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Research Article

Evaluation of an Abbreviated Impactor for Fine Particle Fraction (FPF) Determination of Metered Dose Inhalers (MDI)

Changning Guo,[1,3] Diem Ngo,[1] Shafiq Ahadi,[1,2] and William H. Doub[1]

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Abstract. Abbreviated impactors have been developed recently to allow more rapid evaluation of inhalation products as alternates to the eight-stage Andersen Cascade Impactor (ACI) which has been widely used in the pharmaceutical industry for assessing aerodynamic particle size distribution. In this paper, a two-stage abbreviated impactor, Westech Fine Particle Dose Impactor (WFPD), was used to characterize the aerodynamic particle size of metered dose inhaler (MDI) products, and the results were compared with those obtained using the standard eight-stage ACI. Seven commercial MDI products, with different propellants (chlorofluorocarbon/hydrofluoroalkane) and formulation types (suspension/solution, dry/normal/wet), were tested in this study by both WFPD and ACI. Substantially equivalent measures of fine particle fraction were obtained for most of the tested MDI products, but larger coarse particle fraction and extra-fine particle fraction values were measured from WFPD relative to those measured using the ACI. Use of the WFPD also produced more wall loss than the ACI. Therefore, it is recommended that the system suitability be evaluated on a product-by-product basis to establish substantial equivalency before implementing an abbreviated impactor measurement methodology for routine use in inhaler product characterization.

KEY WORDS: abbreviated impactor; cascade impactor; fine particle fraction; MDI; particle size distribution.

INTRODUCTION

Metered dose inhalers (MDIs) are popular products designed to deliver aerosolized drugs to human lungs. An MDI combines a therapeutic formulation and a delivery device, where formulation characteristics and device capabilities must be harmonized to accomplish consistent and effective drug delivery.

Aerosols with particles in the aerodynamic particle size range of 1 to 5 μm can penetrate deep into the lungs, permitting ready absorption of the drug into the blood. For this reason, the US FDA and other regulatory agencies throughout the world require extensive particle size distribution data from drug sponsors (1,2).

The eight-stage Andersen Cascade Impactor (ACI) is the standard apparatus for the *in vitro* testing of inhalation drugs (US Pharmacopeia (USP) Apparatus 1), and has been widely used in the pharmaceutical industry for assessing the aerodynamic particle size distribution (APSD) in the aerosols produced by MDIs and dry powder inhalers (DPIs). In practice, an ACI procedure is very time consuming and labor intensive. There is a pressing need to replace the ACI with an alternative technique capable of concurrently performing APSD determination and chemical identification.

The drug dose delivered beyond the MDI mouthpiece can be categorized into four fractions: the induction port deposition fraction (IPF), the coarse particle fraction (CPF), the fine particle fraction (FPF), and the extra-fine particle fraction (EFPF). Induction port deposition includes the drug deposited in the USP throat/glass sampling chamber, and the preseparator (if applicable). The IPF approximates the delivered drug that is deposited in the throat and mouth. The CPF corresponds to particles larger than 5 μm collected within the cascade impactor and is analogous to particles that penetrate through the throat but collect in the upper airway due to their relatively large particle size. The FPF (particles<5 μm) is representative of those particles that have a high probability of penetrating into the deep lung. The EFPF corresponds to particles smaller than 1 μm that are likely to reach the peripheral airways and alveoli or be exhaled.

Use of the abbreviated impactor measurement (AIM) concept for quality control of the final product is a potential solution to the labor-intensive full-resolution cascade impactor (FRCI) methodology for inhaler aerosol aerodynamic particle size measurement. The AIM concept involves eliminating all stages from a multi-stage CI except those required to establish fine and coarse particle fractions. AIM is simpler and quicker to execute than the FRCI. At the same time, improved measurement

[1] Division of Pharmaceutical Analysis, US Food and Drug Administration, 1114 Market Street, Room 1002, St. Louis, Missouri 63101, USA.
[2] Office of Regulatory Affairs, US Food and Drug Administration, 15 Sunnen Drive, Suite 113, Saint Louis, Missouri 63143, USA.
[3] To whom correspondence should be addressed. (e-mail: changning.guo@fda.hhs.gov)

precision could be possible by eliminating stages upon which little or no drug mass is collected, with the sacrifice of the capability to collect detailed APSD information such as MMAD, GSD, and span.

However, the reduced jet and plate stack of an abbreviated impactor potentially may exhibit changed air flow patterns that can significantly affect inertial impaction behavior and thus influence the measurement results. A necessary part of developing the AIM concept as a viable alternative to the current compendial procedures involving full-resolution cascade impactors (3,4) is to establish that abbreviated impactors are capable of reproducing *in vitro* performance metrics that are descriptive of the APSD of inhaler-produced aerosols.

Mitchell (5–8), Keegan (9,10), and Chambers (11) have evaluated a variety of abbreviated impactor systems for HFA MDIs. Overall, all observed substantial agreements between most of the abbreviated impactors and the FRCI for FPF indicate that abbreviated impactors could be substituted for the full-resolution ACI in certain situations, such as inhaler QC testing, when appropriate. However, some of the results also suggested that performance of an AIM device might be formulation/product specific. Since only a limited number of MDI formulations/products were tested using each abbreviated impactor in the abovementioned studies, this problem has not been well addressed.

In this project, seven commercially available MDI products, including three chlorofluorocarbon (CFC) and four hydrofluoroalkane (HFA) products (six suspensions and one solution formulation), were evaluated with a two-stage abbreviated impactor, the Westech Fine Particle Dose Impactor (WFPD, Westech, Atlanta, GA), and those results were compared with results from parallel measurements made using an eight-stage ACI. Comparisons were made on the basis of the accuracy and precision for measurements of FPF of MDIs.

DEVICE

As shown in Fig. 1, the WFPD impactor is a two-stage, multijet impactor with a final filter incorporating a unique interlocking system (patent pending) for fast assembly and disassembly, removing the need for springs or clumsy clamping mechanisms. The two WFPD stages are specifically designed to have aerodynamic cut points at 5 and 1 μm with a flow rate at 28.3 L/min.

The design of the WFPD is based on the Andersen six-stage viable impactor, the earliest version of the Andersen multi-stage CIs to be developed (12). It is similar in operating principle to the non-viable ACI, with the important exception that the stage wells are larger so that each can accommodate a Petri dish instead of a collection plate. The WFPD uses two glass Petri dishes as the collection media with a cassette-type final filter holder. A WFPD (viable CI) stage is higher than the non-viable ACI stage; therefore, it provides a larger jet-to-plate separation and a larger space between stages.

SAMPLES

Seven commercial MDI products were tested in this study. Detailed product information is listed in Table I. Three of the tested products are CFC formulations, and four are HFA formulations. Flovent is a "dry" MDI formulation without any surfactant or co-solvent. ProAir, Proventil, and Atrovent are "wet" MDI formulations containing co-solvents. Aerobid, Combivent, and MaxAir are categorized as "normal" formulations since they contain small amounts of surfactants but no co-solvents. All the tested products are suspension formulations, except Atrovent which is a solution formulation. Combivent is a combination formulation containing two active pharmaceutical ingredients (APIs), albuterol sulfate and ipratropium bromide, which are labeled as "AS" and "IB" in this paper. Other tested products are all single-API formulations.

METHODS

All measurements were undertaken at a 28.3-L/min flow rate for both WFPD and ACI with uncoated collection plates and performed under ambient conditions. At least two MDI canisters from each product were tested, and not less than six experiments were performed using each impactor. The number of canisters tested and total number of experiments performed are listed in Table I. For each formulation, the MDI canisters from the same lot were used, and were actuated

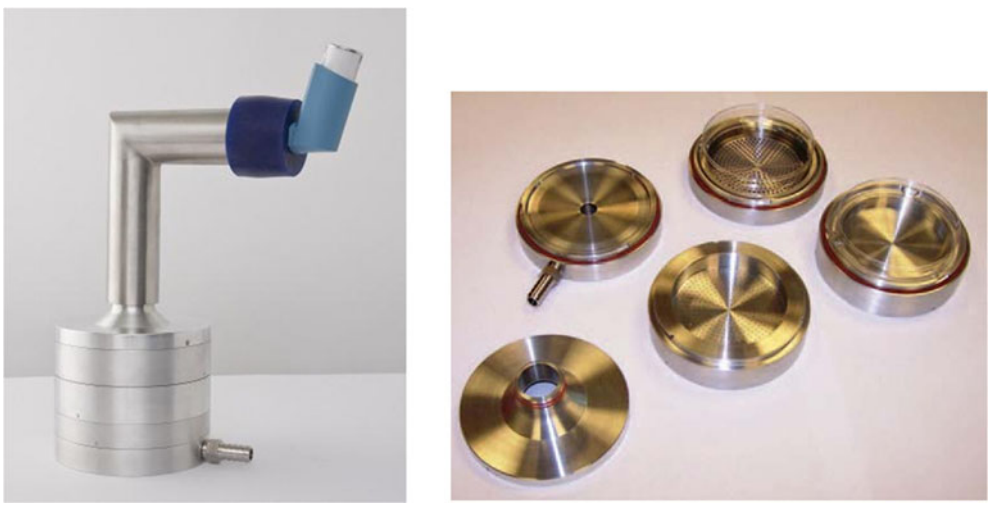

Fig. 1. WFPD

Table I. Detailed Information on the Seven Commercial MDI Products Tested in This Study, the Number of Canisters Being Tested, Total Number of Experiments, and Spray Intervals Between Each Actuation

Product	Manufacturer	API	Lot number	Propellant	Co-solvent	Surfactant	Formulation type	Number of canisters tested	Total number of experiments	Spray interval (s)
Aerobid	Forest Pharmaceuticals	Flunisolide	80350	CFC	None	Sorbitan trioleate	Suspension	3	6	10
Combivent	Boehringer Ingelheim	Ipratropium bromide and albuterol sulfate	865055A	CFC	None	Soya lecithin	Suspension	6	12	5
MaxAir	Graceway Pharmaceuticals	Pributerol acetate	70840	CFC	None	Sorbitan trioleate	Suspension	6	6	10
Flovent 110	GlaxoSmithKline	Fluticasone propionate	F0567	HFA	None	None	Suspension	3	6	30
ProAir	TEVA Pharmaceuticals	Albuterol sulfate	AEE52C	HFA	Ethanol	None	Suspension	3	12	5
Proventil	Key Pharmaceuticals	Albuterol sulfate	080004	HFA	Ethanol	Oleic acid	Suspension	6	12	5
Atrovent	Boehringer Ingelheim	Ipratropium bromide	080449W	HFA	Water, ethanol	Citric acid	Solution	2	7	15

API active pharmaceutical ingredients, *CFC* chlorofluorocarbon, *HFA* hydrofluoroalkane

by the same operator, to minimize the variation from product and measurement.

For each experiment, ten actuations were delivered into WFPD or ACI through an induction port (either the USP throat or a glass chamber) to ensure adequate API was collected for recovery and assay from all stages. The MDI canisters were well shaken between each actuation. The spray intervals between each actuation varied from product to product and are listed in Table I. API was then washed off from every part of the WFPD or ACI and subject to quantitative chemical analysis performed by HPLC or UV–vis spectroscopy using a validated procedure.

ACI and WFPD experiments were performed in an alternating sequence. An ACI measurement was first used to determine the benchmark APSD data, and a WFPD experiment followed immediately after, with actuations performed by the same operator, to minimize possible variations in manual actuations and life stage of the drug canister.

For each MDI product, inter-stage drug losses (wall losses) were quantified and evaluated for ACI by recovering API deposited on interior surfaces other than the collection plates during method development and/or validation periods. If the wall losses were greater than 5% of the total drug collected inside the impactor, they were included along with the associated collection plate for PSD calculation. For ACI, APIs deposited on the stage and plate were washed together into a beaker and combined as one sample for HPLC or UV–vis spectroscopy assay to save time and labor. For WFPD, APIs on the stage and collection Petri dish were washed off and analyzed separately.

CPF>5 μm, FPF<5 μm, and EFPF<1 μm were used as metrics to evaluate the performance of the WFPD in comparison with the ACI. Since the ACI does not have stages with cutoff diameter at 5 and 1 μm, cumulative APSD curves were interpolated to determine the CPF, FPF, and EFPF values.

The results from ACI and WFPD were directly compared statistically *via* Student's *t* test for a probability of 0.10 using Microsoft Excel XP (Microsoft Corporation, Redmond, WA).

RESULTS AND DISCUSSION

The total recovery (percent of label claim), IPF, CPF> 5 μm, FPF<5 μm, EFPF<1 μm, and wall losses, determined by WFPD and ACI for the seven tested products, are summarized in Table II.

Total Recovery

Total mass recovery of an MDI product was defined as the mass of API emitted from the MDI actuator and was calculated as the mass sum of API particles collected from the mouthpiece adaptor, USP throat, preseparator (if applicable), impactor stages (if applicable), impactor collection plates or dishes, and filter. The total mass recovery was converted to %LC values for easy comparison.

As shown in Fig. 2, equivalent total recovery values were observed between WFPD and ACI for all the tested products. The total mass recoveries for most of the tested products were within ±15% of label claim, except ProAir which shows a low %LC with values averaging around 70%. The reason for the low total recovery of ProAir is unknown. Since the focus of

Table II. Total Recovery as Percent Label Claim (%LC), Key Size Fraction Metrics, and Wall Losses Determined for the Seven Tested Products by WFPD and ACI

Product (API)	WFPD						ACI					
	%LC	IPF	CPF>5	FPF<5	EFPF<1	Wall loss	%LC	IPF	CPF>5	FPF<5	EFPF<1	Wall loss
Aerobid	95.3% (13.0%)	63.5% (3.2%)	13.9% (0.7%)	22.6% (3.2%)	1.2% (0.2%)	3.8% (0.3%)	98.2% (8.2%)	64.0% (2.6%)	10.5% (1.0%)	25.6% (2.6%)	0.3% (0.1%)	<5%
Combivent (AS)	97.0% (13.2%)	32.9% (5.1%)	7.7% (2.9%)	59.3% (6.0%)	7.1% (1.8%)	8.4% (1.8%)	102.0% (4.6%)	41.5% (7.9%)	4.1% (1.3%)	56.9% (10.0%)	3.8% (0.9%)	<5%
Combivent (IB)	94.0% (14.3%)	34.9% (5.2%)	9.7% (2.9%)	55.4% (5.6%)	3.0% (0.7%)	8.8% (2.4%)	98.3% (6.8%)	43.5% (9.6%)	4.8% (2.1%)	53.8% (10.4%)	1.4% (0.6%)	<5%
MaxAir	117.5% (13.4%)	40.9% (7.5%)	13.5% (4.15)	45.6% (6.6%)	7.4% (4.9%)	6.2% (1.3%)	109.2% (10.4%)	49.5% (7.6%)	3.8% (0.8%)	46.7% (7.1%)	2.0% (0.4%)	>5%
Flovent	93.7% (7.4%)	41.3% (3.6%)	17.9% (4.0%)	40.8% (2.6%)	4.2% (1.1%)	2.7% (1.2%)	94.8% (9.1%)	40.3% (2.9%)	13.6% (4.1%)	46.2% (3.0%)	1.0% (0.1%)	<5%
ProAir	71.5% (11.0%)	44.7% (4.6%)	10.3% (3.7%)	45.0% (6.6%)	8.6% (2.2%)	9.4% (6.8%)	75.3% (13.7%)	38.6% (2.1%)	5.3% (2.3%)	56.2% (3.5%)	4.4% (0.7%)	>5%
Proventil	83.1% (7.6%)	47.0% (3.8%)	8.1 (1.4%)	44.9% (4.5%)	8.6% (2.0%)	2.8% (1.2%)	89.1% (8.5%)	50.6% (4.2%)	4.6% (2.6%)	44.8% (6.0%)	2.5% (0.6%)	<5%
Atrovent	101.0% (6.7%)	62.0% (7.7%)	7.1% (4.5%)	30.9% (9.5%)	20.7% (8.1%)	8.5% (2.4%)	107.9% (5.6%)	59.8% (7.5%)	3.4% (0.4%)	36.8% (7.7%)	22.6% (5.1%)	<5%

The values in the parenthesis are standard deviations of the measurements
API active pharmaceutical ingredients, *%LC* percent label claim, *IPF* induction port deposition fraction, *CFC* chlorofluorocarbon, *FPF* fine particle fraction, *EFPF* extra-fine particle fraction

this paper is on comparing the performance of WFPD and ACI, the low total recovery of ProAir will not influence the evaluation and will not be discussed here.

IPF

The IPF values measured by WFPD and ACI are shown in Table II. There are no statistically significant differences observed for all the tested products. This is expected since the exact same induction port was used for both WFPD and ACI for each MDI product.

Wall Loss

By definition, IPF+CPF>5 μm+FPF<5 μm=100%, while the sum of CPF>5 μm and FPF<5 μm is the percentage of the mass of aerosol entering the impactor. When calculating CPF and FPF, wall loss is a key factor that cannot be overlooked.

For most of the products tested in this study, the wall losses from WFPD were higher than those from ACI. The average wall loss values from WFPF experiments for Combivent, MaxAir, ProAir, and Atrovent, and from ACI experiments for MaxAir and ProAir, were over 5% of total delivery. For these experiments, the combinations of stage and collection plate/dish were used in CPF, FPF, and EFPF calculations.

The disagreement observed in wall loss between WFPD and ACI may be largely due to the impaction surface material, glass for WFPD and stainless steel for ACI, which respond differently to the impacting API particles. The different collection surface will show more influence when API particles carry electrostatic charges. As a nonconductive surface, the Petri dishes in WFPD cannot neutralize the electrostatic charges on the impacted particles. The buildup of electrostatic charges from the early depositions may repulse later impacting particles and cause more bounce and re-entrainment.

The dryness or wetness of a formulation will also influence the aerosol bounce and re-entrainment. Theoretically, aerosols coming out of a dry MDI comprise mostly dry particles, having comparatively higher coefficients of restitution, and are more likely to be subject to bounce and re-entrainment from a given impaction surface than liquid droplets or partly dry solid particles containing low-volatility solvents such as water or ethanol (13).

However, as the only "dry" MDI in the tested candidates, the wall loss values of Flovent for both WFPD and ACI were lower than 5% and substantially lower than most of the "wet" MDI candidates. These results imply that although the abovementioned theory could be true for different formulations of the same API, it apparently cannot be extended to all MDI products, especially to formulations with different APIs. The chemical and physical properties of different API particles may interact differently with the impaction surface resulting in different bounce and re-entrainment behaviors. More importantly, the interaction between excipients and different API particles could vary significantly from formulation to formulation, which would substantially influence the evaporation of propellants and co-solvents and thus affect the bounce and re-entrainment of the aerosols.

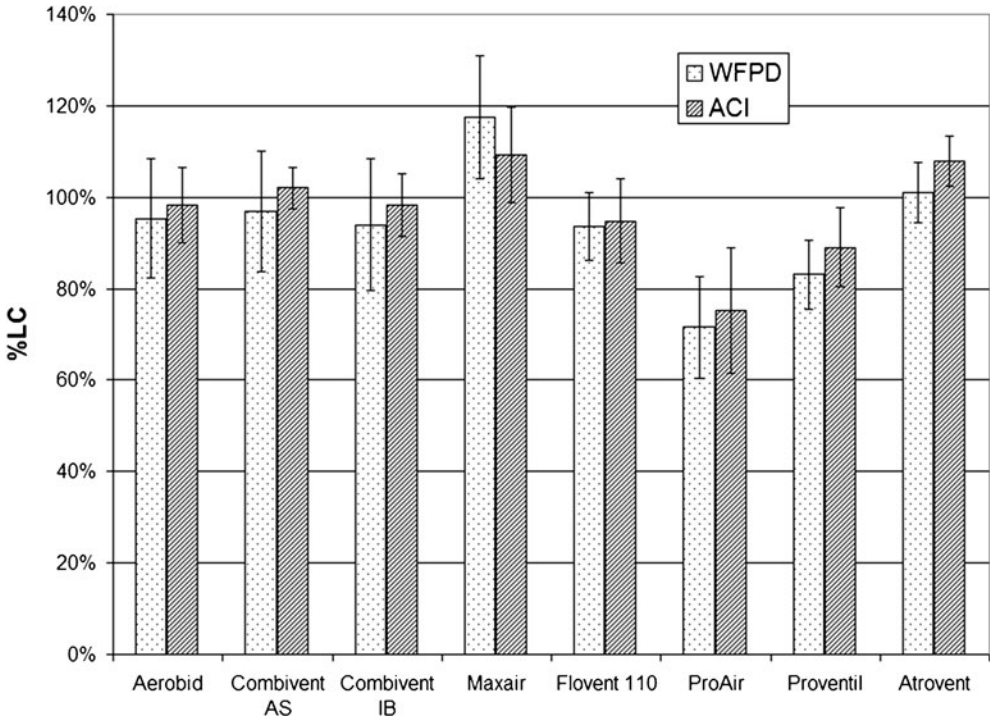

Fig. 2. Comparison of the total recovery values, as the means of %LC, measured by WFPD and ACI for the seven tested MDI products

CPF>5 μm

Figure 3 shows the comparison of the coarse particle fraction (CPF>5 μm) measured by WFPD and ACI for the seven tested MDI products. The CPF values for all products except Flovent showed statistically significant differences between WFPD and ACI measurements.

The result for Flovent, the only "dry" MDI formulation in the tested products, can be well explained by the "dead space" theory mentioned in the literature (5,6). According to a previous study by Mitchell's group, equivalent performance between the ACI and AIM impactors was easier to achieve when testing a dry MDI. Their explanation was that the absence of low-volatility excipients avoided the possibility of size-related bias in the

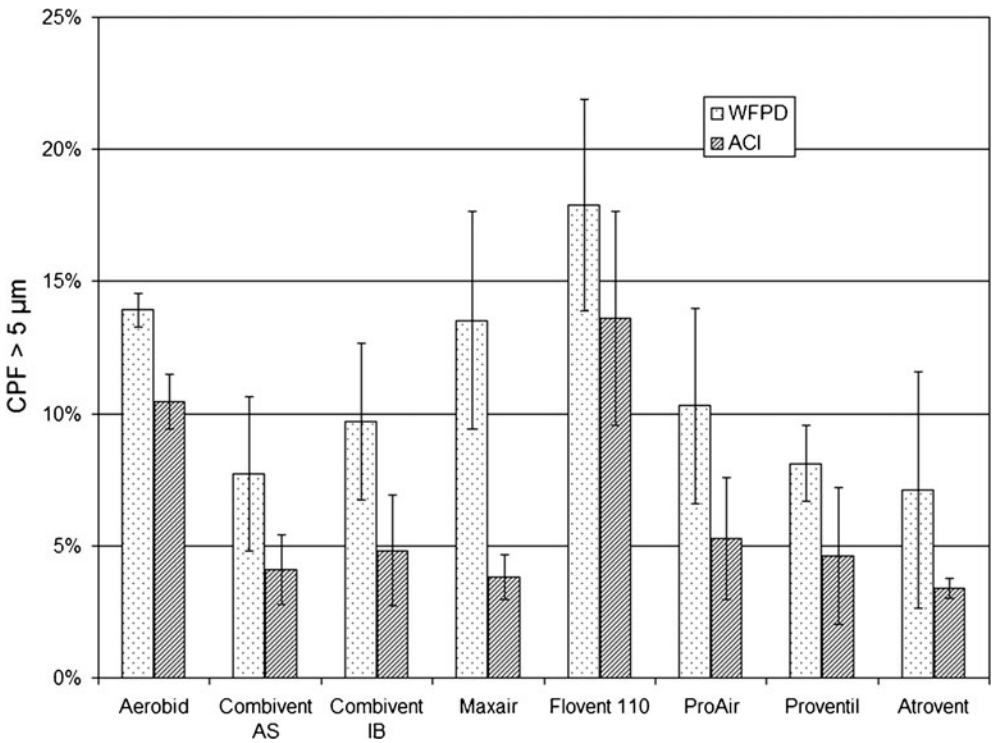

Fig. 3. Comparison of the CPF measured by WFPD and ACI for the seven tested MDI products

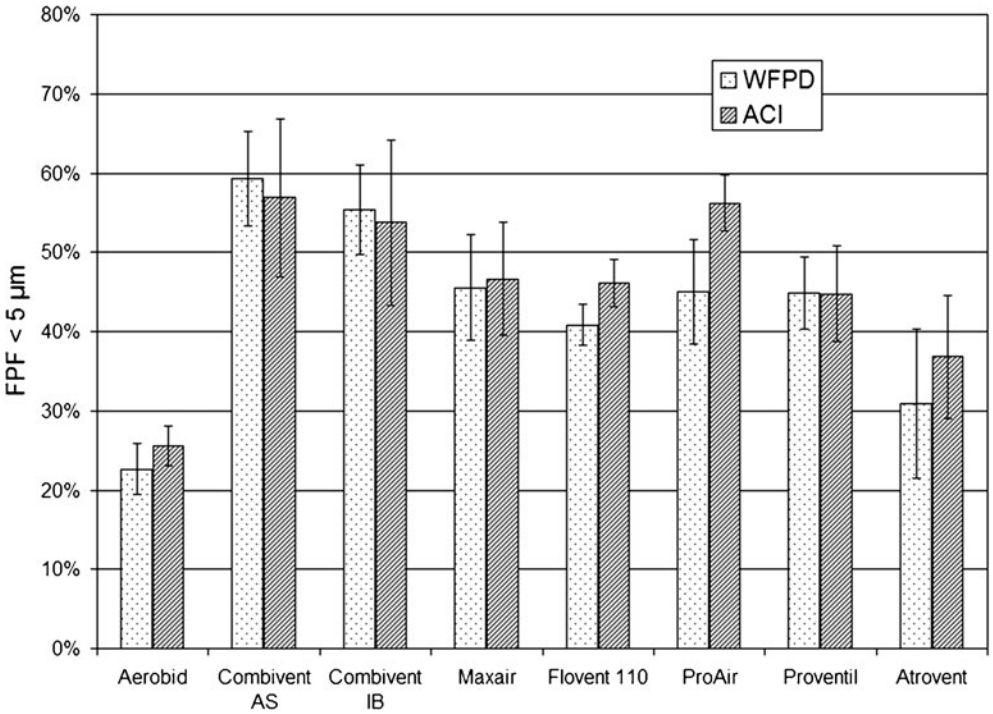

Fig. 4. Comparison of the fine particle fraction (FPF<5 µm) measured by WFPD and ACI for the seven tested MDI products

abbreviated systems as the result of changes in evaporation behavior taking place within the smaller dead space of AIM impactors compared with that in the ACI.

The evaporation behavior of a formulation will influence the upper stages where CPF is calculated rather than the middle and lower stages where evaporation is closer to complete. As a "dry" formulation, Flovent evaporates faster than other tested products and resulted in a smaller CPF difference between WFPD and ACI measurements than the other products.

FPF<5 µm

Figure 4 shows the comparison of FPF<5 µm values measured by WFPD and ACI for the seven tested products.

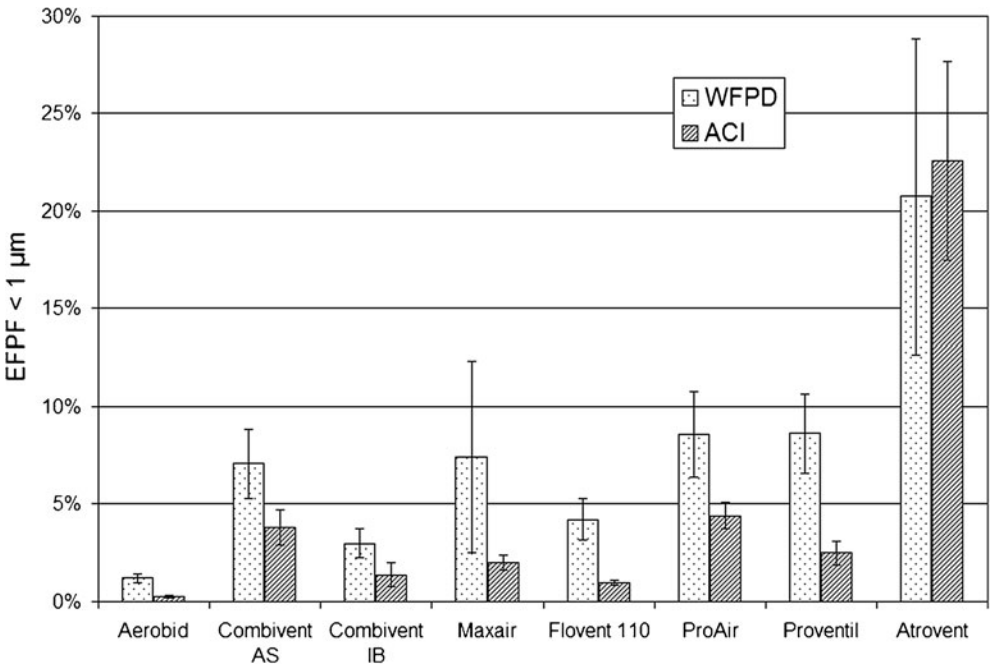

Fig. 5. Comparison of the extra-fine particle fraction (EFPF<1 µm) measured by WFPD and ACI for the seven tested MDI products

For the three CFC MDIs, Aerobid, Combivent, and MaxAir, WFPD and ACI showed equivalent performance. However, mixed results were observed for the four HFA MDIs. WFPD and ACI delivered statistically equivalent FPF<5 μm results for Proventil and Atrovent ($p<0.05$), while lower FPF<5 μm values were obtained by WFPD measurements for Flovent and ProAir. Flovent is an API-propellant only "dry" MDI product, and ProAir is a "wet" MDI formulation containing ethanol as a co-solvent.

The "dead space" theory helps explain the observed differences between CFC and HFA formulations. All three CFC MDIs showed equivalent FPF<5 μm between WFPD and ACI, but not all HFA MDIs did. Since CFC evaporates faster than HFA, the smaller dead space in WFPD has more influence on HFA MDIs and produced the biased results in particle size as observed for Flovent and ProAir.

However, the "dead space" theory does not provide a complete explanation since two of the wet MDIs, Proventil and Atrovent, show equivalent performance between WFPD and ACI. This indicates that the internal volume of the impactor is only one of the factors that influence results obtained when using an AIM impactor. In this study, we see that physical properties of the API, excipients, and their interactions may exert an equal or greater effect on the results as does the impactor's internal volume.

EFPF

As shown in Fig. 5, the EFPF values measured by WFPD and ACI showed significant differences for all products except Atrovent. Atrovent also showed substantially greater EFPF values (>20%) than all other products (<10%).

Atrovent is the only solution formulation in the tested products. The lower end of the APSD for a solution formulation is much more dependent on the evaporation process than for a suspension formulation. Therefore, the aerosol size of Atrovent will be primarily determined by the evaporative processes occurring within the MDI device. As a result, a larger amount of submicron droplets was observed for Atrovent.

The *in vitro* EFPF has been considered as a metric more diagnostic of particle bounce and re-entrainment than either FPF or CPF since once particles have bounced from a particular stage, their high retained kinetic energy will most likely carry them through to the filter at the base of the impactor (14). This theory has been verified by our results in which larger EFPF values from WFPD correspond to more wall losses for all products expect Atrovent.

CONCLUSION

In this study, the performance of an abbreviated CI, WFPD, was compared to the full-resolution ACI over a broad range of MDI products with different propellants (CFC/HFA) and formulation types (suspension/solution, dry/normal/wet). Our results demonstrate that substantially equivalent measures of FPF can be obtained for most of the tested MDI products. However, the WFPD tends to give out larger CPF and EFPF values than the ACI.

There are various factors which contribute to the performance differences observed between WFPD and ACI; the relationship between these factors is complicated and could come from both the CI and the tested products. The reduced dead space of WFPD, uncontrolled particle bounce and re-entrainment, and solvent evaporation rate all make contributions.

In general, use of the WFPD produced more wall loss than the ACI. Application of a coating to the collection surface could potentially reduce the particle bounce and re-entrainment, and could enable better equivalence to results obtained using the ACI.

The formulation physical properties, especially the existence of solvent/co-solvent, can significantly influence the performance of an abbreviated CI in terms of producing equivalent results to a full-resolution CI. These types of apparatus comparisons need to be made on a product basis to establish substantial equivalency before implementing an AIM methodology for routine use in inhaler product characterization.

In summary, an AIM system, such as WFPD, provides a simplified method for characterizing inhalation drugs. Equivalent performance can be obtained from WFPD with the full-resolution ACI for FPF in most cases. However, users need to be aware of biases associated with the AIM reduced dead space and collection surface, and contributions from drug formulation properties.

Disclaimer The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy.

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