Evaluating the Alberta Throat: An innovation to support the acquisition of more clinically applicable aerosol aerodynamic particle size distribution (APSD) data in oral inhaled product (OIP) development

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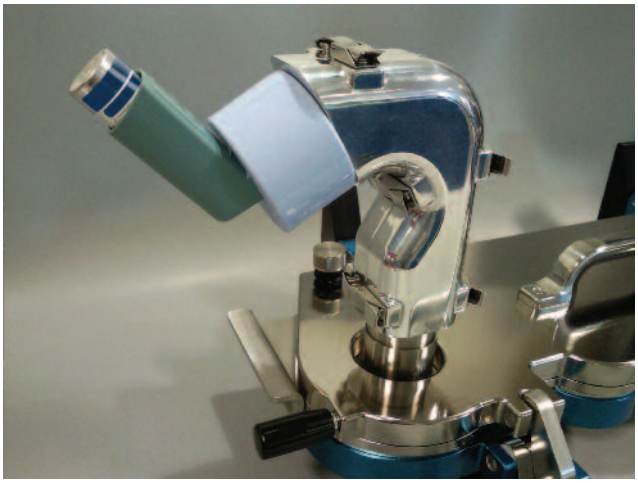


For those developing new inhaled products, establishing robust *in vitro-in vivo* relationships (IVIVRs) is an important issue. Currently, the inhaled products sector relies exclusively on *in vitro* test methods, such as cascade impaction combined with dose content uniformity, to verify product quality. These methods are simultaneously applied during development in order to shape both formulation and device performance. In the quality control (QC) environment, repeatability and method robustness are paramount, even if the method is an over-simplification of the inhalation process. In contrast, in product development, the degree to which test results correlate with clinical success is crucial to their relevance and ability to efficiently support the formulation process through a successful conclusion. The introduction of Quality by Design (QbD) into the development process has brought the question of improving the IVIVRs that exist for inhaled products into sharper focus, stimulating discussion as to whether the most appropriate tools are in place to adopt the knowledge-based strategies that QbD implies.

Cascade impactor (CI) testing is the principal technique for determining metrics that describe the aerodynamic particle size distribution (APSD) of aerosols emitted from oral-inhaled products (OIPs), primarily because mass is quantified directly in terms of the active pharmaceutical ingredient(s) of the product. Typically, it involves either an Andersen Cascade Impactor (ACI) or Next Generation Impactor (NGI) with the USP/Ph.Eur. induction port being the standard interface physically connecting the inhaler with the CI. Its purpose in the compendial methods is to provide a uniform and robust representation of the human throat and upper airway for testing purposes in the context of product quality control.

For some time, it has been evident that the USP/Ph.Eur. inlet may not provide the most accurate *in vitro* realization of aerosol transport through the upper respiratory tract.[1] Recent research undertaken at the University of Alberta on this problem resulted in the development of an "idealized" adult throat geometry from which a new inlet accessory was commercialized (Copley Scientific, UK). The "Alberta" Idealized Throat (AIT) is designed to provide a more realistic representation of behavior in a patient throat with the aim of improving IVIVRs for cascade impaction data.[2] This arti-

cle reviews the importance of such relationships in inhaled product development and discusses the development of the AIT, presenting the first set of data that assesses its performance relative to the standard USP/Ph.Eur. induction port when used as the inlet to a CI.

The laboratory testing environment

Cascade impaction is used for APSD measurement from development through QC. The data the technique delivers are therefore applied in one of two ways:

- verification of product quality (batch release);
- prediction and optimization of drug deposition characteristics in the human respiratory tract.

Recognizing the quite different demands of these applications is important in evaluating the way to fashion this aerosol measurement technique to more closely suit today's requirements.

For product quality testing, the emphasis is primarily on measurement speed and sensitivity, given that release is dependent upon the outcome of these measurements. Analytical simplicity is important, as is the ability of the technique to reliably differentiate between samples in order to detect out of specification product. The accurate representation of *in vivo* behavior is therefore less critical, provided that the technique broadly measures performance in a way that reflects trends in clinical efficacy.

In contrast, testing during the development process is perhaps more demanding, since the user is looking for detailed information about the way in which the product will behave during patient use. Obtaining data that more closely predict *in vivo* behavior and/or correlate with clinical performance is highly desirable. These goals are especially significant in light of the advent of QbD as a tool for smarter, more informed product development, in which the design space of product performance in the clinic is identified and mapped.

Establishing IVIVRs

A recently published review of the relationship between APSD and clinical efficacy concluded that, while there is evidence to support the expectation that APSD influences clinical efficacy, there are few published studies demonstrating robust correlations for OIPs.[3] This outcome is perhaps unsurprising, given the number of variables that can complicate such analysis.

A starting point for correlating clinical efficacy with *in vitro* results is to consider whether cascade impaction data accurately reflect deposition behavior within the lung. Comparative experimental work, in which lung deposition data were measured using the technique of gamma scintigraphy for a number of inhaler types, has confirmed that a correlation exists, but not direct equivalence between pertinent size-related measures of drug mass and total lung deposition.[4] Defining fine particle fraction (FPF) with an upper aerodynamic diameter limit of either 5.8 or 6.8 μm is known to result in a significant overestimation of the amount of drug deposited in the lung, deposition data showing closer absolute correlation with the amount of drug mass in the < 3 μm fraction.

If it is accepted that the mechanism of a CI does not replicate the more complex sedimentation and impaction behaviors that occur within the lung,[5] then this discrepancy is, at least in part, relatively easy to rationalize. However, imperfect simulation of the upper respiratory tract may also be a significant contributory factor,[3] since the USP/Ph.Eur induction port used with most CIs is a simple right angled bend known to only crudely reflect deposition in the mouth-throat region of the respiratory tract.[6]

Extending the link from such *in vitro* measurements beyond respiratory tract deposition to embrace clinical efficacy complicates the situation significantly, as the number of possible confounding variables greatly increases. A major factor is variability in clinical response, which may be associated with a myriad of causes; including, for example, the patient-specific form of lung-disease associated with loss of airway patency. There is also the issue of the amount of drug needed to achieve clinical efficacy and the associated complication of determining the point on the dose-response curve at which tests are carried out. Observing changes in clinical behavior when dose rates approach the plateau of the dose response curve is very difficult because, in this region, incremental increases in dose may induce an almost imperceptible change in clinical effect. Such issues help to explain the conclusion that, in many cases, there is no clear understanding of the extent of change in APSD required to change clinical impact.

In summary, while robust IVIVRs may be advantageous for development work, establishing them is complicated. However, it is reasonable to suppose that the acquisition of more clinically representative APSD data increases the prospect of providing a firmer foundation for such relationships, and is therefore a worthwhile goal that can be addressed through the evolution of more sophisticated testing strategies. The interface between the device and the CI has been identified as an important area for such improvement.[3]

Development of the Alberta Throat

One way to accurately simulate the deposition in the throat is to use an anatomically correct human throat cast to connect the inhaler and cascade impactor during testing. The major drawback is that the geometry represented by such a cast is that of a single human subject. Experimental work has shown significant differences in

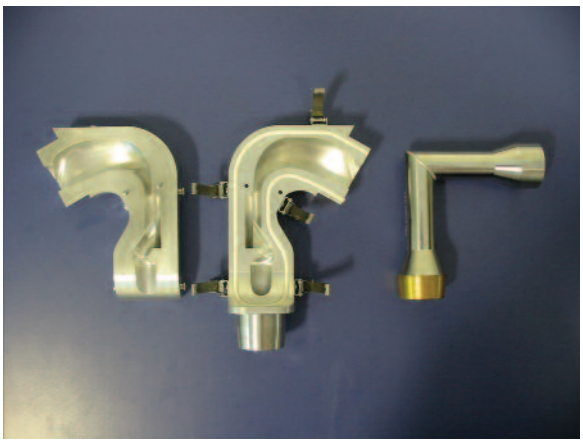
deposition behavior between various throat casts, attributable to inter-subject variability in the geometry of the mouth and throat.[7] Furthermore, such throats are complex to manufacture, handle and interface with CIs, inhibiting their wider use in routine measurement.

Arguably, the USP/Ph.Eur. induction port represents the opposite approach in inlet design to that of the cast. Developed with testing standardization in mind, it has a simple, well-defined geometry that lends itself to high-precision manufacture and consistent performance, both desirable attributes in product QC testing. Unfortunately, these benefits come at the cost of *in vivo* relevance, as this inlet design is recognized as having a tendency to provide CI-based data that significantly under-predict the amount of material captured by the upper respiratory tract.[6]

For more than a decade, researchers at the Aerosol Research Laboratory of Alberta (University of Alberta, Canada) have been working to develop a more suitable representation of the mouth-throat for routine cascade impactor testing, aiming to produce an interface that is both easy to manufacture and reflective of *in vivo* behavior, a solution that lies some way between the human throat cast and the USP induction port. Utilizing an extensive database of CT scans and reviews of anatomical texts to develop the required internal geometry, the AIT is the direct outcome of this work, now commercially available as a standardized design (Figure 1).

Figure 1

The Alberta Idealized Throat and the USP/Ph.Eur. induction port



Precision manufactured to close tolerances; the AIT has a highly reproducible, human-like geometry and delivers flow-rate-independent performance.[8] In experiments with both pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI) formats, undertaken during its development,[6] the AIT collected more of the emitted dose than did the USP/Ph.Eur. induction port, thereby replicating *in vivo* data more accurately. However, these early tests only compared deposition in the AIT with that in the USP/Ph.Eur. inlet, rather than assessing any wider impact on OIP-generated aerosol APSDs. The present study extends the experimental base by contrasting full resolution CI APSD data measured using the AIT with comparable measures gathered with a USP/Ph.Eur. induction port utilizing both pMDI and DPI formats to illustrative expectations with OIPs in general.

Comparing the performance of the AIT and USP/Ph.Eur. induction port

The relative effect of the AIT and USP/Ph.Eur. induction port on CI-measured APSD was experimentally investigated (Melbourn Scientific, UK) for two commercially available inhaler formats: a pMDI (active ingredient salbutamol sulphate) and a DPI (active ingredient formoterol fumarate.) Full resolution data were collected for both devices using the Next Generation Impactor (NGI) equipped with either the AIT or USP induction port. Six replicate measurements were conducted for each variant, resulting in 24 separate APSDs, from which the summary data in Tables 1 and 2 were derived.

Table 1

Summary data for the pMDI for the USP induction port and AIT. T/MP = throat/mouthpiece. Values are reported as µg salbutamol sulphate/ actuation. The derived metrics are based on total emitted mass/actuation from the inhaler. MMAD is reported in µm.

	USP induction port		Alberta Idealized Throat	
Stage	**Mean**	**SD**	**Mean**	**SD**
T/MP	54.2	1.6	66.8	5.1
1.0	2.9	0.6	1.1	0.2
2.0	1.8	0.1	0.7	0.1
3.0	4.0	0.3	2.2	0.6
4.0	16.0	1.9	12.7	2.0
5.0	14.2	1.5	15.5	0.9
6.0	38.0	0.6	4.3	0.5
7.0	0.7	0.2	0.7	0.1
MOC	0.5	0.1	0.5	0.1
TOTAL	98.0	3.6	104.4	8.4
FPD	37.3	2.6	34.8	3.3
FPF	38.0	1.4	33.4	1.3
GSD	1.9	0.2	1.6	0.0
MMAD	2.5	0.1	2.2	0.1

The pMDI-based product was evaluated with the NGI operated at 30 L/min and the DPI was tested at 60 L/min. All collection stages of the NGI were coated with silicone oil applied in n-hexane solution (1% w/v) for both sets of measurements. The AIT was also coated with the same solution, but the USP induction port remained

uncoated, in line with standard practice. A pre-separator was incorporated between the inlet and CI for the testing of the DPI.

Table 2

Summary data for the DPI for the USP induction port and AIT. T/MP = throat/mouthpiece. Values are reported in µg formoterol fumarate/ actuation. The derived metrics are based on total emitted mass/actuation from the inhaler. MMAD is reported in µm.

	USP induction port		Alberta Idealized Throat	
Stage	**Mean**	**SD**	**Mean**	**SD**
T/MP	1.4	0.2	3.2	0.2
Pre-separator	4.3	0.2	3.4	0.2
1.0	0.7	0.1	0.3	0.0
2.0	1.0	0.1	0.7	0.0
3.0	1.2	0.1	1.1	0.1
4.0	1.1	0.1	1.0	0.0
5.0	0.4	0.0	0.4	0.0
6.0	0.1	0.1	0.1	0.0
7.0	0.1	0.0	0.1	0.1
MOC	0.0	0.0	0.0	0.0
TOTAL	10.2	0.3	10.4	0.3
FPD	3.2	0.1	3.0	0.2
FPF	31.0	0.8	28.4	1.3
GSD	2.2	0.1	1.9	0.0
MMAD	3.5	0.1	3.1	0.0

Tables 1 and 2 show profiles of the data throughout each component of the aerosol measurement equipment (mean ± 1 SD) for the pMDI and DPI measurements respectively, combining the mass collected in the throat and inhaler mouthpiece. From these data, values were calculated for: (a) fine particle dose (FPD); (b) fine particle fraction (FPF); (c) geometric standard deviation (GSD); and (d) mass median aerodynamic diameter (MMAD). FPD and FPF were determined assuming an upper size limit of 5 µm aerodynamic diameter, based on the total dose emitted by the OIP into the AIT or USP/Ph.Eur. induction port. All calculations were carried out using CITDAS software, assuming the APSD to be uni-modal and log-normal (Copley Scientific, UK).

Focusing first on deposition in the throat/mouthpiece, it is clear that in both cases, the AIT reduces the mass of drug entering the CI. These results are entirely consistent with previously reported data[8] and strengthen the case for adopting the AIT in a research and development environment. The results from the previous study,[6] which involved internal coating of both the USP induction port and the AIT internal geometry, indicate that it is the geometry, rather than the coating, that is the primary source of the differences in drug deposition between these inlets.

The effect of the AIT becomes more evident when only the CI-sized mass is considered. Figures 2 and 3 show the deposition data interpreted as cumulative APSDs based on CI-sized mass, i.e. just assessing that part of the dose that exited the throat/mouthpiece, entering the stages of the CI that have an upper-bound size limit that is based on the effective cut-off diameter of the preceding stage (i.e., stages 2 to the back-up filter). In the case of the measurements with the pMDI-generated salbutamol aerosols, the use of the AIT shifted the APSD to finer sizes across the entire sized range. This shift is reflected in an increase in FPF (< 5 µm aerodynamic diameter) of approximately 8%, based on the impactor-sized mass/actuation. The associated

Figure 2

Cumulative aerodynamic particle size data for pMDI based on impactor sized mass for the USP induction port and AIT

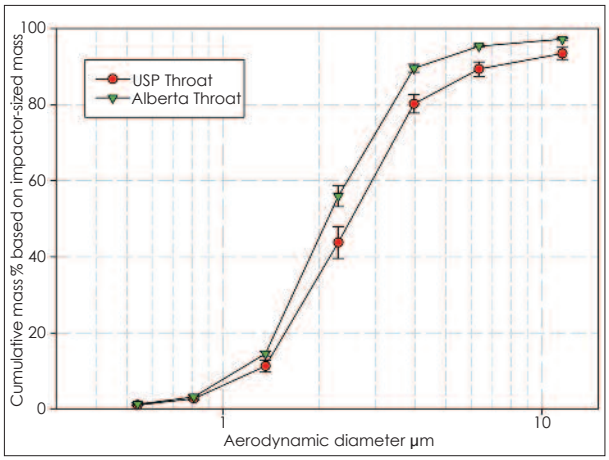
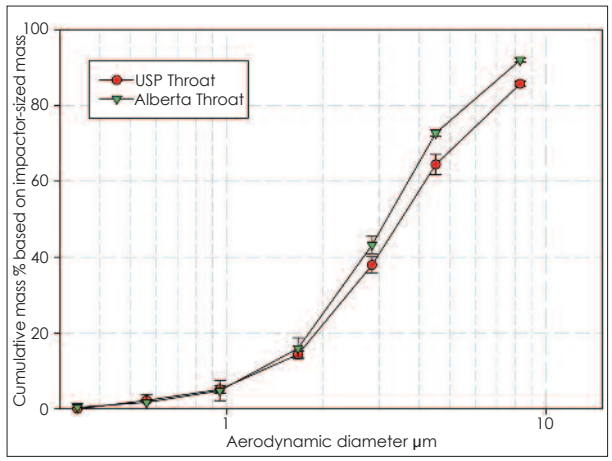


Figure 3

Cumulative aerodynamic particle size data for DPI based on impactor sized mass for the USP induction port and AIT



reduction in MMAD is 2.5 ± 0.1 μm to 2.2 ± 0.1 μm together with an observable narrowing of the GSD from 1.9 ± 0.2 to 1.6 ± 0.0. All these changes are statistically significant (un-paired t-test, $p \leq 0.05$). Identical trends are observed with the DPI, confirming the reproducible nature of the effect of the inlet change, despite the different way in which the CI is operated for such inhalers (start-up from no flow to the final nominal flow rate) compared with the constant flow rate operation throughout the measurement with pMDIs. The increase in FPF using the AIT is approximately 10%, again based on the impactor-sized mass, associated with a reduction in MMAD from 3.5 ± 0.1 μm to 3.1 ± 0.1 μm and GSD narrowing from 2.2 ± 0.1 to 1.9 ± 0.0. Again, all these changes are statistically significant ($p \leq 0.05$).

Looking ahead

The evolving requirements for OIP testing continue to stimulate interest in modifying the core analytical technique to determine emitted aerosol APSD by CI testing. While for QC the emphasis is on speed and sensitivity and the existing compendial methods appear to be satisfactory, for development work the need to achieve better IVIVRs is a driver for methodology improvements. A more representative OIP-CI interface has been identified consistently as a priority, but hitherto the lack of standardized upper airway geometries has limited the scope for method improvement. The AIT appears to offer a way forward from this situation, at least for studies associated with the development of inhalers for adult use. Beyond this development, the simulation of clinically realistic breathing from inhaler to the CI inlet would be the next logical step towards clinical reality. Although this is an issue complicated by the need to decouple flow through the device and CI, due to the requirement for CI operation at constant flow, enabling technology is already commercially available to support efforts in this area.[9]

The experimental studies reported herein indicate that the AIT may be a valuable new aid towards achieving a more clinically realistic simulation of aerosol transport from the inhaler to the CI than that provided by the current USP/Ph.Eur. induction port. The AIT captures more of the emitted dose, compared with the USP induction port that, from earlier studies, appears to underestimate mouth-throat deposition. These new data also imply that the AIT does not retain all particle sizes to an equal extent, but has a greater influence on the larger-sized particles emitted by either the chosen pMDI or DPI. These are, however, early results and more work remains to be done, first with a wider variety of inhaler types then by covering the range of flow rates achievable with currently available DPIs. Nevertheless, these findings show the potential of the AIT in terms of supporting aspirations towards the ultimate achievement of *in vitro* APSD data that more precisely represent *in vivo* lung deposition. Securing such data will be an important next step towards the development of better IVIVRs required to formulate the next generation of orally-inhaled products towards optimized clinical efficacy.

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