AAPS PharmSciTech **2003; 4 (4) Article 54 (http://www.aapspharmscitech.org).**

Aerodynamic Particle Size Analysis of Aerosols from Pressurized Metered-Dose Inhalers: Comparison of Andersen 8-Stage Cascade Impactor, Next Generation Pharmaceutical Impactor, and Model 3321 Aerodynamic Particle Sizer Aerosol Spectrometer

Submitted: July 14, 2003; Accepted: September 2, 2003

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ABSTRACT

The purpose of this research was to compare three different methods for the aerodynamic assessment of (1) chloroflurocarbon (CFC) -fluticasone propionate (Flovent), (2) CFC-sodium cromoglycate (Intal), and (3) hydrofluoroalkane (HFA) -beclomethasone dipropionate (Qvar) delivered by pressurized metered dose inhaler. Particle size distributions were compared determining mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and fine particle fraction <4.7 μm aerodynamic diameter ($FPF_{<4.7\ \mu m}$). Next Generation Pharmaceutical Impactor (NGI)-size distributions for Flovent comprised finer particles than determined by Andersen 8-stage impactor (ACI) (MMAD = 2.0 ± 0.05 μm [NGI]; 2.8 ± 0.07 μm [ACI]); however, $FPF_{<4.7\ \mu m}$ by both impactors was in the narrow range 88% to 93%. Size distribution agreement for Intal was better (MMAD = 4.3 ± 0.19 μm (NGI), 4.2 ± 0.13 μm (ACI), with $FPF_{<4.7\ \mu m}$ ranging from 52% to 60%. The Aerodynamic Particle Sizer (APS) undersized aerosols produced with either formulation (MMAD = 1.8 ± 0.07 μm and 3.2 ± 0.02 μm for Flovent and Intal, respectively), but values of $FPF_{<4.7\ \mu m}$ from the single-stage impactor (SSI) located at the inlet to the APS (82.9% ± 2.1% [Flovent], 46.4% ± 2.4% [Intal]) were fairly close to corresponding data from the multi-stage impactors. APS-measured size distributions for Qvar (MMAD = 1.0 ± 0.03 μm; $FPF_{<4.7\ \mu m}$ = 96.4% ± 2.5%), were in fair agreement with both NGI (MMAD = 0.9 ± 0.03 μm; $FPF_{<4.7\ \mu m}$ = 96.7% ± 0.7%), and ACI (MMAD = 1.2 ± 0.02 μm, $FPF_{<4.7\ \mu m}$ = 98% ± 0.5%), but $FPF_{<4.7\ \mu m}$ from the SSI (67.1% ± 4.1%) was lower than expected, based on equivalent data obtained by the other techniques. Particle bounce, incomplete evaporation of volatile constituents and the presence of surfactant particles are factors that may be responsible for discrepancies between the techniques.

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KEYWORDS: pressurized metered-dose inhaler, impactor, time-of-flight, aerodynamic size distribution, aerosol measurement

INTRODUCTION

The particle size analysis of aerosols from pressurized metered-dose inhalers (pMDIs) by compendial procedures[1,2] is typically undertaken using a multistage cascade impactor equipped with United States Pharmacopeia/European Pharmacopeia (USP/EP) induction port. This technique provides a direct link with the mass of therapeutically active pharmaceutical ingredient (API) and particle aerodynamic size, which is accepted as an indication of the likely deposition location within the respiratory tract.[3] The recently introduced the Next Generation Pharmaceutical Impactor (NGI) (MSP, St Paul, MN[4]) was designed with the intent of improving the aerodynamic characteristics compared with the Andersen 8-Stage Cascade Impactor (ACI) (Thermo Andersen, Smyrna, GA) that is in widespread use for pMDI performance testing. The resulting impaction-stage collection efficiency curves of the NGI at 30 L/min[5] are generally steeper than those obtained with the ACI,[6] offering the prospect that the size fractionation process within the former will be more accurate. However, apart from a study involving prototype instruments,[7] there is as yet almost no information to guide users as to the performance of the NGI with this class of inhaler. Cascade impaction is labor intensive whichever multistage impactor is used, even with aids

to speed up sample recovery.[8] There is therefore a continued interest in the development of more efficient techniques that can be used particularly for early-stage product development.[9] In the absence of a more rapid multistage impactor-based technique, the use of so-called 'real-time' aerodynamic particle size analyzers based on the time-of-flight (TOF) principle has become quite commonplace.[10] These instruments are capable of making a particle size measurement in typically less than a minute, depending on the concentration of the aerosol that is sampled. However, TOF analyzers are susceptible to coincidence measurement problems when more than one particle is present in the measurement zone.[11,12] Furthermore, the inability of at least one type of analyzer in this class, Aerosizer, (TSI, St Paul, MN) to discriminate between particles comprising API and those of excipient/surfactant has been shown to result in significant bias when sizing the aerosol from a particular pMDI-produced suspension formulation.[13] More recently, however, studies with both the Aerosizer-LD[14] and predecessor model 3320 Aerodynamic Particle Sizer (APS) aerosol spectrometer[15] (TSI) have indicated that closer agreement with multistage impactor measurements may be possible for solution formulations where surfactant is absent. The APS is also supplied with the option of using a model 3306 Single-Stage Impactor Inlet (SSI) (TSI), having a cut-point size of 4.7 µm aerodynamic diameter, to verify the magnitude of the so-called 'respirable' mass fraction determined by the TOF analyzer.

MATERIALS AND METHODS

Formulations

Three pMDI-produced anti-asthmatic aerosols having distinctly different particle size distribution properties were evaluated (**Table 1**). Five canisters were chosen at random from each of these formulations.

ACI

Benchmark measurements were made using an aluminum ACI, sampling at 28.3 L/min ± 5%, following the procedure described in the USP.[1] The ACI contained uncoated glass collection plates with a backup glass microfiber filter (934-AH, Whatman, Clifton, NJ) located after the bottom impaction stage. In the case of the measurements with hydrofluoroalkane (HFA)-beclomethasone dipropionate (Qvar) (3M Pharmaceuticals, London, ON, Canada), 2 filters were used together in order to optimize collection of the small mass of extra-fine particles that penetrated beyond the impactor. Each canister was shaken for 10 seconds and then primed by actuating 3 times to waste; then each of 5 actuations was delivered at 30-second intervals, with the mouthpiece of the inhaler coupled on axis with the entry to the induction port. Flow through the impactor was maintained until 30 seconds following the last actuation. The impactor was subsequently disassembled and the API recovered quantitatively from the induction port, collection plates, and after filter, and then assayed by high performance liquid chromatography (HPLC)-UV spectrophotometry in accordance with established internal procedures. The size distribution from each of the canisters was determined using the generic stage cut sizes supplied by the manufacturer, in accordance with compendial practice.[1]

NGI

The NGI measurements were made at 30.0 L/min ± 5%, also following the practice described for the ACI in the compendial method.[1] The 304 stainless steel collection cups were not coated with an adhesive agent, based on previous experience using this impactor with pMDI-based aerosols.[7] The NGI was used as supplied for measurements with both chlorofluorocarbon (CFC)-fluticasone propionate (Flovent, GSK Inc., Research Triangle Park, NC) and CFC-sodium cromoglycate (Intal, Rhône-Poulenc Rorer Canada Inc., Montréal, QC, Canada), since the micro-orifice collector (MOC) acted as a substitute for a backup filter. However, measurements made with a prototype instrument with Qvar had indicated that the MOC by itself might not have captured all of the extra-fine particles that penetrated beyond stage 7.[7] An external filter unit (MSP) containing 2 layers of 934-AH glass microfiber was therefore connected to the outlet of the NGI for measurements with this formulation. The operation of the pMDI canisters was as described for measurements by ACI.

APS and SSI

The APS and SSI were operated together. The APS counts particles as they pass individually through the measurement zone where their aerodynamic size is determined, so it was necessary to transform the raw TOF data to a mass-weighted size distribution using the proprietary software provided (Aerosol Instrument Manager, rev B [2002], TSI). The aerosol emitted from the inhaler was withdrawn at the nominal 28.3 L/min flow rate via a USP/EP induction port into the SSI, where the incoming aerosol was sampled isokinetically at

Table 1. pMDI Produced Aerosols Evaluated by the Aerodynamic Particle Sizing Methods*

Name	Manufacturer	Formulation Description
Flovent-125	GSK Inc (Canada)	CFC-11/12 propellant mixture Lecithin surfactant 125 µg/actuation fluticasone propionate†
Intal-1 mg	Rhône-Poulenc Rorer Inc (Canada)	CFC-11/12 propellant mixture Sorbitan trioleate surfactant 1000 µg/actuation sodium cromoglycate†
Qvar-100	3M Pharmaceuticals (Canada)	HFA-134a propellant Ethanol cosolvent No surfactant 100 µg/actuation beclomethasone dipropionate†

*CFC indicates chlorofluorocarbon; HFA, hydrofluoroalkane; and pMDI, pressurized metered-dose inhaler.
†Mass API/actuation expressed ex metering valve.

0.062 L/min (0.2% of the sample) directly to the APS (**Figure 1**).

The remainder of the flow passed through the SSI. The portion of the mass entering this impactor contained in particles smaller than 4.7 µm aerodynamic diameter (defined as the fine particle or "respirable" fraction [$FPF_{<4.7\ \mu m}$]) was determined by HPLC-UV spectrophotometric assay for the API collected on the after-filter of the impactor (containing 2 layers of 934-AH glass microfiber) and used to verify the equivalent result presented by the TOF-based particle size measurements made using the APS. On this basis, $FPF_{<4.7\ \mu m}$ could be determined as a percentage of the total mass entering the SSI in accordance with:

$$FPF_{<4.7\mu m} = \left[\frac{M_{filter}}{(M_{stage} + M_{filter})}\right]100 \qquad (1)$$

where M_{stage} and M_{filter} are the masses of API that collect on the stage impaction plate and backup filter of this impactor, respectively.

Where appropriate, a correction was applied to the APS-measured size distribution data to account for size-related losses in the sampling system. This correction was based on the 100:1 size-efficiency relationship obtained for the Aerosol Diluter (model 3302A, TSI), also available for use with the APS, on the basis that the capillary dimensions and aerosol pathway from the isokinetic nozzle to the exit of the impactor inlet were similar [T. J. Beck, TSI Inc, November 2002 conversation]. The operation of the pMDI canisters was again as described for the measurements using the multistage impactors.

Interpretation of Data and Statistical Analysis

The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), representing the measures of central tendency and spread, respectively, were used as metrics with which to compare the size distribution data. Since the central region (between 16th and 84th percentiles) of the size distributions of all 3 formulations obtained from the multistage impactors was in general well described by a log-normal distribution function, the raw data were subjected to nonlinear regression analysis in accordance with the technique described by Thiel[16] in order to establish values of MMAD without the need to interpolate. The APS provides 43 size classes between 0.52 and 10.4 µm aerodynamic diameter, so that error associated with interpolation between adjacent size classes to determine the MMAD was judged in this instance to be sufficiently small to be acceptable.

$FPF_{<4.7\ \mu m}$, was also determined from the size distribution data since this parameter is appropriate as a measure of the therapeutically beneficial portion of the inhaled mass of anti-asthmatic medications capable of reaching the airways of the lower respiratory tract.[17]

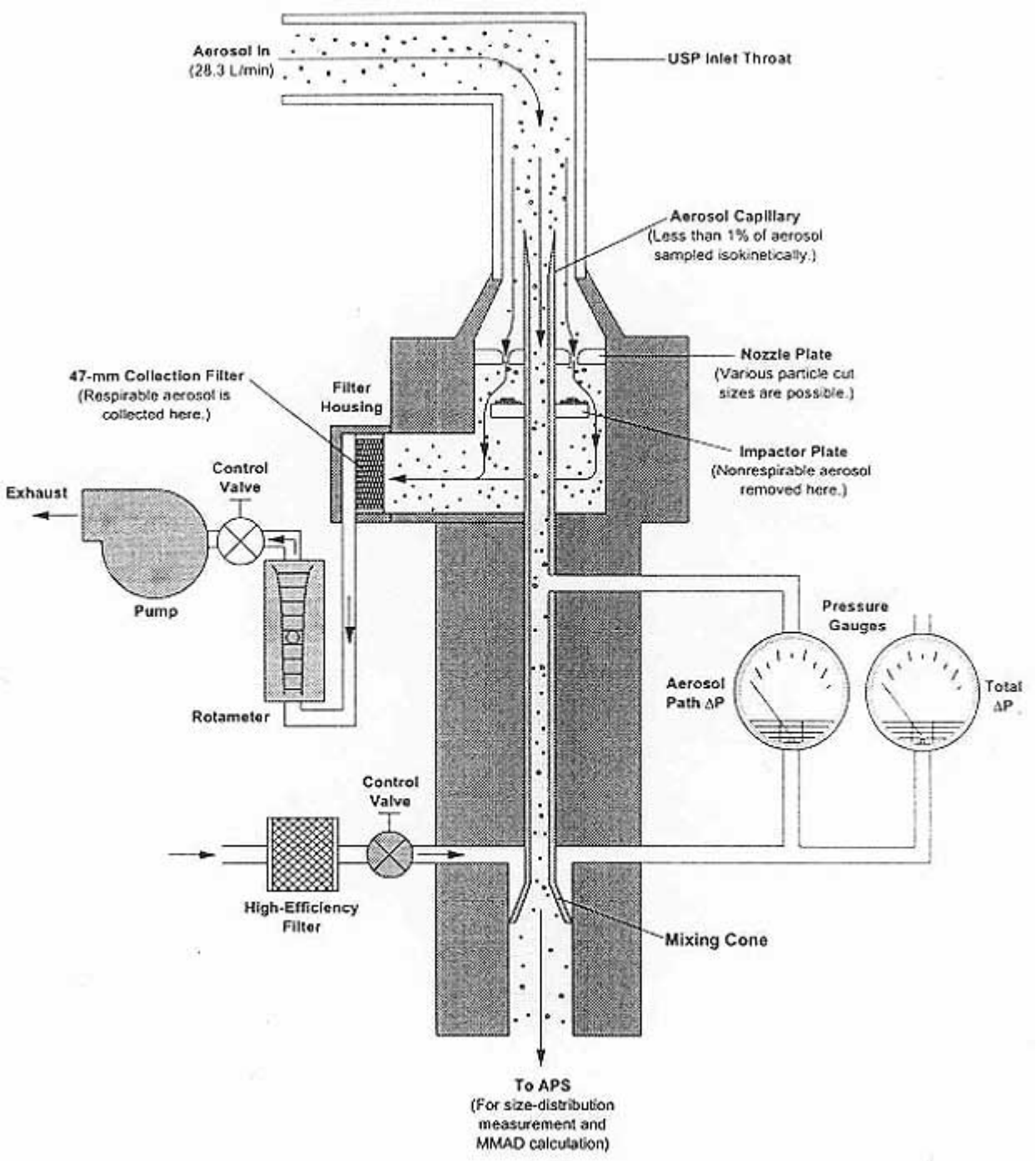

Figure 1. Schematic of model 3306 showing flow pathways to the single-stage impactor and APS. (Courtesy TSI Inc).

This parameter was obtained directly from the size distributions measured by both ACI and APS as both instruments have size class limits that correspond exactly to 4.7 μm aerodynamic diameter. $FPF_{<4.7\ \mu m}$ could also be determined directly from the SSI, since its cut size is fixed at 4.7 μm aerodynamic diameter. $FPF_{<4.7\ \mu m}$ was estimated by linear interpolation for the NGI since stages 2 and 3 have cut sizes of 6.4 and 4.0 μm aerodynamic diameter, respectively, at 30 L/min.

Statistical interpretation of the data derived from the size distributions obtained by the various procedures was undertaken using appropriate tests of significance (SigmaStat, version 2.3, SPSS Science, Chicago, IL). Differences were deemed significant when $P < .05$.

Values of the reported performance metrics represent mean ± SD based on 5 replicate measurements unless otherwise stated.

RESULTS AND DISCUSSION

The choice of the ACI as the benchmark device for the present study reflects the widespread use of this impactor for the measurement of pharmaceutical aerosols by the compendial procedure.[1] The results from this study do not enable any claim to be made in terms of the accuracy of this impactor in comparison with the other techniques.

Mass recovery of API was within ± 20% of label claim for the measurements with both ACI and NGI. The mean mass loading of the NGI, based on 5 actuations per measurement and considering only the mass that penetrated beyond the induction port to the impactor, was substantially greater for Intal (1443 µg) compared with either Qvar (227 µg) or Flovent (246 µg). Similar total mass loading data (not shown) were obtained for the ACI.

Comparative size distributions for the ACI, NGI, and APS for Flovent, Intal, and Qvar are summarized on a cumulative mass-weighted basis in **Figures 2**, **3**, and **4**, respectively, using log-probability scaling.

Only minor differences were observed in GSD values between the 3 measurement techniques for Qvar and Intal (**Table 2**), and GSDs for Flovent aerosols were equivalent (P = .87). No technique, therefore, consistently produced size-distribution data that were consistently less or more disperse than data obtained by the other 2 instruments. However, although values of MMAD for Intal determined by either of the multistage impactors (4.3 ± 0.19 µm [NGI], 4.2 ± 0.13 µm [ACI]) were comparable (unpaired t test, P = .29), the NGI-measured MMAD for Flovent (2.0 ± 0.05 µm) was significantly finer than that obtained by ACI (2.8 ± 0.07 µm) (P < .001). The ACI-based MMAD was, however, within the range from 2.4 to 2.8 µm reported by Cripps et al for this formulation, also using this type of impactor.[18]

Overlap of the collection efficiency curves of neighboring stages of either impactor is an unlikely cause of the observed differences between MMAD values obtained from the multistage impactors for Flovent, as the effect is reported to be small below stage 2 based on a previously published calibration of an ACI,[6] and should be even less apparent with the NGI in view of its sharp and well-separated stage collection efficiency curves.[5]

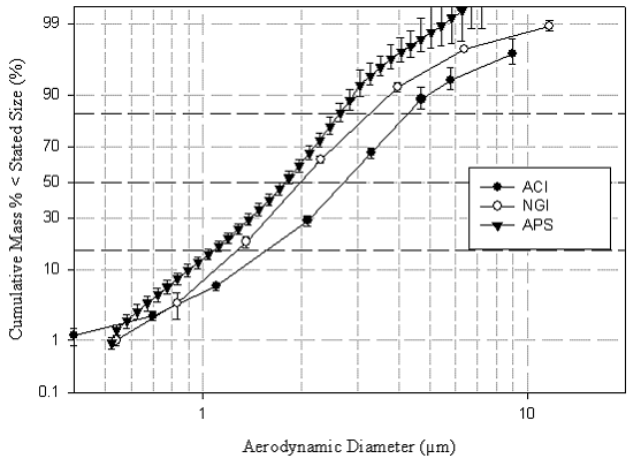

Figure 2. Comparison of ACI-, NGI-, and APS-measured size distributions for Flovent.

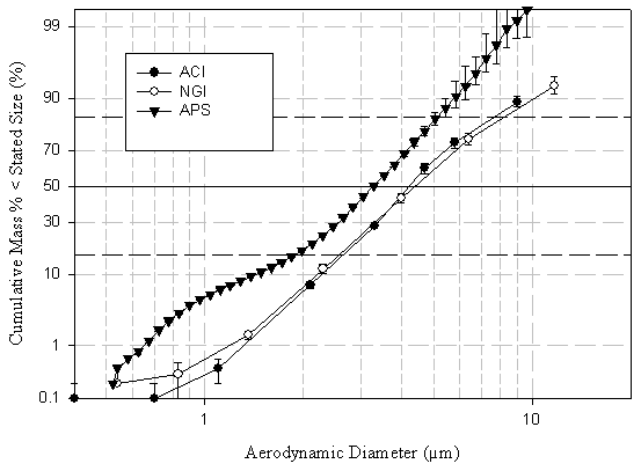

Figure 3. Comparison of ACI-, NGI-, and APS-measured size distributions for Intal.

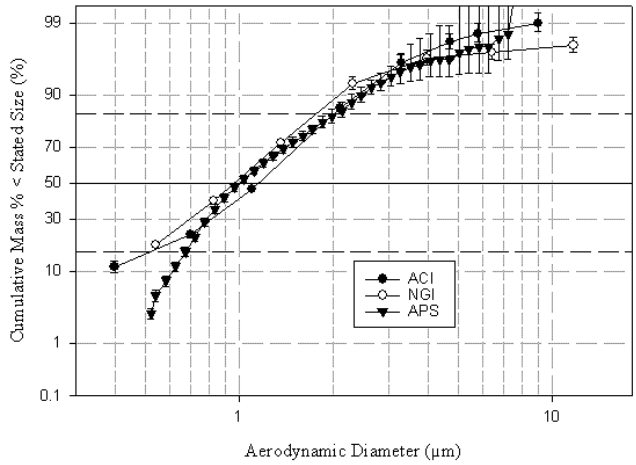

Figure 4. Comparison of ACI-, NGI-, and APS-measured size distributions for Qvar.

Table 2. Size Distribution Parameters Obtained From the ACI, NGI, and APS*

	Flovent		Intal		Qvar	
	MMAD (μm)	**GSD**	**MMAD (μm)**	**GSD**	**MMAD (μm)**	**GSD**
ACI†	2.8 ± 0.07	1.56 ± 0.03	4.2 ± 0.13	1.63 ± 0.04	1.2 ± 0.02	1.84 ± 0.06
NGI†	2.0 ± 0.05	1.55 ± 0.07	4.3 ± 0.19	1.75 ± 0.04	0.9 ± 0.03	1.82 ± 0.03
APS	1.8 ± 0.07	1.57 ± 0.02	3.2 ± 0.02‡	1.66 ± 0.04‡	1.0 ± 0.03	1.74 ± 0.05

*ACI indicates Andersen 8-stage cascade impactor; APS, aerodynamic particle sizer; GSD, geometric standard deviation; MMAD, mass median aerodynamic diameter; and NGI, next generation pharmaceutical impactor. Except where indicated, n = 5 replicates/technique.
†Size distribution parameters are based on mass penetrating the induction port and entering the impactor.
‡4 replicate measurements.

There are at least 2 other possibilities to consider, and both potential causes may have contributed to the observed behavior. Kamiya et al[19] have recently reported that the NGI, if used with uncoated collection cups, undersized a CFC-suspension formulation (Vanceril, Schering-Plough, Kenilworth, NJ) that has similar size distribution characteristics to Flovent. They obtained close agreement between NGI- and ACI-measured data when their cups were precoated with silicone oil to improve particle adhesion. The NGI does appear to be at greater risk than the ACI of bias caused by this effect. Stage Reynolds numbers, which govern particle velocity and therefore kinetic energy at the point of collection in an impactor,[20] are in the range from 324 to 2938 at 30 L/min for the NGI, as a direct consequence of optimizing its aerodynamic performance,[4] whereas the equivalent range for the ACI is from 110 to 782.[20] At first sight, the agreement achieved between NGI- and ACI-measured size distributions for Intal is difficult to reconcile. However, although the sodium cromoglycate particles are in general larger than those formed from Flovent, they are hygroscopic,[21] likely making their surfaces tacky under the conditions of the present study, and therefore more prone to adhere to an uncoated surface. In view of these observations, it may be prudent to coat the collection cups of the NGI with an adhesive agent to be sure that particle bounce does not occur, unless it can be demonstrated that this phenomenon is not occurring to a significant extent with a given formulation.

It is also possible that propellant evaporation was not fully complete by the time that sampling of particles produced from Flovent took place. Under these circumstances, the size distribution measured by the impactor having the larger internal volume (1000 mL, NGI; 450 mL, ACI) might be expected to be finer as a result of more complete evaporation having taken place by the time that the particles were collected. The boiling point of CFC-11 is 23.8°C at 101.3 kPa, so that at room ambient conditions close to 22°C, evaporation of this component would be expected to be relatively slow compared with that of CFC-12 (boiling point -26.1°C). However, published data on this effect are scant. Morén[22] commented that the initial flashing of liquid propellant to vapor as pressure is relieved upon actuation is so rapid that heat required for the change of phase is taken from the liquid remaining, therefore resulting in cooling of the droplets. Further evaporation then occurs as energy is acquired from the surrounding air molecules; this evaporation is slow compared with the flashing process. Morén and Anderson,[23] in a study involving a formulation containing terbutalene sulfate in a CFC-11:12:114 mixture, reported MMAD values that decreased from 43 μm immediately after actuation to 14 μm at a distance of 10 cm from the canister. On this basis, aerosol transport beyond the induction port might therefore have taken place before propellant evaporation was complete. However, precise evaporation behavior will depend on actuator orifice diameter, the mass of formulation metered per actuation, and aerosol pathway into the impactor, as well as physical properties of the propellant,[24] so that data from studies, such as that of Morén and Anderson can only provide a general indication of the magnitude of this effect.

The agreement between measurements by both impactors for Intal in the present study is also explicable in terms of propellant evaporation behavior if the kinetics of evaporation of propellant from droplets containing a large mass concentration of solids (as is the case with Intal) approached equilibrium more rapidly. Furthermore, the relatively large particles produced by Intal compared with those formed from Flovent, travel a shorter distance into either impactor before being collected, so that differences in internal volumes between the NGI and ACI would be expected to be less important.

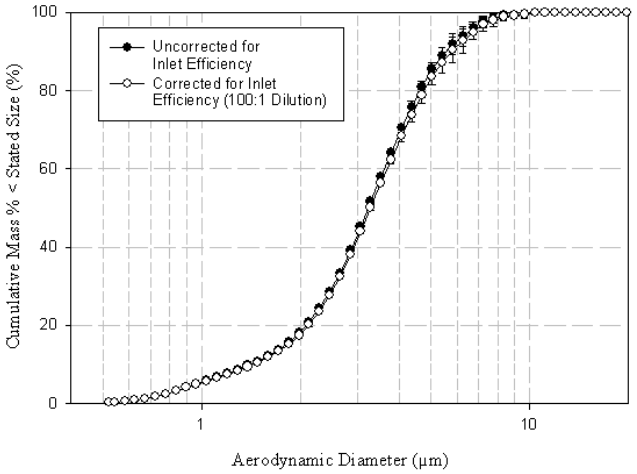

Figure 5. Effect of correction for inlet sampling efficiency on APS-based size distribution measurements for Intal.

NGI-measured particle size distributions for Qvar were also finer than those obtained by the ACI (MMAD = 0.9 ± 0.03 [NGI]; 1.2 ± 0.02 [ACI]) ($P < .001$). Again the ACI-based MMAD was in close agreement with 1.1 µm reported previously for this formulation, also using this type of impactor.[25] In the case of this formulation, the finer MMAD measured by the NGI compared with ACI can also be explained in terms of differing evaporation behavior. However, in this instance, the ethanol solubilizer (boiling point 78°C) is more likely than HFA-134a propellant (boiling point -26.5°C) to have been incompletely evaporated when the particles were collected. This explanation is supported by data from a study by Gupta et al,[26] who demonstrated that ethanol evaporation is incomplete at the distal end of a USP induction port, working with a range of solution formulations similar in composition to Qvar.

It should be noted that the APS-measured size distributions were not corrected for particle counting efficiency as a function of particle size, since Peters and Leith[27] recently indicated that counting efficiency is size independent in the range of 45% to 60% between 0.7- and 4-µm aerodynamic diameter for the model 3321 APS. However, a correction was made for the sampling efficiency of the SSI (see Materials and Methods section). The effect of this correction on the reported size distribution data was found to be negligible, except for Intal (**Figure 5**), since the majority of the particles sampled by the APS for Flovent and Qvar were finer than 4-µm aerodynamic diameter, where the efficiency of the Aerosol Diluter is close to 100%.[28]

The APS undersized aerosols from both Flovent and Intal, compared with either multistage impactor. Thus, the MMAD measured by the APS was 1.8 ± 0.07 µm for Flovent and 3.2 ± 0.02 µm for Intal (1-way analysis of variance [ANOVA] for each formulation, $P < .05$). The cause is believed to be the presence of surfactant particles that are formed together with particles comprising API with both formulations. It is pertinent that in a previous study using an Aerosizer TOF aerodynamic particle size analyzer, the Aerosizer-measured MMAD of a suspension formulation containing budesonide with sorbitan trioleate surfactant was found to be 2.4 ± 0.2 µm, compared with 3.9 ± 0.1 µm by ACI.[13] The surfactant particles were observed by microscopy to have collected further into the impactor (finer sizes) compared with particles of API, and the Aerosizer-measured size distributions were shown to have included both surfactant and API particles. The APS, like the Aerosizer, cannot discriminate between particles of surfactant and API, since no assay for drug substance is undertaken.

In the case of Flovent, the ACI-measured $FPF_{<4.7\ \mu m}$ (88.8% ± 2.9%) was slightly lower than 93.4% ± 0.7% obtained with the NGI ($P < .001$) (**Table 3**), consistent with the larger MMAD obtained by the ACI. $FPF_{<4.7\ \mu m}$ from the SSI (used in conjunction with the APS [82.9% ± 2.1%]) was only slightly smaller than the ACI-measured value ($P = .006$). However, the SSI-determined $FPF_{<4.7\ \mu m}$ was considerably less than the 97.9% ± 1.2% obtained using the APS ($P < .001$), as a consequence of the tendency for the APS to undersize compared with the impactors. For Intal, $FPF_{<4.7\ \mu m}$ measured by the SSI (46.4% ± 2.4%) was also markedly smaller than 78.8% ± 2.1% obtained by the APS ($P <.001$), and also slightly lower than corresponding values determined by the multistage impactors (60.2% ± 2.8% [ACI]; 52.0% ± 2.9% [NGI]) ($P < .05$). This slight discrepancy between SSI- and multistage impactor data can be explained if the CFC-11 propellant evaporation was incomplete by the time that the particles entered the SSI, whose internal volume is less than 200 mL [G. Pence, TSI Inc, letter, February 2003].

In contrast to the behavior with Flovent and Intal, the APS-measured MMAD (1.0 ± 0.03 µm) for Qvar, which is a solution formulation containing no surfactant, was located between the corresponding values from the NGI and ACI, and the difference between this value and the NGI-measured MMAD was barely significant ($P = .011$). Hence, $FPF_{<4.7\ \mu m}$ from both the APS and the multistage impactors were in close agreement (98.0% ± 0.5% [ACI]; 96.7% ± 0.7% [NGI]; 96.4% ± 2.5% [APS]) ($P = .18$). The steeper

Table 3. Values of $FPF_{<4.7\mu m}$ (%) Obtained From the ACI, NGI, and APS*

	Flovent	Intal	Qvar
ACI†	88.8 ± 2.9	60.2 ± 2.8	98.0 ± 0.5
NGI†	93.4 ± 0.7	52.0 ± 2.9	96.7 ± 0.7
APS	97.9 ± 1.2	78.8 ± 2.1‡	96.4 ± 2.5
3306 Impactor	82.9 ± 2.1	46.4 ± 2.4	67.1 ± 4.1

*ACI indicates Andersen 8-stage cascade impactor; APS, aerodynamic particle sizer; $FPF_{<4.7\ \mu m}$, fine particle fraction <4.7 μm aerodynamic diameter; and NGI, next generation pharmaceutical impactor. Except where indicated, n = 5 replicates/technique.
†Values are based on mass penetrating the induction port and entering the impactor.
‡ Based on 4-replicates.

slope of the APS-measured data for particles finer than 0.8 μm aerodynamic diameter (**Figure 4**) can be explained by loss of sensitivity of the TOF detection system, which reaches its limit of detection at about 0.5 μm aerodynamic diameter.[29] However, $FPF_{<4.7\ \mu m}$ determined by the SSI (67.1% ± 4.1%) was surprisingly much smaller than any of the other values for this formulation, which ranged from 96% to 98% ($P < .001$) (**Table 3**). Similar behavior was reported by Gupta et al[26] and explained in terms of incomplete ethanol evaporation in the SSI. A solution might be to extend the passageway to the SSI to match more closely the aerosol transit time with that for the APS, as was done by Gupta et al, who found that as much as 40 cm of inlet extension was needed to achieve good agreement between techniques. Such a change would also be expected to improve the agreement between SSI- and multistage impactor-measured $FPF_{<4.7\ \mu m}$ for formulations, such as Flovent and Intal that contain relatively low volatile CFC-11 propellant. However, it will be necessary to be careful not to introduce additional surfaces for impaction if a design change of this nature is contemplated. An alternative strategy, avoiding such problems, might be to heat the existing transfer channel so that the ethanol/propellant is more rapidly evaporated. Whichever solution is implemented, some flexibility will be needed for the user to set up the aerosol transport conditions in the SSI and APS on a formulation-by-formulation basis, given the variety of volatile species that may be present within the range of pMDIs that are available.

CONCLUSION

These in vitro comparisons indicate how 3 pMDI-generated formulations behaved in laboratory-based sampling systems. Discrepancies in size distributions were identified in data from 2 different designs of cascade impactor operated under near equivalent conditions. Aerosols from Flovent and Intal were undersized by the APS, most likely because of its inability to discriminate between particles containing API and finer surfactant particles. Further work is merited to resolve whether apparent undersizing observed with the NGI with both Flovent and Qvar is caused either by particle bounce and/or incomplete evaporation of volatile constituents. The SSI should be modified to ensure comparable evaporation of volatiles to that obtained in the APS, if formulations such as Qvar are to be sized accurately. It is strongly recommended that both NGI and APS/SSI data be evaluated on a formulation-by-formulation basis in relation to the large database that already exists for ACI-based measurements.

ACKNOWLEDGEMENTS

The authors acknowledge the support of Dr. Daryl Roberts, MSP Corp, St Paul, MN, for advice and assistance with the modifications to the NGI, and Mr. Greg Pence and Mr. Tyler Beck, TSI Inc, St Paul, MN, for the loan of a model 3321 APS with model 3306 Impactor Inlet and advice on use and interpretation of data.

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