Comparison between *in vitro* performance of the Child "Alberta" Idealized Throat and Ph.Eur./USP induction port for the delivery of salbutamol sulfate inhalation aerosol by pressurized metered dose inhaler

An initial experimental investigation

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Introduction

The right-angle bend European Pharmacopeia/United States Pharmacopeia (Ph.Eur./USP) throat (also referred to as the induction port) is recognized as the standard upper airway model for the laboratory evaluation of emitted aerosol aerodynamic particle size distribution (APSD) from orally inhaled products (OIPs).[1,2] Although this inlet has proven to be satisfactory as a means of establishing a standardized testing regime for the assessment of product quality in the regulatory environment, it is well established that its characteristics with respect to aerosol transfer through its interior are not well matched to the actual flow behavior that takes place in the adult upper airway.[3] As a result, it has proven difficult to develop robust *in vitro/in vivo* correlations (IVIVCs), when assessing the performance of OIPs in the clinical setting.[4]

The flow dynamics within the Ph.Eur./USP throat are complex at the flow rates used to evaluate OIPs, involving turbulent as well as inertial deposition of particles in transit.[5] However, evidence shows that the compendial inlet removes fewer of the larger particles entering than would be the case in an adult oropharynx, based on displacement of curves describing the movement of deposition efficiency to larger particle aerodynamic diameters, when this inlet was used in a comparative study with anatomic inlets.[6] Following from the theoretical work of Stapleton, et al. on the flow dynamics in the adult oropharynx,[7] Finlay and coworkers at the University of Alberta, Edmonton, Canada, developed an "idealized" upper airway model to mimic aerosol interaction as would be the case with an average adult human oropharynx. This adult "Alberta" idealized throat (A-AIT) can be manufactured relatively easily in aluminum, in contrast with anatomically-correct oropharyngeal models.[8] Apart from its ability to mirror the behavior of particle transport through the oropharynx, the use of metal rather than non-conducting materials in its construction may be important in the context of possibly mitigating the influence of electrostatic charge that is known to be present with all types of inhaler-generated aerosols.

The acquisition of electrostatic charge by inhaler-generated aerosols is highly probable, given the processes of triboelectrification with dry powder inhaler-generated aerosols[9] and charge transfer associated with ligament formation and break-up during the liquid atomization processes that are associated with nebulizing systems and pressurized metered dose inhalers.[10] There is evidence that aerosol electrostatic charge can influence lung deposition,[11] but the underlying physical processes have not thus far been explained. For this reason, any coating of internal surfaces of a (conducting) metal inlet to mimic mucosa should be undertaken using an electrically-conducting substance.

A scoping study was undertaken to compare APSDs of pMDI-delivered salbutamol sulfate (SS) aerosols through the A-AIT and Ph.Eur./USP inlets (at a flow rate of 30 L/min representing adult inhalation) to a Next Generation Pharmaceutical Impactor (NGI).[10] The authors concluded that the former slightly reduced the mass of coarser particulate emitted from the pMDI entering either the full resolution ACI or abbreviated impactor measurement apparatus configured to collect fractions of possible relevance in terms of particle deposition at key locations in the human respiratory tract (AIM-pHRT configurations), compared with the situation in which the compendial Ph.Eur./USP induction port was used. The overall outcome with the A-AIT was a slight, but

measurable, shift of the impactor-sized APSD of the product to finer sizes.

Since this study was undertaken, Finlay's group has developed a child version of the AIT (C-AIT), whose aerosol pathway is based on computed tomography (CT) upper airway data from nine children aged 6 to 14 years, in similar materials to those used with the adult version.[11] This inlet is now available commercially (Copley Scientific Ltd., Nottingham, UK). The aim of the present investigation was, therefore, to repeat the original study but this time operating the NGI at the lowest flow rates for which an archival calibration data-set is available (15 L/min),[12] deemed to be more suited to mimic an average inhalation flow rate by a tidal-breathing small child aged approximately 4 to 10 years.

Materials and methods

All measurements were undertaken using the NGI as the particle size fractionating instrument, delivering the SS aerosol emitted from primed, commercially-available pMDIs (100 µg/actuation ex metering valve), directly to the entry of the inlet on test, with sampling at 15.0 L/min ± 5%, as illustrated in Figure 1. The patient instructions for the inhaler used were non-specific as to detailed preparation for use, so the authors chose to actuate the inhaler 10 times, with each actuation consisting of a 5-second shake, a 2-second actuation, followed by a 5-second hold, before removing the device for the next actuation cycle.

Two different analysts and two different inlets of the same type (Devices 1 and 2) were evaluated following the scheme outlined in Table 1 to minimize possible bias from operator and test order. Each inlet configuration was therefore tested 6 times.

Following each measurement, the apparatus was dismantled and the mass of SS recovered from the interior of the throat and each stage of the NGI was assayed by a validated HPLC-spectrophotometric procedure. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) for each configuration were determined using CITDAS v.3.10 statistical analysis software (Copley Scientific Ltd., Nottingham, UK).

Results

Figure 2 represents the mass deposition profiles through the entire measurement system, including the inlet. Each contribution is represented in percentage terms based on the total mass/actuation of SS emitted from the pMDI on test. This approach was chosen rather than presenting the data in terms of absolute mass because the values of total mass ex inhaler (mean ± SD) with either inlet were insignificantly different (Ph.Eur./USP Inlet = 101.5 ± 5.5 µg/actuation; C-AIT = 103.0 ± 7.1 µg/actuation [unpaired t-test, p = 0.93]).

Examining the data as a whole, regardless of analyst or pMDI, the bulk of the SS (mean ± SD) was recovered from either inlet, but significantly more (82.4 ± 1.6%) was collected from the C-AIT than from the Ph.Eur./USP design (67.4 ± 2.1%) [un-paired t-test, $p < 0.001$]. The choice of device had minimal effect on this outcome (C-AIT inlet: device 1 = 82.8 ± 0.8%; device 2 = 81.7 ± 2.2%; Ph.Eur./USP inlet: device 1 = 69.3 ± 2.2%; device 2 = 65.6 ± 1.3%). Figure 3 illustrates the same data, but without the throat deposition, so that the difference in the mass deposition on size-classifying stages contributing to the APSD is more evident.

The cumulative mass-weighted APSDs for the two inlets, combining the data from both devices in each instance, are compared in Figure 4. If these APSD data for each inlet type are plotted on a log-probability scale (not shown), the results were straight lines between 1% (bottom of range measured by CI) and 90% (stage 2 of CI). There was also no evidence of bi-modality at higher probability values, both lines just curved slightly to become less sensitive to changes in aerodynamic diameter. Both APSDs were unimodal and close to log-normal in overall profile. Although the spread of each APSD (based on its GSD value) was unchanged, there was a small but discernable shift in APSD to finer sizes when the C-AIT was used. Thus, the average values of the derived metrics MMAD and GSD were 2.4 µm and 1.81 for the C-AIT and 2.6 µm and 1.77 for the Ph.Eur./USP inlet configuration (Table 2). The shift in APSD also resulted in a movement of fine particle mass fraction < 5.0 µm aerodynamic diameter based

Figure 1

Set-up for inlet assessment by NGI operated at 15 L/min to simulate average inspiratory flow rate associated with small child inhalation.

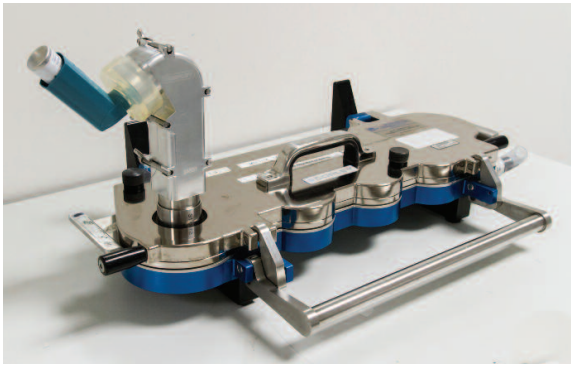


Table 1

Test order for inhalers, NGIs and analysts

		Analyst	
Test	Device	Ph.Eur./ USP Throat	C-AIT Inlet
1 2 3	Device 1	Analyst 1	Analyst 2
4 5 6	Device 2	Analyst 2	Analyst 1

Figure 2

Deposition profiles including the Child "Alberta" Idealized Throat with the Ph.Eur./USP and C-AIT inlets as alternative entries to the NGI operated at 15 L/min; error bars denote maximum/minimum range of data.

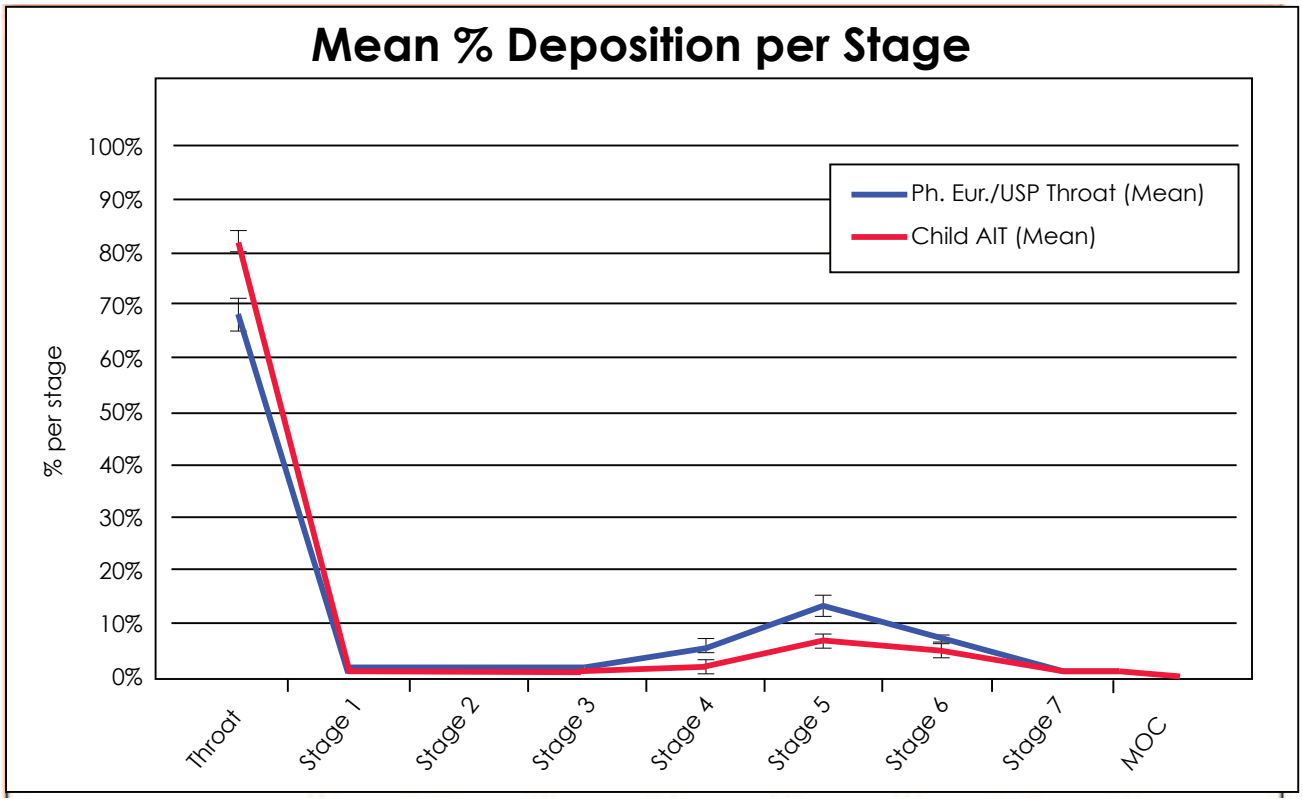


Figure 3

Impactor stage deposition profiles with the Ph.Eur./USP inlet and C-AIT inlets as alternative entries to the NGI operated at 15 L/min; error bars denote maximum/minimum range of data.

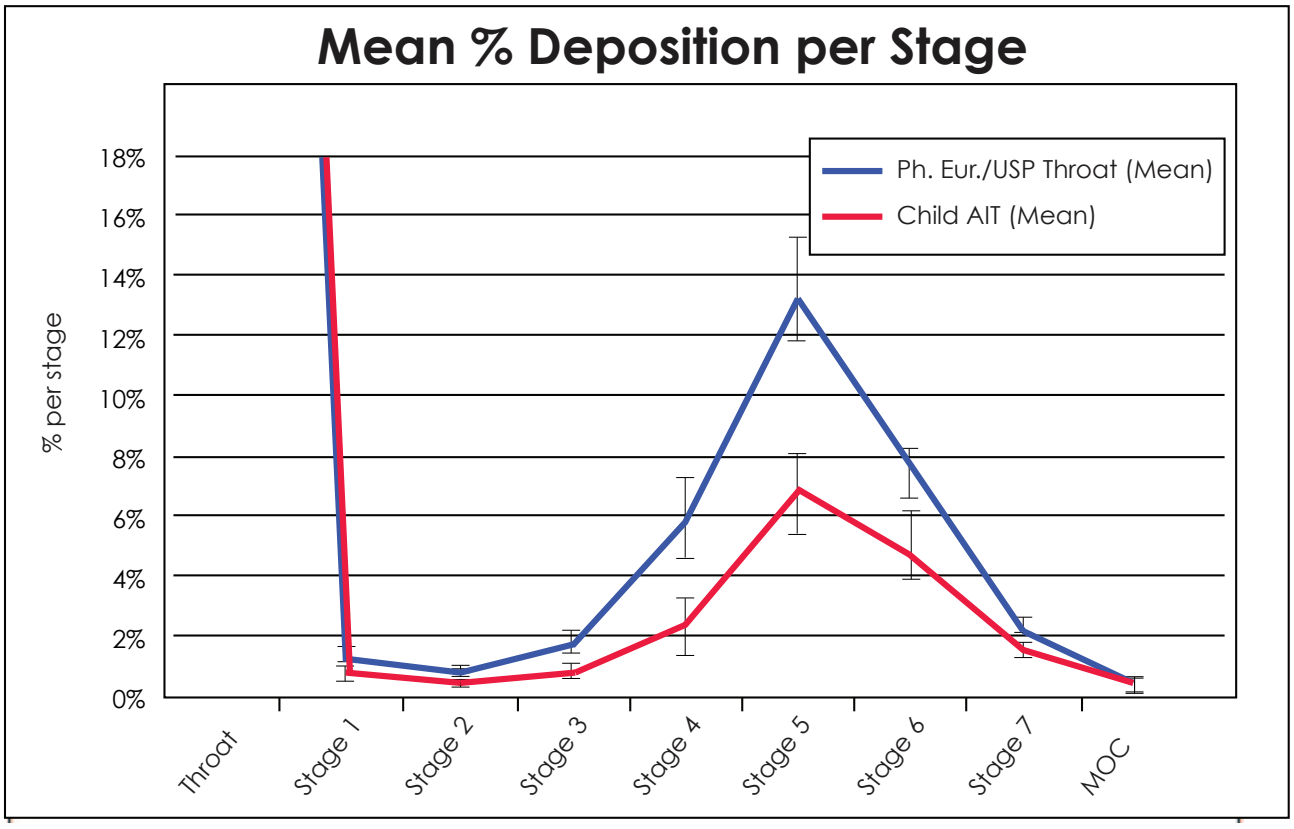
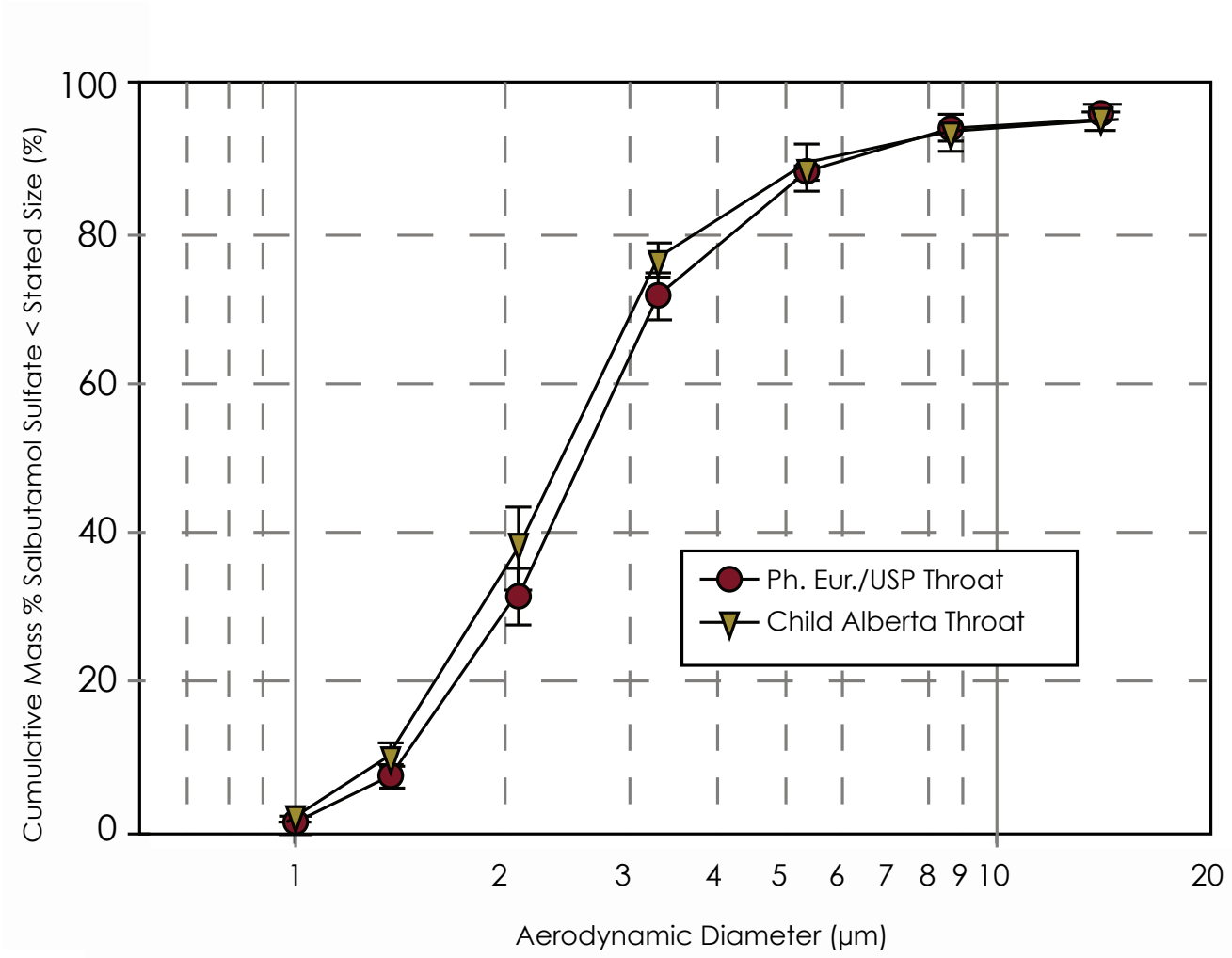


Figure 4

Cumulative mass-weighted APSDs for pMDI-delivered salbutamol sulfate, sampling by NGI at 15 L/min with the two different inlet configurations.



on the total emitted mass ex inhaler (FPF < 5.0 µm) from 28.0% for the Ph.Eur./USP inlet to 15.6% when the C-AIT was substituted. Fine particle mass per actuation, also based on total emitted mass (FPM < 5.0 µm), decreased from 28.2 µg to 16.0 µg for the same change in inlet.

Discussion

The results from the present investigation are broadly similar to the outcomes from the previous evaluation of the A-AIT with a pMDI-delivered aerosol (Figure 5),[10] confirming the trend that the Ph.Eur./USP inlet removes fewer of the larger particles from the incoming aerosol than is likely to be the case in reality. Interestingly, taking the Ph.Eur./USP inlet as reference, the magnitude of the shift of the MMAD to finer sizes was smaller for the C-AIT (7%, from 2.6 µm to 2.4 µm) compared with the equivalent movement reported previously with the A-AIT (16%, from 2.5 µm to 2.2 µm).[10] This small difference may reflect the fact that measurements were made at a lower flow rate (15 L/min), compared with 30 L/min for the original work comparing the A-AIT and Ph.Eur./USP inlet. The amount of inertial/turbulent deposition associated with the Ph.Eur./USP inlet would be expected to be reduced at the lower flow velocity (flow Reynolds number) associated with measurements made at 15 L/min rather than 30 L/min. Importantly however, the measurements of MMAD in both studies with the Ph.Eur./USP inlet were consistent (2.6 µm in the present study compared with 2.5 µm in the previous work), regardless of the flow rate reduction from 30 L/min to 15 L/min to more closely mimic child inhalation from the pMDI in the present study. The spread of the APSDs obtained with either inlet were similar, with GSD values both close to 1.8. In summary, both studies with the C-AIT and A-AIT

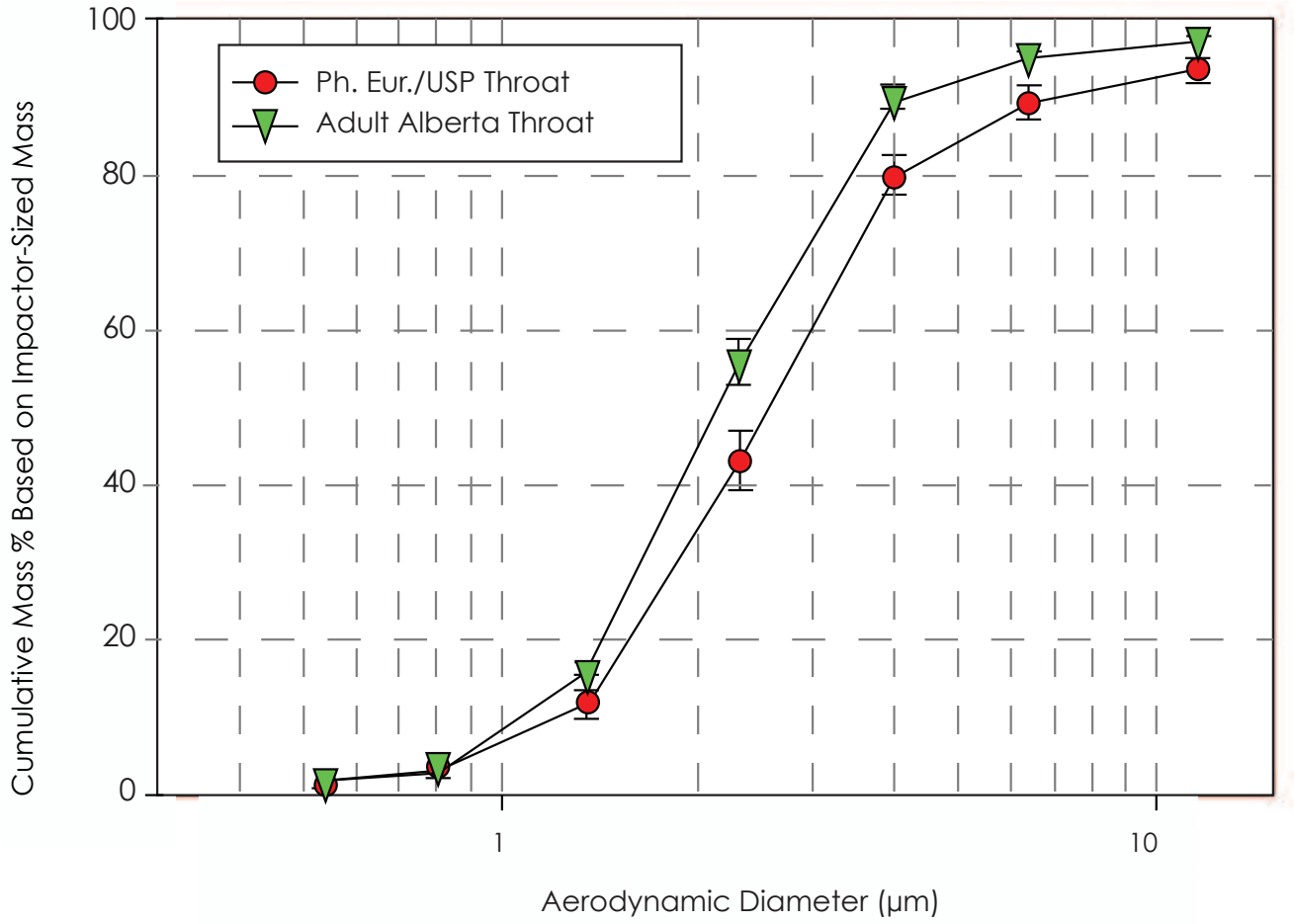
Table 2

APSD-derived metrics, mean ± SD

Measure	Ph. Eur./USP Throat	C-AIT Inlet
MMAD (µm)	2.6 ± 0.1	2.4 ± 0.1
GSD	1.77 ± 0.04	1.81 ± 0.16
FPF < 5.0 µm (%)	28.0 ± 1.2	15.6 ± 1.6
FPM < 5.0 µm (µg/actuation)	28.2 ± 2.1	16.0 ± 1.3

Figure 5

Cumulative mass-weighted APSDs for pMDI-delivered salbutamol sulfate, sampling by NGI at 30 L/min with the two different inlet configurations. Data from reference 10.



add confirmatory evidence that the idealized inlet design significantly increases the capture of the coarse fraction compared with that collected by the Ph.Eur./USP induction port.[13] This behavior is consistent with the theoretical assessment of the Ph.Eur./USP inlet by Zhou, et al., in which they predicted from considerations of inertial deposition behavior, that more of the ballistic/coarse particle fraction should penetrate downstream to the impactor from this relatively simple internal right-angle bend geometry at a given flow rate than would be the case with other more clinically-appropriate inlets that they investigated.[3]

This study and its predecessors can be criticized, in that all measurements were made at constant flow rates, rather than simulating the continuously-variable flow rate associated with tidal breathing. In defense of the approach chosen, the selection of a constant-operating flow rate (15 L/min in this particular investigation) was a compromise to keep the measurement process as simple as possible. It is important to note that the NGI, like all cascade impactors, needs to be operated in accordance with the principles of inertial impaction theory, so that stage cut-off sizes remain constant during each APSD measurement.[14] However, recent studies, in which the Nephele mixing inlet (Copley Scientific Ltd., Nottingham, UK) has been interposed between the inlet and the impactor may may offer offer a more satisfactory way forward in the future towards more clinically-appropriate testing.[15-16] In both investigations, tidal-flowing air from a breathing simulator supplied the inlet, so that patient use of the inhaler could be mimicked closely. At the same time, a fixed flow of make-up air was supplied to the impactor, located distal to the mixing inlet. Given the potential for this method to provide more clinically-appropriate data than sampling the OIP-generated aerosol at constant flow rate,[17] it is therefore recommended that these scoping studies with both C-AIT and A-AIT be repeated in due course, simulating either patient-generated breathing cycle waveforms or age-appropriate standardized breathing patterns, such as those provided in a Canadian Standard for laboratory evaluation of spacers and valved holding chambers (VHCs) used with pMDIs.[18] Furthermore, it is acknowledged that testing at a higher flow rate, such as 30 L/min, would also be a useful extension of the work to cover the upper end of the intended age range for the C-AIT, of 14 years of age.[11]

A further criticism that might be raised is that, in the clinical situation, a small child would likely have been prescribed a VHC for use with their pMDI, and so this testing should have included such an add-on device. In defense of the methodology that was undertaken, a

VHC would have retained much of the coarse component of the dose from the inhaler, preventing it from reaching the inlet of the sampling apparatus. The inclusion of a VHC was therefore considered inappropriate since the purpose of the study was to characterize the performance of the C-AIT. However, it is foreseen that a future investigation focusing more on clinically-appropriate testing by evaluating pMDI-VHC performance with the C-AIT might be a useful extension of the present work.

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