

# The Abbreviated Impactor Measurement (AIM) Concept: Influence of Particle Bounce and Re-Entrainment – Application to the Copley Fast Screening Andersen Impactor (C-FSA)

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## Summary

The Abbreviated Impactor Measurement (AIM) concept has been promoted as a solution to the labour-intensive full resolution cascade impactor (CI) methodology for inhaler aerosol particle aerodynamic size measurement. We report the evaluation of two abbreviated Andersen-type fast screening impactors (C-FSA and T-FSA) with pressurized metered dose inhaler (pMDI)-based formulations producing representative dry and evaporating particles to investigate the potential for non-ideal behaviour associated with particle bounce, internal losses and differences in evaporation behaviour. Both reduced impactors are substantially equivalent to the ACI provided that precautions are taken to coat collection plates to minimize bounce and entrainment. The introduction of additional dead space in the T-FSA improves agreement with the ACI in terms of fine particle fraction by providing similar conditions for ethanol evaporation.

## Introduction

Measures of coarse, fine and possibly extra-fine particle fractions may be sufficient to define the size-related behaviour of inhaled particles in the human respiratory tract (1). The Abbreviated Impactor Measurement (AIM) concept has been promoted as a possible solution to provide such metrics (2). At the same time it has the potential to improve inhaler testing efficiency by greatly reducing the labour-intensive methodology associated with full resolution cascade impactor (CI) aerodynamic particle size distribution (APSD) measurements (2). In the context of assessing the size-properties of inhaled medications either by pressurized metered dose inhalers (pMDIs) or dry powder inhalers (DPIs) that are performance-evaluated by CI, most interest is in particles finer than about 5  $\mu\text{m}$  aerodynamic diameter that are likely to penetrate the oropharynx to reach receptors in the airways of the lungs (3). Fundamentally, the size selectivity (resolving capability) of multi-stage CIs is much greater than size-related deposition selectivity in the human respiratory tract. It follows that such CIs are not an analogue of the respiratory tract with regards to describing particle deposition (4). Furthermore, many stages of full resolution CIs capture little or no active pharmaceutical ingredient (API), reducing the overall precision of the method (5). AIM-based systems offer the opportunity to improve precision by eliminating such components. However, reducing the number of operating stages of a full resolution CI to achieve this capability may result in changes to particle bounce, entrainment and losses on internal surfaces from which API is not recovered. In the case of formulations where low-volatile components such as ethanol are present, changes in internal dead space may also result in size shifts if evaporation behaviour changes. We report the outcome of an experimental study in which two fast screening Andersen cascade impactors have been compared with the full-resolution 8-stage instrument (ACI) to help validate the AIM-concept from the standpoint of having equipment that is capable of making accurate and precise measurements of the critical metrics representing APSD. These prototype systems are two out of several alternative ways by which the AIM concept can be realized (2, 6, 7). We investigated two representative pMDI-delivered formulations with these systems. Flovent™-125 (GSK Inc.) produces dry particles after flash-evaporation of the HFA 134 propellant, the other (Qvar™-100, TEVA Specialty Pharmaceuticals LLC) contains liquid ethanol in the particles emitted from the actuator of the inhaler after propellant evaporation is complete.

## Materials and Methods

The version of the Copley Fast Screening Andersen (C-FSA, Copley Scientific Ltd., Nottingham, UK) evaluated is a 2-stage impactor with back-up filter having similar design to the ACI, but with cut-point sizes of 1.0 and 4.7  $\mu\text{m}$  aerodynamic diameter to permit extra-fine particle fraction (EPF) and fine particle fraction (FPF) determinations respectively (Figure 1). A variant of the C-FSA termed the Trudell T-FSA, for convenience in differentiating these systems, (Figure 2) was also evaluated, in which stage 0 of an ACI without its collection plate was added in order to slightly increase the internal dead space. All measurements were made at a flow rate of 28.3 L/min.

In the first part, the significance of particle bounce and re-entrainment on the performance of the C-FSA versus the ACI was investigated using pMDI-delivered HFA Flovent\*-125 (125  $\mu\text{g}$ /actuation fluticasone propionate (FP)) as a representative formulation delivering dry particles mostly in the range 1-5  $\mu\text{m}$  aerodynamic diameter after flash-evaporation of the propellant (8). ACI-measured aerodynamic particle size distribution (APSD) data were used as a control, with surfactant-coated collection plates (Brij-35 polyoxyethylene 23 lauryl ether (Sigma-Aldrich, Canada) used to mitigate particle bounce. 5-actuations from the inhaler (n=5 replicates) were delivered to the impactor, representing normal practice. The C-FSA was evaluated initially with uncoated collection plates, delivering 1, 2, 5 and 10-actuations per measurement and the sequence of measurements was subsequently repeated using surfactant-coated plates. Collected FP was assayed by HPLC-UV spectrophotometry.



Figure 1: Copley C-FSA



Figure 2: Trudell T-FSA containing stage 0 without collection plate

The performance of the T-FSA was subsequently compared with that of the C-FSA, based on 5-actuations/ measurement and using coated collection plates.

In the second part, the significance of internal dead space on evaporative behaviour was examined with the abbreviated systems. A pMDI-delivered formulation containing 8% v/v ethanol in addition to API and propellant (Qvar\*-100, 100 µg/actuation beclomethasone dipropionate (BDP)/actuation) was used in this evaluation (9). Data from the full resolution ACI was again used as a control. Measurements of EPF and FPF were made after delivering 5-actuations to each CI equipped with coated plates as described in part 1. Collected BDP was assayed by HPLC-UV spectrophotometry.

Finally, the magnitude of internal losses of FP and BDP were quantified for the C-FSA and T-FSA, based on 10-actuations of each formulation, undertaken in separate experiments.

## Results and Discussion

### Measurements with Flovent\*-125

Coating of the C-FSA plates was found to be necessary to control particle bounce, demonstrated by a reduction in  $EPF_{< 1.0 \mu m}$  for single actuation data from  $9.4 \pm 0.7\%$  (uncoated, Figure 3) to  $3.1 \pm 0.6\%$  (coated, Figure 4), compared with  $1.2 \pm 0.2\%$  for  $EPF_{< 1.1 \mu m}$  in the ACI). Increasing the number of actuations/measurement onto uncoated plates to ten ( $EPF_{< 1.0 \mu m} = 5.3 \pm 0.5\%$ ) reduced, but did not eliminate bounce entirely (Figure 3). These observations are similar to those reported by Kamiya for the full resolution ACI (10). Corresponding values of  $EPF_{< 1.0 \mu m}$  were unchanged at close to 3% irrespective of the number of actuations when the plates were coated (Figure 4) and total internal losses were close to 3.4% of label claim.

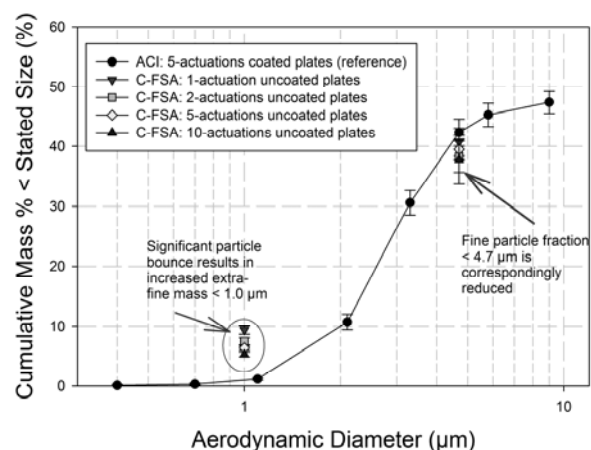
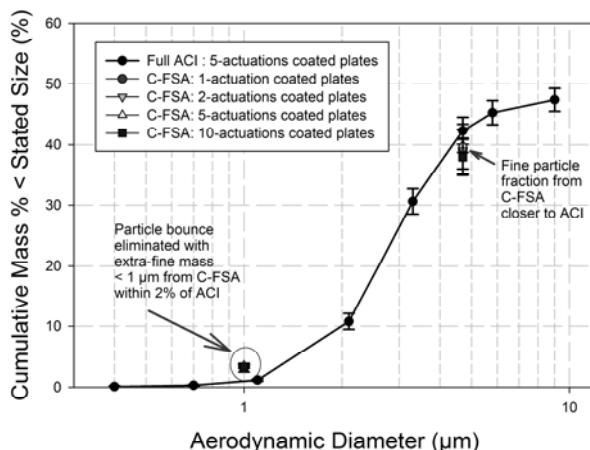


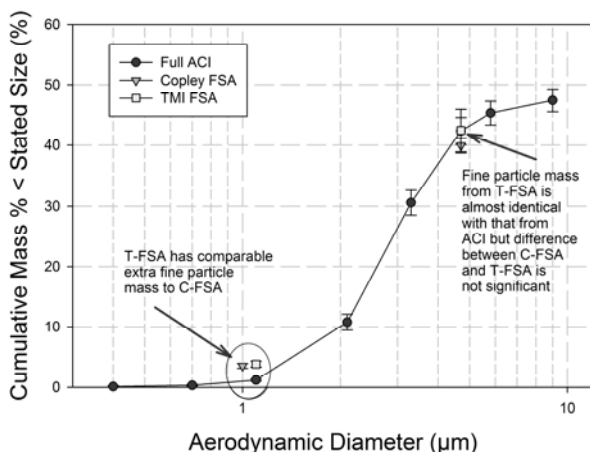
Figure 3: Collection of FP particles onto uncoated collection plates in the C-FSA

Transfer of particulate that would have been captured as internal losses on the missing stages 3-5 of the ACI (11,) to the second stage of the C-FSA is believed to explain the slight discrepancy in values of EPF between this impactor and the ACI. Irrespective of the number of actuations, values of  $FPF_{<4.7 \mu m}$  by C-FSA were close to 39% of the mass entering the impactor and about 3% lower than equivalent measures obtained by ACI. Most of this missing mass was recovered from the stage-1 metalwork, which could in practice be assayed and added to the collected stage-1 mass to render substantial equivalence between the two methods.



**Figure 4: Collection of FP particles onto Brij-35 coated collection plates in the C-FSA**

The T-FSA had similar performance with these FP-aerosols to the C-FSA (Figure 5).



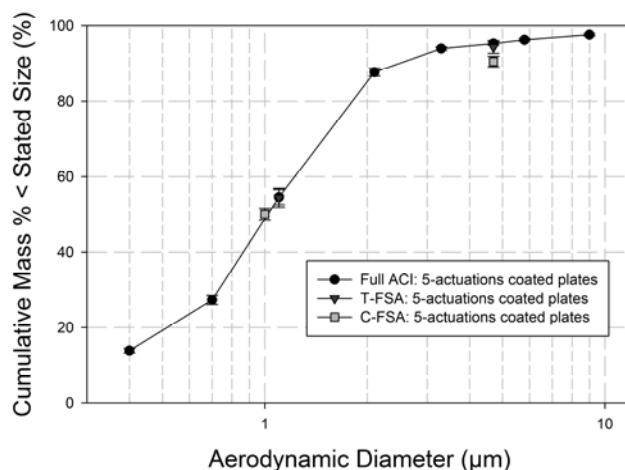
**Figure 5: Comparison of C-FSA and T-FSA for Collection of FP particles**

### Measurements with Qvar\*-100

The use of liquid ethanol-sensitive paper as collection surfaces located on top of the existing plates confirmed that the particles from Qvar\*-100 had not fully evaporated by the time that they entered any of the impactors. However, the particles collected in the lower stage of either the C-FSA or T-FSA and beyond stage 0 of the ACI were substantially dry.  $EPF_{<1.0 \mu m}$  (C-FSA) and  $EPF_{<1.1 \mu m}$  (T-FSA) were almost exactly where expected (Figure 6), and  $FPF_{<4.7 \mu m}$  from the T-FSA ( $94.4 \pm 1.7\%$ ) was almost identical with the equivalent metric for the ACI data ( $95.3 \pm 0.4\%$ ). Internal losses with the C-FSA were close to 2% of label claim, but slightly higher (nearer 3%) for the T-FSA, due to the additional stage in the latter configuration. The inclusion of the additional but inoperative stage 0 in the T-FSA appeared to achieve comparable evaporative behaviour to that which took place in the ACI.

### Conclusions

We conclude that both AIM-based approaches to determine EPF and FPF from these pMDI-based formulations provide substantially equivalent data to that which could be obtained by a full resolution ACI, as long as its collection surfaces are coated to minimize particle bounce and re-entrainment. There may be an advantage in including an inoperative stage 0 as an addition to the C-FSA to obtain closer agreement in FPF to that from the ACI. However, the effect of the slightly reduced dead space with the standard C-FSA on this metric is small, and may therefore be acceptable, particularly for quality control applications.



**Figure 6: Comparison of C-FSA and T-FSA to ACI for ethanol-containing Qvar™-100 Particles**

These validation experiments indicate that fast screening ACI designs have the potential for use with other pMDI-delivered formulations. However, it will likely be necessary for the suitability of other pMDI-based formulations as well as alternative inhaler types to be evaluated on a formulation-by-formulation basis to establish equivalency with full-resolution impactor data. This is best undertaken as part of the product development process.

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