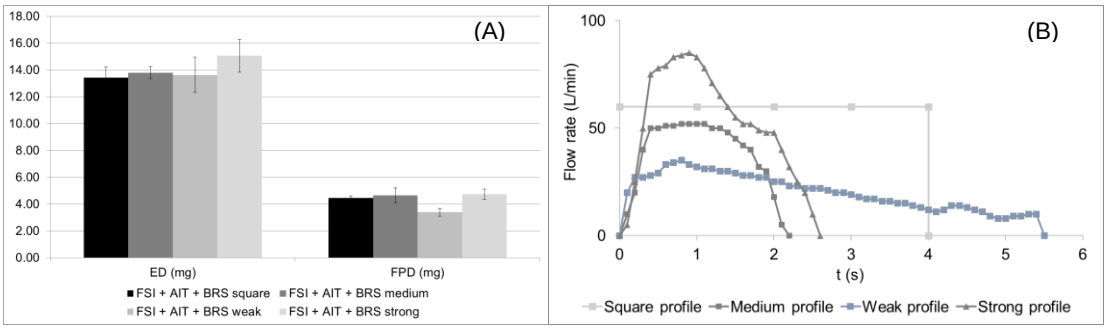

Figure 3 – (A) ED and FPD results obtained by gravimetric FSI with the Plastiape device, where the error bars correspond to one standard deviation; (B) Different inhalation profiles: square, medium, weak and strong.

Once again, it was observed that BRS improves reproducibility of the aerodynamic product performance. When comparing the ED and FPD parameters of the square and medium profiles, although the 4L inhaled volume is not achieved when mimicking a medium profile, no significant differences are observed between them, which might indicate that the formulation is mostly dispersed in the initial part of the inhalation. When comparing to the weak profile, the ED presents higher variability that might be related to a deficient powder dispersion when exiting the capsule/device, leading also to a reduced FPD.

In relation to the strong inhalation profile, the dose that leaves the capsule/device is higher, which could be related to a higher dispersion energy at the peak inhalation flow rate during the inhalation peak flow rate. However, the respirable fraction is similar to the one observed in a medium / square inhalation profile.

Conclusions

With the pharmacopoeial standard conditions, no significant differences are observed when applying either the conventional set up of FSI or FSI + AIT and FSI + AIT + BRS, for this particular formulation and device (considering the three replicates performed for each set up). It is known that one of the advantages of carrier-free composite particles formulations is that they tend to be less sensitive to shifts in aerodynamic performance at different inhalation conditions; therefore, as future work, carrier-based systems will be evaluated using the three different set-ups and benchmarked against composite systems.

The use of breath simulators enables a better understanding of the product performance, specifically for patients with impaired lung function where it was shown that the product performance is patient dependent. In addition, it was also seen that the use of the AIT yielded lower results in the ED parameter than the standard Induction Port, which could be related to the fact that it better mimics the human throat geometry, enabling a better prediction of the upper respiratory tract drug deposition.

These tools can help to predict in vivo performance of DPIs and expedite product development, especially the development of generic products, where the characterisation of flow rate dependency in the different patient populations must be presented and the demonstration of bioequivalence is a mandatory requirement [7].

References

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