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Research Article

The Abbreviated Impactor Measurement (AIM) Concept: Part II—Influence of Evaporation of a Volatile Component—Evaluation with a "Droplet-Producing" Pressurized Metered Dose Inhaler (pMDI)-Based Formulation Containing Ethanol as Cosolvent

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Abstract. The abbreviated impactor measurement (AIM) concept is a potential solution to the labor-intensive full-resolution cascade impactor (CI) methodology for inhaler aerosol aerodynamic particle size measurement. In this validation study, the effect of increasing the internal dead volume on determined mass fractions relating to aerodynamic particle size was explored with two abbreviated impactors both based on the Andersen nonviable cascade impactor (ACI) operating principle (Copley fast screening Andersen impactor [C-FSA] and Trudell fast screening Andersen impactor [T-FSA]). A pressurized metered dose inhaler-delivered aerosol producing liquid ethanol droplets after propellant evaporation was chosen to characterize these systems. Measures of extrafine, fine, and coarse particle mass fractions from the abbreviated systems were compared with corresponding data obtained by a full-resolution ACI. The use of liquid ethanol-sensitive filter paper provided insight by rendering locations visible where partly evaporated droplets were still present when the "droplet-producing" aerosol was sampled. Extrafine particle fractions based on impactor-sized mass were near equivalent in the range 48.6% to 54%, comparing either abbreviated system with the benchmark ACI-measured data. The fine particle fraction of the impactor-sized mass determined by the T-FSA (94.4±1.7%) was greater than using the C-FSA (90.5±1.4%) and almost identical with the ACI-measured value (95.3±0.4%). The improved agreement between T-FSA and ACI is likely the result of increasing the dead space between the entry to the induction port and the uppermost impaction stage, compared with that for the C-FSA. This dead space is needed to provide comparable conditions for ethanol evaporation in the uppermost parts of these impactors.

KEY WORDS: cascade impactor; inhaler testing; particle evaporation; particle size distribution.

INTRODUCTION

The rationale underlying the development of the abbreviated impactor measurement (AIM) concept was explained in Part I of this study, in terms of achieving the following goals (1):

1. method simplification with associated improved productivity for inhaler *in vitro* testing to assess appropriate aerosol aerodynamic particle size distribution (APSD)-based metrics that can be used to predict likely deposition behavior in the respiratory tract;
2. improved overall method precision by the elimination of impaction stages containing little or no mass of active pharmaceutical ingredient (API).

A necessary part of developing the AIM concept as a viable alternative to the current compendial procedures involving full-resolution cascade impactors (2,3) is to establish if abbreviated impactors are capable of reproducing *in vitro* performance metrics that are descriptive of the APSD of inhaler-produced aerosols (4).

In this second part of the investigation, two fast screening cascade impactors (fast screening Andersen impactor; Copley Scientific, Nottingham, UK), termed the Copley fast screening Andersen impactor (C-FSA) and the Trudell fast screening Andersen impactor (T-FSA), constructed entirely from components from a full-resolution Andersen Mark-II nonviable cascade impactor (ACI), were evaluated with a pressurized metered dose inhaler (pMDI)-generated aerosol in which one component was still evaporating when the aerosol was sampled. In brief, the C-FSA comprises two

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ABBREVIATIONS: ACI, Andersen cascade impactor; AIM, abbreviated impactor measurement; API, active pharmaceutical ingredient; APSD, aerodynamic particle size distribution; BDP, beclomethasone dipropionate; CI, cascade impactor; C-FSA, Copley fast screening Andersen impactor; CPF*, coarse particle fraction (based on impactor-sized mass); EPF*, extrafine particle fraction (based on impactor-sized mass); FPF*, fine particle fraction (based on impactor-sized mass); MMAD, mass median aerodynamic diameter of impactor-sized aerosol; pMDI, pressurized metered dose inhaler; T-FSA, Trudell fast screening Andersen impactor.

fractionation stages having cut-point sizes of 4.7 and 1.0 μm aerodynamic diameter to size-classify coarse and fine particle mass fractions, followed by a backup filter to capture the extrafine particle fraction of the sampled aerosol. The T-FSA is similar in design, but utilized stages, including stage "0" without its collection plate, taken from an existing ACI in order to augment the internal dead volume in the upper part of the impactor to be closer to that for the full-resolution CI.

The focus of the experimentation was to determine if differences in internal space (dead volume) between the abbreviated and full-resolution systems might result in discernable changes in the reported mass fractions when aerosols containing partly evaporated low volatile component (s) are sampled. Such so-called solution formulations are an important category of products delivered by pMDI (5), with ethanol widely used as a low volatile cosolvent (6).

MATERIALS AND METHODS

The investigations were undertaken using Qvar™-80 (80 μg beclomethasone dipropionate [BDP]/actuation ex inhaler mouthpiece. TEVA Specialty Pharmaceuticals LLC, Horsham, PA, USA). Qvar is a pMDI-delivered formulation that contains 8% *w*/*v* ethanol (7). Myrdal *et al*. have confirmed that particles entering full-resolution impactor systems contain partly evaporated ethanol following flash evaporation of the HFA-134 propellant that takes place almost immediately after inhaler actuation (7,8). The fully evaporated particles from this formulation have a mass median aerodynamic diameter (MMAD) that is close to 1.1 μm (9) and are, therefore, appreciably finer than those produced by Flovent®-110 (GSK Inc.) studied in Part I. However, the APSD of Qvar is sufficiently dispersed that appreciable mass of API can be collected on almost all stages of a full-resolution ACI when operated at 28.3 L/min (9). In all the situations that were investigated, recovery of collected particulate and subsequent assay for BDP was undertaken by high-pressure liquid chromatography with UV detector spectrophotometry using a validated procedure.

All measurements with abbreviated and full-resolution impactors equipped with stainless steel collection plates were undertaken at 28.3 L/min±5%. The same stainless steel ACI equipped with Ph.Eur./USP induction port that had been used in Part I was used to determine the benchmark APSD data, based on five inhaler actuations from primed inhalers, following the procedure provided in the European and US Pharmacopeias (2,3). The collection plates were each coated with polyoxyethylene (23) lauryl ether (Brij-35) surfactant to minimize the risk of particle bounce and re-entrainment, based on the outcome from Part I. Five replicate measurements were undertaken using primed pMDI canisters. Both the C-FSA and T-FSA were also evaluated with Brij-35-coated collection plates. The C-FSA was evaluated with five replicate determinations made after each of one, two, five, and ten actuations of Qvar-80 into the system in order to assess the influence, if any, of mass loading by API on the measurements. The T-FSA was evaluated with five actuations/measurement only, on the assumption than any change in performance of this abbreviated system due to the increase in collected mass of BDP would likely be similar to the characteristics of the C-FSA. Internal losses were quantified for both the C-FSA and T-FSA by recovering BDP deposited on interior surfaces other than the collection plates.

In parallel experiments, liquid ethanol-sensitive filter paper circles, cut to fit the appropriate collection plates, were used to detect the presence of particles still containing unevaporated ethanol with the C-FSA and ACI. This technique has been used successfully by Stein *et al*. in assessment of ethanol evaporation from similar solution formulations within full-resolution cascade impactors (10). These papers were placed directly on top of the uncoated collection plates in the upper three stages of the ACI and on plates for both upper and lower size fractionation stages in the C-FSA. Ten actuations/measurement were delivered to optimize the sensitivity of the procedure.

RESULTS

All measurements were undertaken at room ambient conditions (temperature from 21°C to 22°C, relative humidity from 41% to 52%). The mass recovery of BDP from both the ACI and the abbreviated impactors (data not shown) were always within ±10% of label claim ex actuator mouthpiece

Table I. Cumulative Mass-Weighted Data for Qvar-80 Measured by Full-Resolution ACI

				Cumulative Mass % < Stated Upper Size Limit (mean ± SD)
Location In CI	Size Range[a] (μm)	Upper Size Limit (μm)	Size Fraction	Impactor-sized mass excluding induction port
Induction port	>9	Undefined	$CPF^*_{>4.7\ \mu m}$	
Stage 0	>9	Undefined		100.0
Stage 1	5.8–9.0	9.0		97.6±0.3
Stage 2	4.7–5.8	5.8		96.3±0.3
Stage 3	3.3–4.7	4.7	$FPF^*_{<4.7\ \mu m}$	95.3±0.4
Stage 4	2.1–3.3	3.3		94.0±0.5
Stage 5	1.1–2.1	2.1		87.7±1.0
Stage 6	0.7–1.1	1.1	$EPF^*_{<1.1\ \mu m}$	54.6±2.0
Stage 7	0.4–0.7	0.7		27.3±1.2
Backup filter	<0.4	0.4		13.9±0.6

n=5 replicates
[a] Based on manufacturer's nominal calibration data at 28.3 L/min

Table II. Cumulative Mass-Weighted Data for Qvar-80 Measured by C-FSA with Coating on Collection Plates

				Number of actuations per determination			
				1	2	5	10
				Cumulative mass percent less than stated upper size limit (mean±SD)			
Location In C-FSA	Size range[a] (μm)	Upper size limit (μm)	Size fraction	Impactor-sized mass excluding induction port			
Induction port	>9	Undefined	$CPF^*_{>4.7\ \mu m}$	8.5±1.3	8.9±1.5	9.5±1.4	8.5±1.3
Stage 2	>4.7	Undefined					
Stage 5[b]	1.0–4.7	4.7	$FPF^*_{<4.7\ \mu m}$	91.5±1.2	91.1±1.5	90.5±1.4	91.5±1.3
Backup filter	<1.0	1.0	$EPF^*_{<1.0\ \mu m}$	53.0±1.5	53.2±1.9	50.1±1.5	48.6±1.5

n=5 replicates
[a] Based on manufacturer's nominal calibration data at 28.3 L/min
[b] Based on numbering in full-resolution ACI

(80 μg/actuation), comfortably within the limits of ±15% in guidance from a regulatory agency (11).

The benchmark ACI measurements expressed as cumulative mass percent on a stage-by-stage basis are summarized in Table I. In contrast with the methodology employed in Part I, the cumulative mass percent of BDP less than the stated size was calculated from the raw data (mass BDP/stage) excluding the induction port (impactor-sized mass). The change in data interpretation methodology was made as on this occasion the observation of the small divergences in reported metrics by the abbreviated impactors compared with the benchmark ACI-obtained data could be improved by eliminating the mass that was collected in the induction port (30–35 μg/actuation). Furthermore, due to the use of coated collection plates throughout the investigation, there was no concern about API transfer associated with particle bounce and re-entrainment.

The following metrics based on impactor-sized mass were used to compare the APSD data from the ACI with results obtained by the abbreviated system:

1. Coarse particle fraction >4.7 μm aerodynamic diameter ($CPF^*_{>4.7\ \mu m}$) for all systems,
2. Fine particle fraction <4.7 μm aerodynamic diameter ($FPF^*_{<4.7\ \mu m}$) for all systems,
3. Extrafine particle fraction <1.1 μm aerodynamic diameter ($EPF^*_{<1.1\ \mu m}$) for the ACI and T-FSA, and EPF* <1.0 μm aerodynamic diameter ($EPF^*_{<1.0\ \mu m}$) for the C-FSA.

The asterisk is used to distinguish this family of size fraction metrics from their equivalents reported from data including the induction port in Part I. Since $CPF^*_{>4.7\ \mu m}=[100-FPF^*_{<4.7\ \mu m}]$ for impactor-sized mass, values of $CPF^*_{<4.7\ \mu m}$ are included only to illustrate that this additional metric is obtainable from the systems and are not discussed further.

All metrics for the C-FSA are summarized in Table II. A comparison between this CI (5-actuations/determination only) and the T-FSA is provided in Table III where both sets of abbreviated impactor-measured data are also compared with the benchmark measures obtained by the ACI. Values of $FPF^*_{<4.7\ \mu m}$ and $EPF^*_{<1.0\ \mu m}$ for the C-FSA (one, two, five, and ten actuations/determination) are compared in Fig. 1 with equivalent results ($FPF^*_{<4.7\ \mu m}$ and $EPF^*_{<1.1\ \mu m}$) using the T-FSA. The APSD determined by the full-resolution ACI is included, also based on impactor-sized mass. The MMAD of

Table III. Key Size Fraction Metrics Determined for Five Actuations of Qvar-80 into the T-FSA: Comparison with Equivalent Data from the C-FSA and ACI

				Cumulative mass percent less than stated upper size limit (mean±SD)		
				Impactor-sized mass excluding induction port		
Location	Size range[a] (μm)	Upper size limit (μm)	Size fraction	T-FSA	C-FSA	ACI
Induction port	>9	Undefined	$CPF^*_{>4.7\ \mu m}$	5.6±1.7	9.5±1.4	4.7±0.4
Stage 2	>4.7	Undefined				
Stage 5[b]	C-FSA 1.0–4.7; T-FSA, ACI 1.1–4.7	4.7	$FPF^*_{<4.7\ \mu m}$	94.4±1.7	90.5±1.4	95.3±0.4
Backup filter	C-FSA <1.0; T-FSA, ACI <1.1	C-FSA 1.0; T-FSA, ACI 1.1	$EPF^*_{<1.0\ \mu m}$ or $EPF^*_{<1.1\ \mu m}$	54.4±2.5	50.1±1.5	54.6±2.0

n=5 replicates
[a] Based on manufacturer's nominal calibration data at 28.3 L/min
[b] Based on numbering in full-resolution ACI

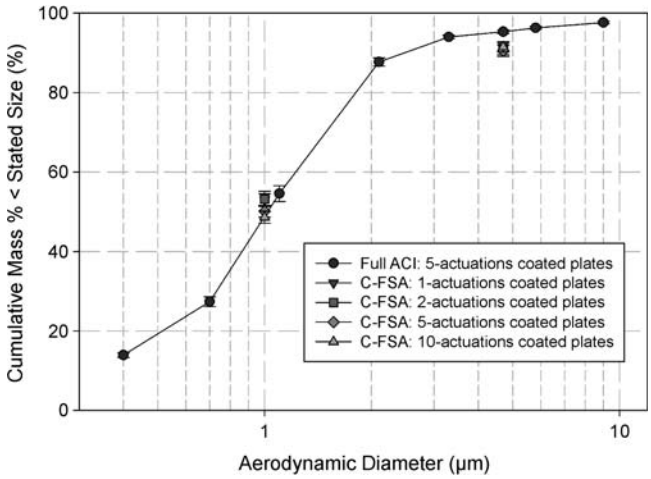

Fig. 1. Comparison of C-FSA and T-FSA to ACI for ethanol-containing particles produced by Qvar-80

the aerosol estimated from these APSD measurements was close to 1.1 μm, in close agreement with corresponding data reported by Leach using the same type of CI (9). C-FSA-measured $EPF^*_{<1.0\ \mu m}$ was not significantly influenced by the number of actuations (Kruskal–Wallis one-way analysis of variance on ranks, $p=0.09$), confirming that the precaution of precoating the plates with a tacky surface layer had been as effective at mitigating particle bounce and re-entrainment as observed with the collection of particles from Flovent-110 in Part I. Values of $EPF^*_{<1.0\ \mu m}$ ranged from 48.6% to 53.0% and were in good agreement with the equivalent value at the slightly larger size limit of 1.1 μm ($EPF^*_{<1.1\ \mu m}$) from either the T-FSA (54.4±2.5%) or the full-resolution ACI (54.6±2.0%).

C-FSA measured $FPF^*_{<4.7\ \mu m}$ varied between 90.5±1.4% (five actuations/measurement) and 91.5±1.3% (ten actuations/measurement) with no obvious trend related to the number of actuations delivered (Fig. 2). Close agreement in values of this metric was anticipated, as FPF would be expected to be less sensitive than EPF to the effect of particle re-entrainment, if any had occurred. Re-entrained particles are likely to avoid capture by stages immediately below the stage where collection should have taken place, instead traveling through the CI to be captured on the lowermost stages and by the filter (12). In comparison, $FPF^*_{<4.7\ \mu m}$ from the T-FSA at 94.4±1.7% was higher (Mann–Whitney rank sum test, $p<0.001$) and equivalent to $FPF^*_{<4.7\ \mu m}$ derived from the ACI measurements (95.3±0.4%).

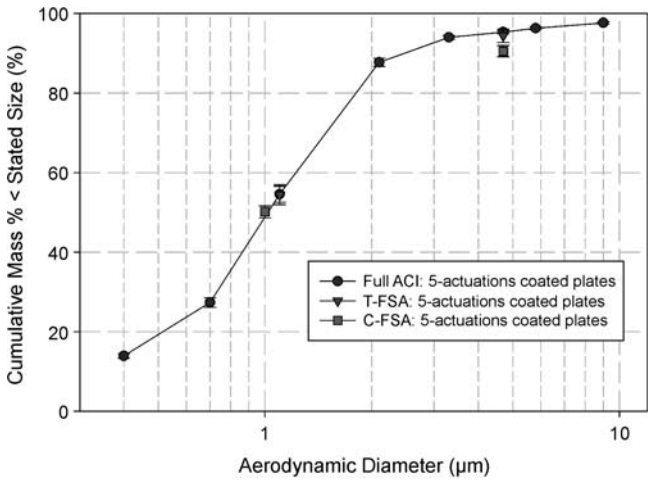

Fig. 2. Comparison of five actuation/measurement data from C-FSA and T-FSA to ACI for ethanol-containing particles produced by Qvar-80

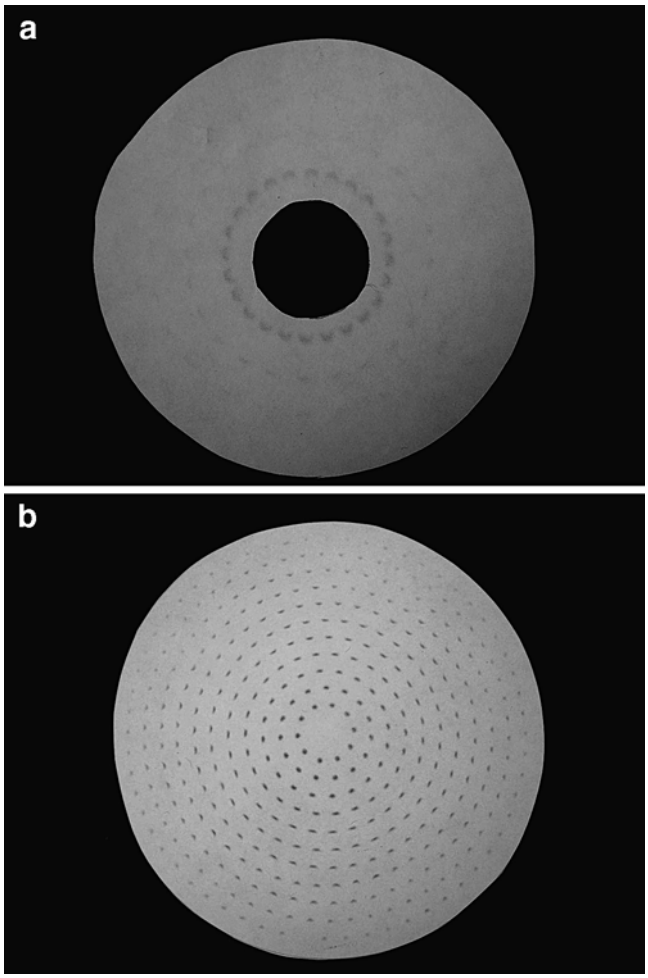

Fig. 3. a and **b** Ethanol-sensitive paper showing the presence of partly evaporated particles from Qvar-80 on the uppermost stages of ACI and C-FSA respectively

Internal losses in the T-FSA were close to 3 μg/actuation (3.75% of mass of BDP ex inhaler actuator) for Qvar-80 and were slightly higher than those obtained with the C-FSA (2.2 μg/actuation [2.75% mass ex actuator]). Almost all the differences (approximately 1 μg/actuation) originated from the mass that was recovered from the additional metalwork introduced by the nonoperational stage "0" in the T-FSA. This behavior is similar to that which was observed in Part I with Flovent-110.

The use of liquid ethanol-sensitive paper as alternative particle collection surfaces located on top of the existing plates confirmed that the particles from Qvar had not fully evaporated by the time that they reached either the first stage (stage "0") of the ACI (Fig. 3a) or the uppermost stage of the C-FSA (Fig. 3b). The absence of blue spots located beyond

either stage "0" of the ACI or beneath the jets of the lower stage of the C-FSA confirmed that the particles had become substantially dry by the time that they had traveled further into either measurement system. Similar behavior to that observed in the C-FSA was seen with the T-FSA (not shown).

DISCUSSION

By removing the influence of the induction port from the analysis of these measurements, it was possible to resolve the differences between the C-FSA and T-FSA for Qvar-80, which produced partly evaporated droplets at the point of sampling. However, it should be recognized at the outset that such differences, though statistically significant, were sufficiently small that they are unlikely to be an impediment to the use of either system as an abbreviated alternative to the full-resolution ACI for this type of formulation. However, the decision whether or not to replace the ACI with T-FSA or C-FSA measurements for such solution formulations is a judgment that will need to be based on the evaporation characteristics of the formulation under consideration because the ethanol content for other pMDI solution formulations similar to Qvar can be as much as 20% (13). Aqueous aerosols from nebulizers pose a particular problem, given the comparatively low evaporation rate of water compared with ethanol and the need to mitigate heat transfer-related evaporation from the impactor (14). Further studies are warranted to explore such aspects before the AIM concept can be adopted for the characterization of this class of inhaler-produced aerosols.

The use of liquid ethanol-sensitive paper provided important direct information about the physical state of the Qvar aerosols as they passed through both abbreviated and full-resolution CIs. Confirmation that the particles still contained liquid ethanol by the time that they reached the uppermost impaction stage of each system (stage "0" for the ACI, stage "2A" for the C-FSA, stage "2" for the T-FSA) is in agreement with the findings of Myrdal *et al.* (8). This group, using the same technique, observed that droplet impaction spots on the uppermost stage of a two-stage impactor were similar to those of the present study. Their system was also equipped with a Ph.Eur./USP induction port and was operated at room ambient conditions. More importantly, however, the liquid ethanol-sensitive paper technique was able to show that the evaporation process was substantially complete by the time that the particles reached the next stage (stage "1" in the ACI or stage "5" in the C-FSA/T-FSA systems). Given this situation, it is reasonable to link the slightly closer agreement between $FPF^*_{<4.7\ \mu m}$ obtained by T-FSA and ACI compared with the C-FSA (Fig. 2) to the fact that the dead space created by the addition of the nonoperating stage "0" within the upper part of the T-FSA (determined by the technique of Copley *et al.* (15)), was close to 70 mL greater than that within the C-FSA. By the same argument, even better agreement between the T-FSA and ACI might be anticipated if a nonoperating stage "1" was to be added as a further augmentation of this abbreviated system. However, the trade-off is the potential for increased internal losses by the presence of additional stage metalwork, as well as the inconvenience of having one more component to handle during a measurement. This investigation was, therefore, useful in confirming that, for solution formulations containing ≤8% *w*/*v* ethanol as cosolvent, the T-FSA is capable of providing near-to-identical APSD metrics to those from the full-resolution ACI.

The inclusion of a nonoperating ACI stage "1" as well as stage "0" in a modified T-FSA could be worthwhile considering when applying this system to the characterization of dry powder inhalers. Closer matching of internal dead space is likely to be advantageous under these circumstances, since it is known that the rise time of the flow rate through the impactor when following the compendial procedures is dependent upon the magnitude of the internal dead space (16).

CONCLUSIONS

The second part of a two-part experimental evaluation of the AIM concept abbreviated impactors based on the ACI principle has demonstrated that both the C-FSA and T-FSA provide values of EPF*, FPF* (and by definition CPF*) that are close to those which could be obtained by a full-resolution ACI when sampling a pMDI-derived solution formulation producing partly evaporated droplet particles. The inclusion of an inoperative stage "0" for the C-FSA may be worthy of consideration to mirror more closely the internal dead volume with that of the ACI. However, the effect of the slightly reduced dead space associated with the currently available C-FSA on values of $FPF^*_{<4.7\ \mu m}$ was so small that it may be acceptable as a systematic deviation between the two techniques. These considerations are particularly appropriate for inhaler product quality control applications where the focus is on the stability of measurements made by one particular system, rather than on the outcomes of comparisons between different measurement techniques.

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