

In Vitro Scoping Study of a Dry Powder Inhaler Using Clinically Possible Abnormal Inhalation Profiles for Emitted Aerosol Aerodynamic Particle Size Distribution at Low Peak Inspiratory Flow Rates

Mark Nagel¹, Rubina Ali¹, Jason A Suggett¹ & Jolyon P Mitchell²

¹ Trudell Medical International, 725 Baransway Drive, London, Ontario, N6S 5G4, Canada

² Jolyon Mitchell Inhaler Consulting Services Inc., 1154 St. Anthony Rd., London, Ontario, N6H 2R1, Canada

Summary

Inhalation profiles are often used in the clinic to evaluate how the patient interacts with their prescribed dry powder inhaler (DPI). The magnitude of the peak inspiratory flow rate (PIF) achievable is viewed as diagnostically important from the viewpoint of device-patient compatibility. This laboratory-based investigation sought to evaluate an Easyhaler[®] DPI delivering salbutamol sulphate for aerosol aerodynamic particle size distribution (APSD) using a USP/PhEur induction port located upstream of a Mixing Inlet (MI) and a Next Generation Impactor (NGI). The DPI could therefore be subjected to a range of different inhalation profiles, decreasing PIF from 60 to 50 and then to 40 L/min, mimicking potential use by an asthmatic patient experiencing increasingly severe exacerbations. Total delivered mass (TM) and fine particle mass <4.5 µm aerodynamic diameter (FPM_{<4.5µm}) were each comparable between PIFs of 50 and 60 L/min and between 40 and 50 L/min (paired t-test, $p \geq 0.12$). However, FPM_{<4.5µm} decreased slightly, comparing the outcomes between 40 and 60 L/min ($p = 0.03$). Fine particle fraction <4.5 µm aerodynamic diameter (FPF_{<4.5µm}) values at all three PIFs were comparable (2-way ANOVA, $p \geq 0.05$). Even allowing for an increase of about 1.5 µg, estimated by interpolation of the data from stages 1 and 2, to increase the upper size limit for FPM to the compendially recognized upper limit of 5.0 µm, these measures at each PIF were much lower than their equivalent values delivered by pMDI, where aerosol generation is independent of patient effort.

Key Message

Delivery of a rescue medication by the DPI evaluated could be compromised if the inhalation flow rate and associated volume are insufficient to aerosolize the medication fully.

Introduction

Passive DPIs rely on sufficient patient inspiratory effort to convert the stored powder in the format for single actuation delivery to an aerosol that has the intended APSD for effective transport to smooth muscle receptors in the airways of the lungs¹. Both the design of the passive DPI inhaler and the dynamics of the inhalation (along with its intensification) influence the course of the aerosol generation and emission². Although Clark *et al.*³ have pointed out that it is the inspiratory pressure that governs the process of aerosolization, in the clinic it is the inhalation profile or derived measures from spirometry that are often used to evaluate how the patient interacts with their prescribed DPI⁴. In particular, the magnitude of the peak inspiratory flow rate (PIF) achievable is viewed as diagnostically important from the viewpoint of device-patient compatibility⁴. Although therapies involving an inhaled corticosteroid (ICS) in conjunction with a short-acting bronchodilator (SABA) are available^{5,6}, DPIs delivering only the SABA component also remain in widespread use⁷, and the Easyhaler[®] DPI (Orion Pharma, Espoo, Finland) is one such example. This DPI has been extensively evaluated⁸, but mostly with PIF values ≥ 60 L/min, although a claim has been made for complete disaggregation of the dose even at PIFs as low as 30 L/min⁹. The present laboratory-based investigation sought to evaluate an Easyhaler DPI delivering salbutamol for delivered aerosol APSD using a Nephele Mixing Inlet¹⁰ (MI) in combination with Next Generation Impactor¹¹ (NGI). The DPI could therefore be subjected to a range of different standardized inhalation profiles, decreasing PIF from 60 to 40 L/min in two steps, thereby mimicking potential use by an asthmatic patient experiencing increasingly severe exacerbations.

Materials and Methods

The mouthpiece of an Easyhaler DPI (100 µg/actuation salbutamol sulphate; Orion Pharma, Canada) was connected to a USP/PhEur Induction port that was in turn coupled to the pre-separator of a Nephele MI as shown in Figure 1, so that the flow exiting the DPI could be varied using a breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA, USA). The exit from the MI was connected directly to an NGI operated at 60 L/min. The collection cups of the NGI were each coated with Brij-35 polyoxyethylene surfactant to avoid bias from particle bounce. Deposition profiles were obtained using the NGI, with the breathing simulator set to the inhalation flow rate profiles shown in Figure 2. Each measurement was concluded after the initial inhalation manoeuvre. These settings enabled the PIF to be decreased from 60 to 50 and then to 40 L/min. The flow rate profile characteristics are summarized in Table 1. The

inhalation volume was chosen to mimic an adult inhalation, based on the published standard value in the US Pharmacopeia¹² Three replicate measurements were made with each flow profile. An additional 30 s post inhalation was allowed to elapse before turning off flow to the NGI to ensure complete aerosol capture. Recovered salbutamol from the induction port, pre-separator and each of the stages of the impactor, was assayed by HPLC-UV spectrophotometry using an internally validated protocol.

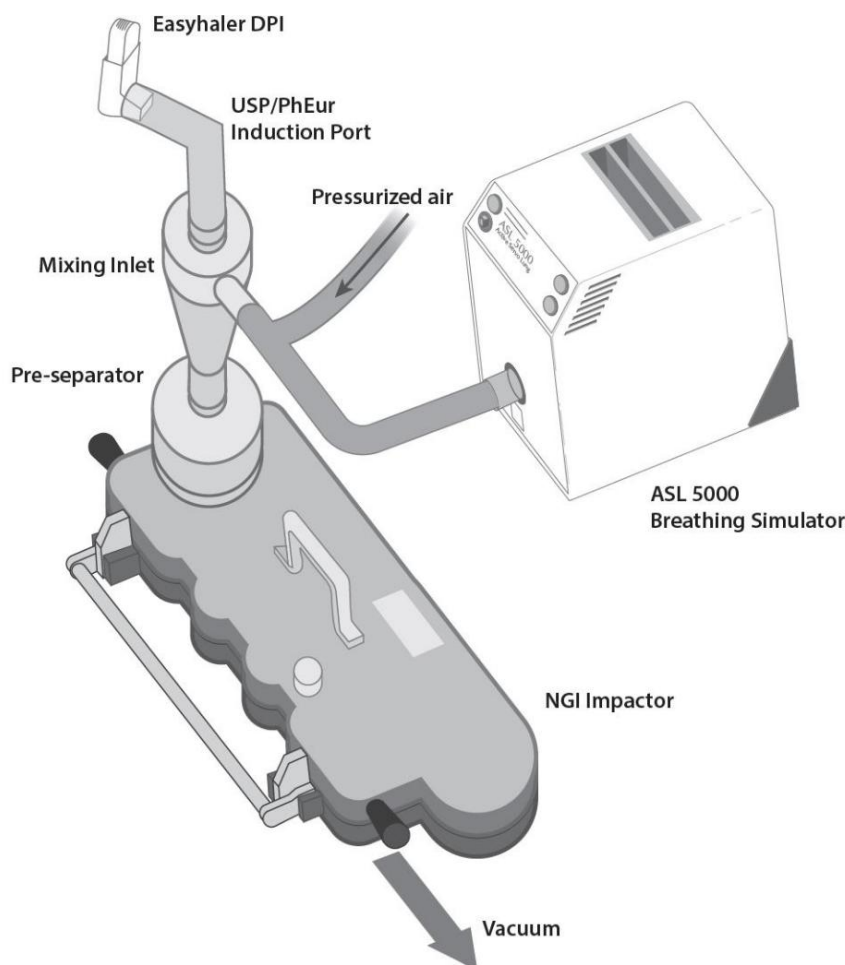


Figure 1: Arrangement for APSD Assessments Showing Mixing Inlet Located so that the NGI Operated at 60 L/min Whilst Flow Rate at DPI Mouthpiece Varied Using the Breathing Simulator

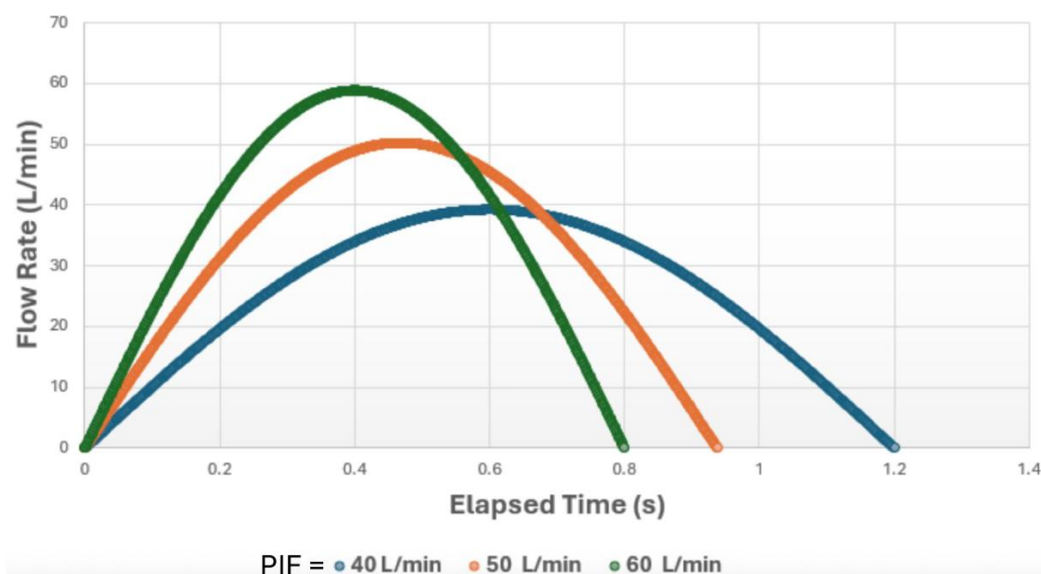


Figure 2: Inhalation Profiles

Table 1: Flow Profile Characteristics

Inhaled Volume (ml)	PIF (L/min)	NGI flow rate (L/min)
500	30	60
	50	
	60	

Results

Key measures of aerosol APSD are summarized in Table 2. The total mass of salbutamol delivered (TM) was calculated as the sum of the mass of this active pharmaceutical ingredient recovered from the pre-separator and stages of the impactor. Internal losses of particles in the MI were assumed negligible. Fine particle mass ($FPM_{<4.5\mu m}$) and fine particle mass fraction ($FPF_{<4.5\mu m}$) were reported from the cumulative mass of API recovered from stages 2 to the MOC. This size limit included almost all the fine particle mass 5.0 μm aerodynamic diameter¹³. Choosing an exact cut-point size enabled statistical comparisons of exact data to be undertaken, as interpolation of the results from stages 2 and 3 with cut-points either side of the 5.0 μm limit would have introduced additional uncertainty.

Table 2: NGI-Derived Metrics for Easyhaler DPI as a Function of PIF

PIF	40 L/min	50 L/min	60 L/min
FPM_{<4.5μm} (μg) (mean $\pm$ S.D.)	8.1 $\pm$ 0.8	10.4 $\pm$ 2.0	10.4 $\pm$ 1.5
FPF_{<4.5} (%) (mean $\pm$ S.D.)	13.9 $\pm$ 1.5	15.4 $\pm$ 2.9	14.8 $\pm$ 2.4
TM (μg) (mean $\pm$ S.D.)	58.8 $\pm$ 11.7	67.8 $\pm$ 6.3	71.7 $\pm$ 1.9

Discussion

All values of $FPM_{<4.5\mu m}$ were lower than would have been anticipated from a nominal 100 μg /actuation product assessed at constant flow rate following ramp-up using conventional cascade impactor testing for DPI products¹². One explanation of the discrepancy could be that insufficient inhaled volume was associated with these breathing profiles to generate sufficient 'power' to disaggregate the powder. Further work will be needed to explore this possibility, perhaps investigating the role of inspiratory pressure on inhalation power generation³.

TM and $FPM_{<4.5\mu m}$ were each comparable between PIF values of 50 and 60 L/min and between 40 and 50 L/min (paired t-test, $p \geq 0.12$. $FPM_{<4.5\mu m}$ decreased slightly, comparing the outcomes between 40 and 60 L/min ($p = 0.03$). However, $FPF_{<4.5\mu m}$ values at all three PIF values were comparable (2-way ANOVA, $p \geq 0.05$. Even allowing for an increase of ca. 1.5 μg , estimated by interpolation of the data from stages 1 and 2, to increase the upper size limit for FPM to 5.0 μm aerodynamic diameter¹², these values at each PIF are much lower than their equivalent values delivered by pMDI¹⁴, where aerosol generation is independent of patient effort. It is conjectured that the slightly reduced values of mass of salbutamol associated with $FPM_{<4.5\mu m}$ when the PIF was only 40 L/min, were associated with the slower rise of the instantaneous flow rate to PIF at this condition (Figure 2).

Further evaluations at lower PIF values would be helpful at confirming the observed trend, and if so, there is the possibility that an asthmatic patient encountering a severe exacerbation necessitating this medication as a rescue attempt, might not receive an adequate dose¹⁵. However, countering this argument, Barnes and Pride¹⁶ have reported that the inhaled salbutamol dose necessary to produce half maximal response in asthmatic adult subjects was as small as 23 $\pm$ 2 μg with a range from 18 to 28 μg , so that repeated inhalations from the Easyhaler may be needed under such a circumstance. Currently, however, the simultaneous inhalation of combination maintenance and reliever therapy (MART) including an ICS to treat the underlying inflammatory disease with the SABA is considered one way that is more effective to avoid or control severe asthma exacerbations⁵. This approach also avoids increasing the number of medications and daily doses, potentially enhancing adherence

The present study was of an exploratory nature and has some limitations. No check was made for internal losses in MI, but the results of a recently published evaluation of this non-ideal behaviour would indicate that they are likely no more than 5% of TM^{17} . It would be helpful to have included other passive DPIs more devices, and to have explored a wider range of inhalation profiles, (i.e. varying I:E ratio and reducing PIF further). Further work is recommended using realistic inhalation profiles of asthmatic subjects with different degrees of airway obstruction.

Conclusions

This exploratory *in vitro* study investigated how a passive DPI delivering salbutamol sulphate as API responded to progressive reduction in PIF using a series of three standardized inhalation profiles. Measures of the principal measure ($FPM_{<4.5\mu m}$), regardless of PIF, were substantially smaller than reported values of $FPM_{<5\mu m}$ for the same API delivered by pMDI. A slight but statistically significant decrease in this measure was observed comparing values obtained at the lowest (40 L/min) and highest (60 L/min) PIFs studied.

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