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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

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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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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]

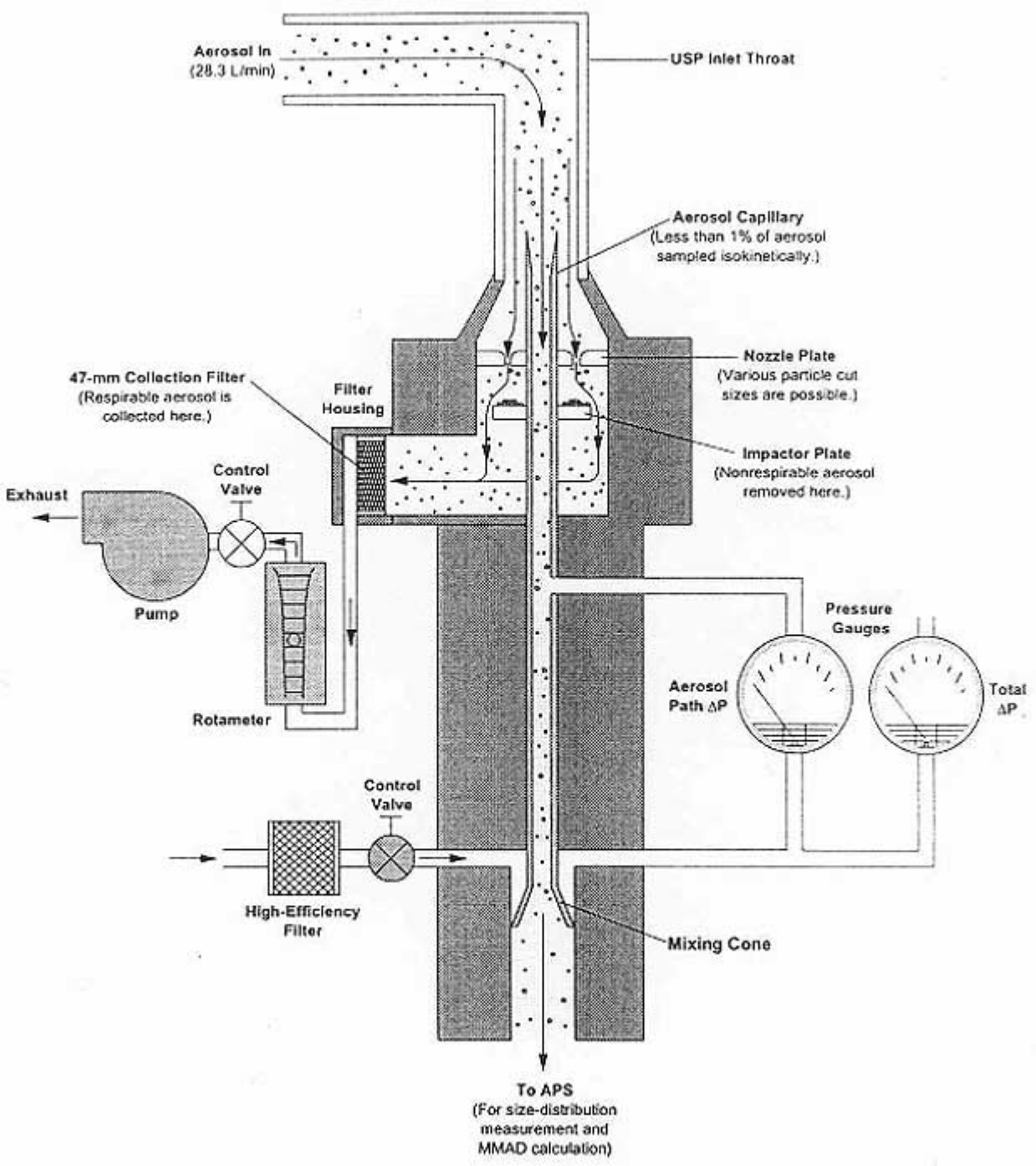

Figure 1. Schematic of model 3306 showing flow pathways to the single-stage impactor and APS. (Courtesy TSI Inc).

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]

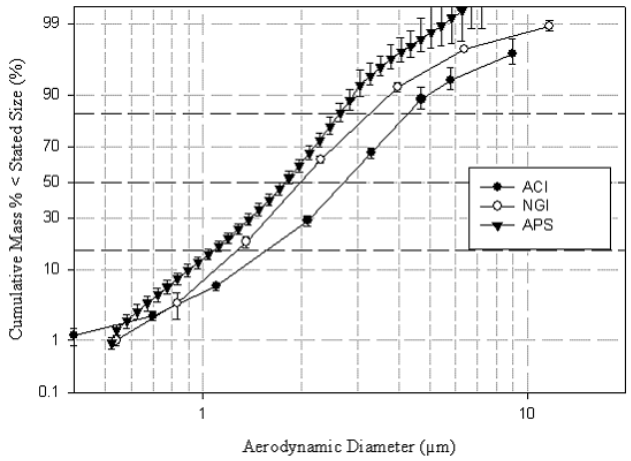

Figure 2. Comparison of ACI-, NGI-, and APS-measured size distributions for Flovent.

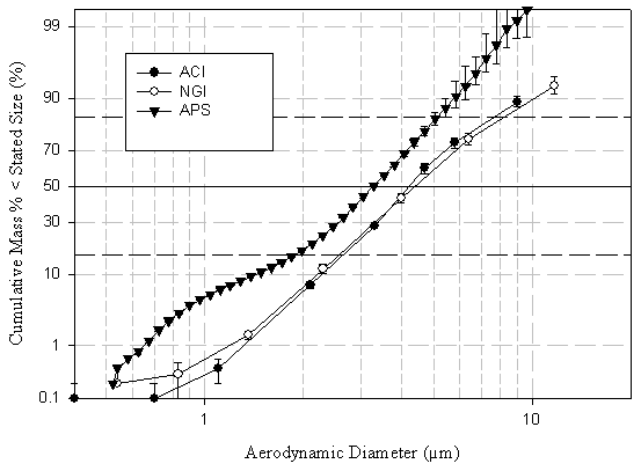

Figure 3. Comparison of ACI-, NGI-, and APS-measured size distributions for Intal.

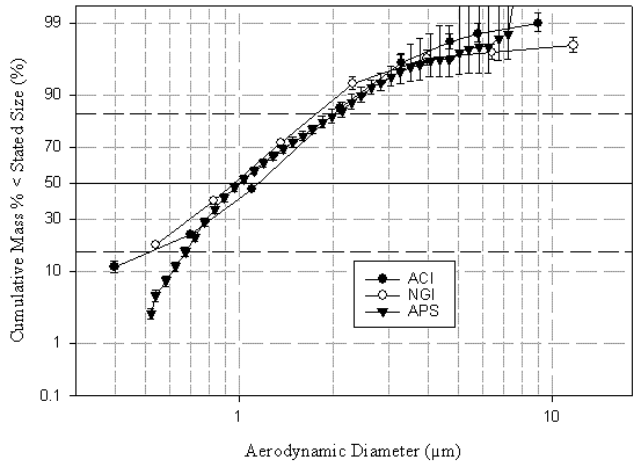

Figure 4. Comparison of ACI-, NGI-, and APS-measured size distributions for Qvar.

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