AAPS PharmSciTech (2019) 20: 170
DOI: 10.1208/s12249-019-1354-7

Research Article

Theme: Paul Myrdal Memorial Issue - Pharmaceutical Formulation and Aerosol Sciences
Guest Editors: Philip J. Kuehl and Stephen W. Stein

The Influence of Electrostatic Controls on MDI Size Distribution Measurements

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Received 6 December 2018; accepted 23 February 2019; published online 19 April 2019

Abstract. Cascade impactor testing is widely used to characterize the aerodynamic particle-size distribution of metered dose inhaler aerosols. Charge is often imparted to MDI aerosols by triboelectrification as formulation rapidly travels through the valve stem and actuator during atomization. The presence of charge on MDI aerosols can impact the accuracy and reproducibility of APSD measurements made using cascade impactors. The aerodynamic particle size distribution of three different experimental MDI formulations were evaluated using the Next Generation Impactor with and without incorporating static controls during testing. The static controls included grounding the analyst and the equipment, using an ionizing air blower and anti-static gun, rinsing and allowing the actuator to air dry prior to testing, and having the analyst not wear gloves or touch the USP throat during testing. For all three formulations, tests that used static controls had lower actuator and throat deposition and correspondingly higher deposition on the impactor stages. While static controls influenced the amount of drug entering into the impactor during testing, the static controls did not otherwise change the aerodynamic particle size distribution of these particles. Static controls had the greatest impact on the ethanol-free HFA-227 formulation. For this formulation, there was a 15% difference in throat deposition for the tests that did or did not incorporate static controls. These results demonstrated that electrostatic effects can lead to meaningful variability in cascade impactor test results. Static controls should be considered when developing cascade impactor test methods for MDI products in order to eliminate variability in test results.

KEY WORDS: metered dose inhaler; electrostatics; aerodynamic particle-size distribution; Next Generation Impactor; cascade impactor.

INTRODUCTION

Metered dose inhalers (MDIs) are the most commonly used treatment of asthma and COPD and have been widely used since the 1950s (1). The aerodynamic particle size distribution (APSD) of the drug delivered from MDIs is a critical quality attribute that influences their deposition in the lung (2) and therefore their therapeutic effectiveness. Cascade impactor (CI) testing is widely used as a quality control test to characterize MDI aerosols during development and product release and stability testing. Due to the importance of accurately measuring the APSD of MDI aerosols and due to the cost associated with generating out of specification test results, it is important to minimize sources of variability during CI testing. There are many potential sources of variability during CI testing including electrostatic effects (3).

The degree and location of particle deposition in the human respiratory tract can be impacted by charge on the particles (4). Charge can be imparted to the aerosol during actuation of the inhaler. Charge can be imparted to dry powder inhaler (DPI) aerosols by triboelectrification as particles collide with other particles or inhaler surfaces and is dependent on the physical and chemical properties of the powder components, the nature of deagglomeration, and the material properties of the device (5,6). The charge on nebulizer aerosols depends on the concentration and physical and chemical properties of the suspended drug (7). Charge generation on MDI aerosols depends on a variety of formulation and device factors and is caused in part by triboelectrification as the formulation rapidly travels through the valve stem and actuator during atomization.

Factors Influencing the Electrostatics of MDI Aerosols

The charging of MDI sprays is highly complex and cannot be fully described by measuring the net charge on the spray or even on a portion of the spray such as the fine particle dose. In reality, the spray consists of individual

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particles with different charge polarity and magnitude which can vary as a function of particle size (8). Adding to the complexity, the composition of the spray from typical suspension MDIs is bimodal with a mode comprised of residual particles and an extra-fine mode comprised of residual particles that consist primarily of non-volatile excipients, such as surfactant, that are present in the MDI formulation (9). Nevertheless, simple early measurements of the net charge on the entire or fine particle fraction of the plume provide significant insight into MDI electrostatics. Peart *et al.* (10) used an aerosol electrometer to measure the net electrical charge on the aerosol fraction with aerodynamic diameters less than about 5.8 μm for various experimental MDI formulations. For an experimental albuterol sulfate MDI containing HFA-134a, ethanol, oleic acid and micronized albuterol sulfate the measured fine particle aerosol was highly electronegative (− 115 pC), whereas the fine particle aerosol for the same formulation without the albuterol sulfate was electropositive (+ 36 pC) and was even more positive (+ 98 pC) for formulation with just the HFA-134a and ethanol. These results demonstrate the formulation composition significantly influences the net charge on MDI aerosols. Peart *et al.* (6) subsequently evaluated 13 commercial suspension MDIs (10 CFC formulations and 3 HFA formulations). Most of the MDIs had net negative charge on the fine particle dose (FPD). Flovent was the only MDI that consistently had net positive charge on the FPD. Proventil® HFA (which uses a valve with a metal stem to deliver formulation consisting of micronized albuterol sulfate, HFA-134a, ethanol and oleic acid) had significantly lower net negative charge than did Ventolin® HFA (which uses a valve with plastic valve stem to deliver formulation consisting of just micronized albuterol sulfate and HFA-134). Kwok *et al.* (11) characterized HFA-134a and HFA-227 MDI aerosols using an Electrical Low Pressure Impactor (ELPI) and found that both propellants produced aerosols with net negative electrical charge which diminished with increasing water content in the formulation.

Chen *et al.* (12) characterized the charge from HFA-134a solution MDIs with 15% ethanol and five different APIs and using actuators machined from three different materials using the ELPI. Actuators with orifice diameters of 0.3 mm were machined using nylon, PTFE and aluminum in order to evaluate positive, negative and conducting triboelectric materials. They concluded that API and actuator material both influenced net charge with API having the more significant effect. Beclomethasone dipropionate (BDP), budesonide (BUD) and flunisolide (FS) solution formulations generated net positive charge while salbutamol base (SB) and ipratropium bromide (IB) solution formulations generated net negative charge regardless of which actuator material was used (Fig. 1). Chen *et al.* (13) concluded that the nozzle design, particularly nozzle exit geometry, can significantly impact the net charge on the atomized aerosol and consequently impact the fine particle dose.

Peart *et al.* (14) comprehensively evaluated the influence of materials of the valve components on the net charge on the fine particle dose from albuterol sulfate and levalbuterol sulfate MDIs. They found that a complex relationship exists between the net charge on the fine particle dose and the drug and valve materials. Levalbuterol sulfate MDIs with nitrile (BK356) elastomers (Bespak, King's Lynn, UK) in the valves produced negative net charge whereas the same formulations with nitrile RB 190NT (BK357) elastomers (Bespak) produced positive net charge. In contrast, albuterol sulfate MDIs using the same valve variants consistently resulted highly charged electronegative aerosols.

The use of the ELPI provides significant information on the size dependence of the charge by measuring net aerosol charge on 12 different size fractions of the aerosol. Using the ELPI, Kwok *et al.* (15) found that charge predominantly is contained in the fine portion of the aerosol that consists primarily of residual particles containing excipient but no drug. For the HFA suspensions Flixotide™ and Intal® Forte, they determined that fine droplets, that do not contain drug, had net positive charge and the drug-containing droplets had net negative charge. For the HFA suspension Ventolin®, both the fine droplets and the drug-containing droplets had net negative charge. In contrast, the drug mass and particle charge were closely correlated for the HFA solution MDI Qvar® (15).

The Influence of Static Charge on Cascade Impactor Measurements of MDI Aerosols

The presence of charge on an MDI aerosol can impact the accuracy and reproducibility of APSD measurements made using cascade impactors. Vinchurkar *et al.* (16) used computational fluid dynamics (CFD) to theoretically evaluate the impact of aerosol charge on stage collection efficiency curves for the ACI and concluded that charge significantly alters collection efficiency curves for stages 4–7 for aerosols with charge levels consistent with the charge on MDI aerosols. Mohan *et al.* (17) used a corona charger to apply unipolar positive or negative charge to atomized aerosols and compared APSD measurements made using the ACI to control measurements made using a neutralized aerosol. They found that the positively and negatively charged aerosols both had increased deposition on Stages 0 through 5 of the ACI compared to the neutralized aerosol.

Charge on MDI sprays can also impact APSD measurements made using cascade impactors by influencing the amount of the aerosol that deposits on the actuator or USP throat during measurement. Mueting and Stein (18) measured net charge on the entire MDI plume using a modified Faraday cup and compared the results to drug deposited on the USP throat during ACI measurements. They found that the total net charge on aerosols from HFA-134a BDP solution MDIs using high density polyethylene (HDPE) actuators with orifice diameters of 0.3 mm was highly correlated to throat deposition from ACI measurements (Fig. 2).

While there is a general agreement that electrostatic effects can influence cascade impactor test results, there is limited information on what, if any, controls are useful in mitigating these effects during testing. The European Pharmaceutical Aerosol Group (EPAG) surveyed experts from seven organizations involved in the development of orally inhaled pharmaceutical drug products to assess what controls are effective at mitigating electrostatic effects during cascade impactor testing as well as to determine what, if any, controls are being used during testing (19). The EPAG study concluded that there is a "lack of information and consensus

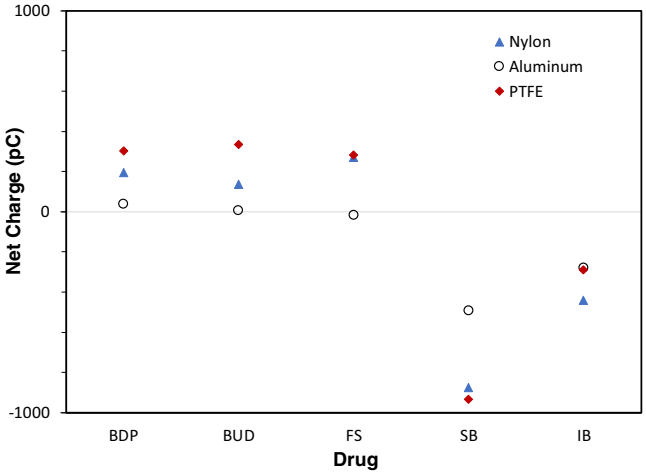

Fig. 1. Net charge measured from solution MDIs with various drugs and actuator materials. Adapted from (1)

on how to measure and minimise electrostatics during aerosol analysis, with the majority of the measures currently available not extensively used by pharmaceutical organisations." Indeed, there is a lack of data in the literature showing the impact of static controls on cascade impactor testing of pharmaceutical inhalers. The objective of this study is to provide quantitative data on the impact of static controls on cascade impactor test of MDI products.

MATERIALS AND METHODS

The APSD of three different experimental MDI formulations was evaluated using the Next Generation Impactor (NGI) with and without incorporating static controls during testing. The formulation and testing of the MDIs are described below.

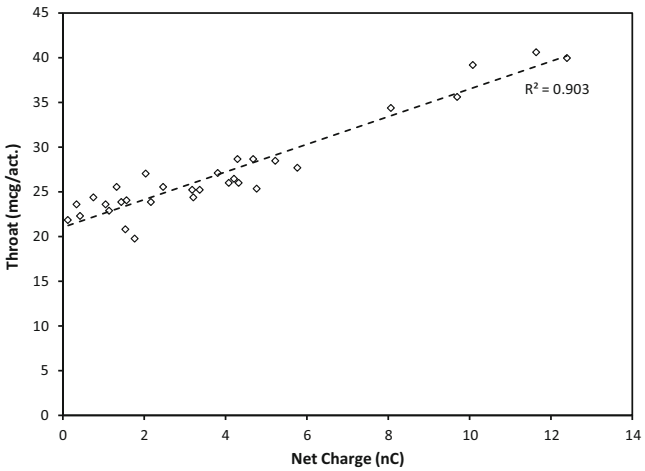

Fig. 2. Correlation between net charge and throat deposition from delivery of HFA-134a BDP solution MDIs delivered using an HDPE actuator. Adapted from (18)

Description of MDIs Used

Three different experimental MDI configurations (Table 1) were manufactured using laboratory-scale equipment. The MDI configurations encompass a variety of formulations (solution and suspension, HFA-134a and HFA-227, ethanol-containing and ethanol-free). All formulations were filled into 12 mL plasma treated canisters (H & T Presspart Manufacturing, Blackburn, UK) with 50 μl valves with plastic valves (DF-30 series; polyester (PBT) stem and metering chamber; Aptar Pharma, LeVaudreuil, France). All filled MDI canisters were coupled to proprietary polypropylene actuators with a nominal orifice diameter of 0.4 mm.

Description of APSD Measurements

The APSD delivered from the experimental MDIs was measured by coupling the MDI to a USP induction port ("USP Throat," (20)) attached to a Next Generation Impactor (NGI) and actuating the unit five times. The flowrate through the NGI was set to 30 lpm and was allowed to stabilize for at least 2 min before the inhaler was coupled to the USP throat for testing. Between each dose, the inhaler was removed from the throat and shaken for at least 5 s before being coupled to the throat for the next actuation. Flow was maintained through the apparatus for 30 s after the last actuation. All testing was done at 20–22°C and 30–39% RH. The amount of drug collected on the valve stem, actuator, and each component of the NGI assembly was dissolved with a known volume of a suitable solvent for the particular drug being analyzed (75/25 methanol/water for BUD, methanol for BDP, and 45/55 methanol/0.1% phosphoric acid in water for AS). The solution was then analyzed using an appropriate liquid chromatography method (Table 2) to determine the mass of drug collected on each component. The drug collected on the USP throat and the associated coupler were assayed together and are labeled as the "throat" deposition.

A total of five APSD measurements were made for each MDI formulation listed in Table 1 with and without controls in place to minimize the impact of electrostatic effects. In order to further evaluate throat deposition an additional 15 tests with and without static controls were conducted for each formulation in which only the throat deposition was measured. Each measurement was done using a separate MDI unit and consisted of five actuations. In total, 40 units were evaluated for each MDI formulation (20 total units tested without static controls and 20 units tested with static controls). The static controls are described below. *Description of Static Controls.* Two testing conditions were evaluated to assess the impact of static controls on APSD measurements performed using the NGI. One condition, "static controls," utilized various means to minimize electrostatic effects. The other condition, "no static controls," did not incorporate static controls. These conditions are summarized in Table 3.

For the no static controls condition, the analyst wore nitrile gloves during sample preparation and placed their hand on the USP throat (a practice often employed to securely couple the actuator to the USP throat). For the static controls condition, the actuator was rinsed with

Table 1. Description of Experimental MDI Formulations Evaluated

HFA-227 BUD suspension	HFA-134a BDP solution	HFA-134a AS suspension
0.12% budesonide	0.17% BDP	0.19% albuterol sulfate
0.30% PEG-1000 NF	8.00% ethanol	0.03% oleic acid
0.001% povidone K25 (USP)	91.83% HFA-134a	14.44% ethanol
99.58% HFA-227		85.34% HFA-134a

methanol and allowed to air dry until the orifice was clear of methanol and for at least 1 h or prior to testing. After drying, the actuator was treated by discharging a Milty Zerostat 3 Anti-Static Gun (Armour Home, Hertfordshire, UK) approximately 10 times to dissipate charge present on the surface of the actuator. In addition, the NGI was grounded by attaching a grounded cable to the cup holder of the NGI apparatus and the analyst wore a grounded antistatic wrist strap (ESD Safe Anti-Static Wrist Strap 6ft Ground Cord–Blue; CML Supply, Lexington, KY) on the wrist of the hand holding the MDI. A digital voltmeter (Fluke 87 True RMS Multimeter; Fluke Corporation, Everett, WA) was used to confirm that the NGI cups, nozzle plates and body were all grounded). During the test, an ionizing air blower (Volume Static Eliminator VSE 3000; Simco-Ion, Hatfield, PA) was directed towards the testing apparatus approximately 30–50 cm from the USP throat. The position of the ionizing air blower was selected to be close to the device while not interfering with the activities of the analyst. To further minimize the potential for introducing static charge, the analyst did not wear gloves during the sample preparation and did not touch the USP Inlet while actuating the MDIs.

Analysis of Size Distribution Parameters

Copley Impactor Testing Data Analysis Software (CITDAS™, v. 2; Copley Scientific, Nottingham, UK) was used to analyze the size distribution measurements. The fine particle dose, FPD (< 5 μm), provides an estimate of the drug mass contained in particles with aerodynamic diameters smaller than 5 μm. The impactor-sized mass (ISM) is a sum of all drug collected on cup 2 through the micro-orifice collector (MOC) for the two suspension formulations. For the HFA-134a BDP solution formulation, the ISM includes deposition on a filter placed after the MOC during testing. The CITDAS software was also used to calculate the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the delivered aerosol. For each formulation, the results from testing with and without static controls were analyzed for statistically significant differences using a one-way ANOVA (Minitab 17.1.0, Minitab Inc., State College, PA).

RESULTS

The Influence of Static Controls on NGI Profiles

The average NGI profiles from size distribution measurements of the three formulations tested with and without static controls are shown in Fig. 3. For all three formulations, the tests that used static controls had lower throat deposition and correspondingly higher deposition on the impactor stages. These differences are largest for the HFA-227 BUD suspension formulation. The magnitude of differences between tests with or without static controls was smaller than for the HFA-134a BDP solution and HFA-134a AS suspension formulation. Error bars representing the standard deviation are included in Fig. 3, but are difficult to see due to the high reproducibility of the test results. The use of static controls resulted in reduced actuator holdup for the HFA-227 BUD Suspension and HFA-134a BDP Suspension but resulted in no change for the HFA-134a AS Suspension.

The Influence of Static Controls on Throat Deposition During NGI Testing

The influence of static controls on the amount of drug collecting on the USP throat was assessed for each formulation. A total of 20 measurements with and without static control were made on each formulation and are summarized in Fig. 4. For each formulation evaluated, there was an increase in throat deposition when static controls were not used. For the HFA-227 BUD suspension, average throat

Table 2. Description of Liquid Chromatography Methods Used

Parameter	BUD HFA-227 suspension	BDP HFA-134a solution	AS HFA-134a suspension
Analytical column	C18, 2.1 × 50 mm, 1.8 μm	C18, 2.1 × 50 mm, 1.8 μm	C18, 4.6 × 150 mm, 5 μm
Detection	UV at 244 nm	UV at 238 nm	UV at 225 nm
Injection volume	4 μl	4 μl	40 μl
Flow rate	0.87 ml/min	0.75 ml/min	2 ml/min
Separation	Gradient	Isocratic	Isocratic
Mobile phase	0.1% H_3PO_4 in water; 0.1% H_3PO_4 in ACN	60/40 ACN/water (*v*/*v*)	45% methanol:55% water (buffered, pH 2.5)
Run time	3.25 min	1.50 min	6 min

Table 3. Description of Static Controls During NGI Testing

Description of control	"No static controls"	"Static controls"
NGI grounded		✓
Analyst grounded		✓
Ionizing air blower used		✓
Actuator rinsed and air-dried prior to testing		✓
Actuator treated with anti-static gun		✓
Analyst wears gloves during actuation of MDI	✓	
Analyst holds USP throat during actuation of MDI	✓	

deposition was 15% higher (31.6 *vs* 27.5 mcg/act) when static controls were not used compared to when they were used. This difference was statistically significant (p value < 0.001). Statistically significant differences in throat deposition were observed for the HFA-134a BDP solution and HFA-134a AS suspension (p value < 0.001 and p value = 0.019, respectively) tested with and without static controls. However, the increase in throat deposition when static controls were not used during testing of the HFA-134a BDP solution and HFA-134a AS suspension were smaller (5 and 4% increase, respectively) than the differences observed with HFA-227 BUD suspension.

The Influence of Static Controls on Size Distribution Parameters

Copley Impactor Testing Data Analysis Software (CITDAS™, v. 2; Copley Scientific, Nottingham, UK) was used to analyze the size distribution measurements for each formulation tested with and without static controls. The average (± standard deviation) for the key size distribution parameters are summarized in Table 4.

The results in Table 4 indicate that impactor-sized mass and fine particle dose (< 5 μm) results can be significantly influenced by electrostatic effects during testing. In contrast, the MMAD and GSD were insensitive to electrostatic effects. This indicates that, while static controls influence the amount of drug entering into the impactor during testing, the static controls do not change the size of these particles. The average NGI profiles from testing of the HFA-227 BUD suspension were normalized by taking the amount on each stage in the NGI and dividing by the total drug mass on all the NGI stages. The normalized NGI profiles for testing with and without static control are virtually indistinguishable (Fig. 5), further indicating that static controls impact the total mass of drug entering the NGI but not the size of the drug particles.

DISCUSSION

The impact of static controls during NGI testing was evaluated for three different HFA formulations delivered from MDIs that utilized valves with plastic components and a polypropylene actuator with a 0.4 mm orifice diameter. The utilization of static controls resulted in a statistically significant decrease in throat deposition for all three formulations (p value < 0.001 for HFA-227 BUD suspension, p value < 0.001 for HFA-134a BDP solution, and p value = 0.019 for HFA-134a AS suspension). For the HFA-227 BUD formulation, there was a 15% decrease in throat deposition and a

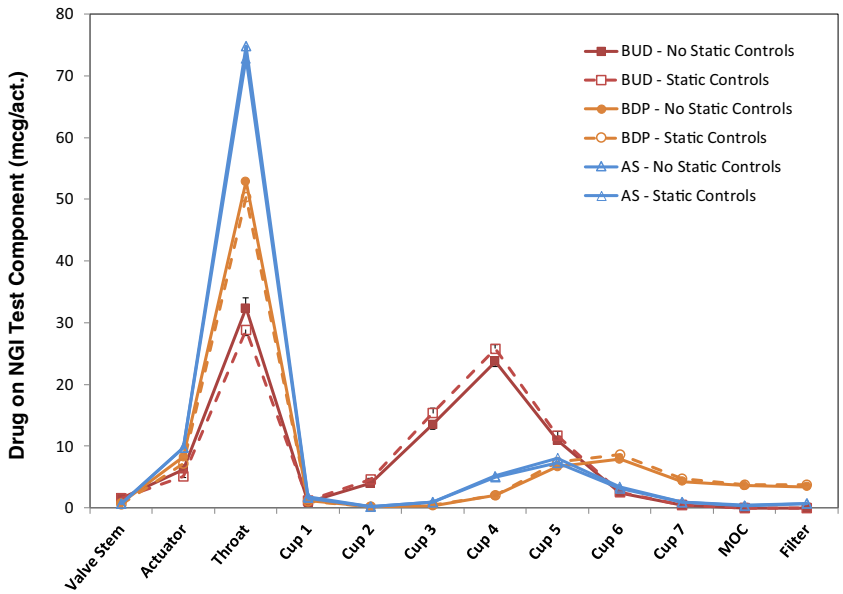

Fig. 3. NGI profiles from testing with and without static controls of three MDI formulations

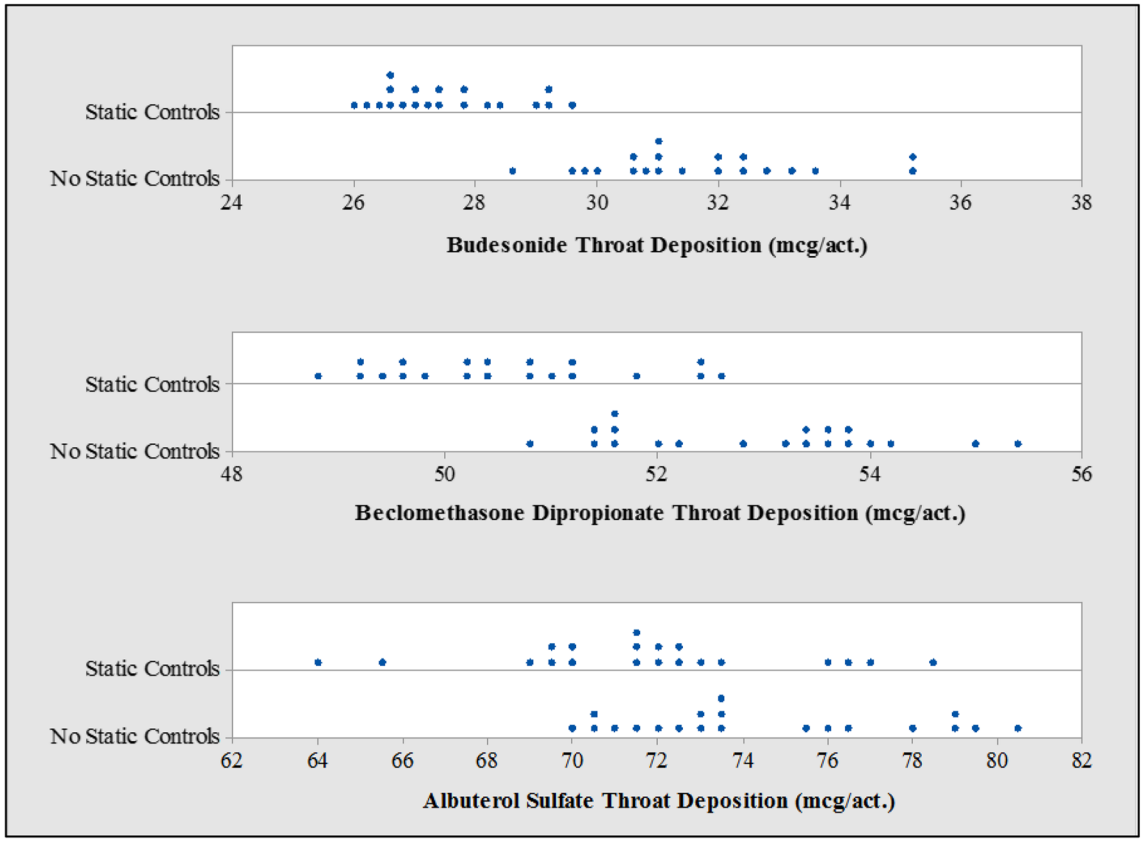

Fig. 4. Comparison of USP throat deposition from NGI testing with and without static controls

corresponding increase in the ISM and FPD when static controls were used. The use of static controls had a statistically significant impact on the other MDI configurations tested, but the relative impact was less significant than for the HFA-227 BUD formulation.

The relative impact that the utilization of static controls have on CI test results for different MDI configurations is likely influenced by the amount of charge present on the atomized MDI aerosol. The amount of charge imparted to MDI aerosols during aerosolization has been shown to be influenced by both formulation and device parameters (6,10,12). Since the same valves, canisters and actuators were used to produce the MDIs tested in this paper, the differences observed in the relative influence of static controls on CI testing is related to the formulation composition. The formulation that was impacted most by the use of static controls was unique from the other two formulations in the drug used (budesonide), the propellant (HFA-227 *vs* HFA-134a), the lack of ethanol, and the excipients used (PVP and PEG-1000). It is unclear which formulation parameter(s) is responsible for the relative differences that static controls had on CI test results (Table 4).

The use of static controls had a significant influence on the amount of throat deposition during CI testing and therefore influenced total mass of drug reaching the impactor. However, static controls had minimal impact on the aerodynamic particle size distribution of the drug reaching the impactor. For all three formulations tested, the measured MMAD and GSD were virtually identical for the tests with and without static controls. That said, MDI APSD measurements associated with regulatory filings are typically evaluated based on the impactor-sized mass (ISM), fine particle dose (FPD), or mass of drug on various plate groupings rather than MMAD and GSD. As such, static controls can

Table 4. Summary of MDI Size Distribution Parameters from Testing

Size distribution parameter	HFA-227 BUD suspension		HFA-134a BDP solution		HFA-134a AS suspension	
	Static controls	No static controls	Static controls	No static controls	Static controls	No static controls
ISM (mcg/act.)	60.5 ± 2.0	55.1 ± 2.2	31.0 ± 0.9	28.3 ± 2.2	19.7 ± 0.6	18.5 ± 1.0
FPD (mcg/act.)	49.3 ± 1.8	45.5 ± 1.8	30.6 ± 0.9	27.9 ± 2.3	19.1 ± 0.6	17.9 ± 0.9
MMAD (microns)	3.27 ± 0.04	3.21 ± 0.03	1.03 ± 0.02	1.04 ± 0.06	1.93 ± 0.03	1.97 ± 0.05
GSD	1.66 ± 0.01	1.65 ± 0.01	1.96 ± 0.04	2.01 ± 0.06	1.88 ± 0.02	1.93 ± 0.10

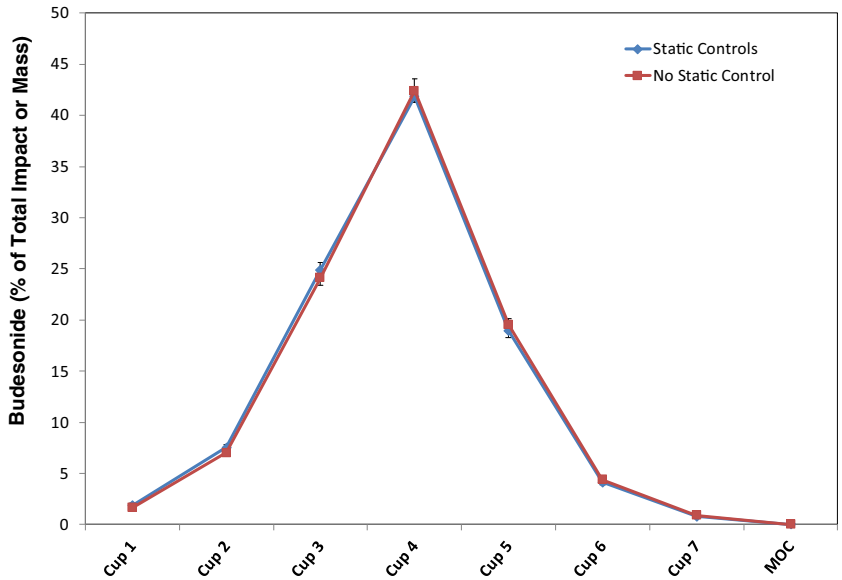

Fig. 5. Normalized NGI profiles from testing of HFA-134a BDP suspension with and without static controls

have a significant influence on whether or not an MDI size distribution measurement will meet regulatory specifications.

The use of static controls can influence CI test results by influencing the amount of charge induced on the aerosol during atomization or by altering electrical fields that the atomized droplets may be exposed to and that could influence when and where they deposit in the CI apparatus. It is difficult to assess which of these factors had the greater influence on the CI measurements reported in this paper. Some controls, such as grounding of the CI apparatus, likely only influenced deposition by altering the electric field that atomized droplets are exposed to in the CI test apparatus. Other controls, such as the use of the static gun to remove charge on the actuator could have affected both the amount of charge imparted to the atomized droplets and the electric fields that these droplets were exposed to as they passed through the actuator mouthpiece during CI testing.

For simplicity, all testing in this study was done using polypropylene actuators. Based on the results of Chen *et al.* (12), who determined that actuator material influenced the net charge on the aerosol, it is possible that CI testing of MDIs using other actuator materials may be more or less sensitive to static controls. In order to compare the relative influence of static controls on different MDI formulations, the same lot of polypropylene actuators with 0.4 mm orifice diameters were used with all of the formulations. This actuator configuration was not optimized for these configurations. Gabrio *et al.* (21) found that USP throat deposition is correlated to the force of the MDI plume. They reported that the plume force from HFA-134a MDIs with an orifice diameter of 0.4 mm are approximately twice that of HFA-134a MDIs with an orifice diameter of 0.3 mm. They also found that the plume force for HFA-134a MDIs is substantially higher than for HFA-227 MDIs. Stein and Myrdal (22) found that formulations with elevated ethanol concentration produced larger droplets that took longer to evaporate and resulted in increased throat deposition compared to formulations without ethanol. Thus, while an orifice diameter of 0.4 mm may provide acceptable performance for an ethanol-free HFA-227 formulation such as the HFA-227 BUD suspension, it resulted in poor performance for the HFA-134a BDP solution and HFA-134a AS suspension formulations. It should be noted that two commercial HFA-134a MDIs that contain substantial concentrations of ethanol, Qvar® and Proventil® HFA, utilize actuators with an orifice diameter of approximately 0.3 mm. It is possible that the HFA-134a BDP solution and HFA-134a AS suspension formulations were impacted less by static controls during CI testing because the more forceful spray and larger droplets they produced overwhelmed electrostatic effects.

Further investigation is needed to more broadly understand the impact that static controls on CI testing of MDIs. It would be helpful to examine a broader range of MDI configurations, including valves with different materials of composition, different actuator materials, different orifice diameters, different formulations, etc. Further insight may be gained by examining the impact of the individual static controls listed in Table 3 rather than grouping them together as was done in this study as well as by characterizing the electrostatic charge generated on the plume for each formulation. In addition, in future testing it may be useful to use a single actuation during testing in order to minimize the possibility of introducing static when the plastic actuator is inserted into the coupler. There would also be value in examining the influence of these static controls on commercial MDI and DPI products.

The clinical implications of these experiments are not known. There is evidence that electrostatic charge on the aerosol can lead to enhanced deposition in the respiratory tract (4,23). Cascade impactor tests provide insight into a parameter, the APSD of the aerosol, that has clinical relevance but the influence of electrostatic effects on the collection of the aerosol in the metal equipment used during cascade impactor testing is not relevant to the influence of

electrostatic effects during clinical use of inhalers. Electrostatic controls are not used during normal patient use, but they may be used in the controlled setting of clinical trials.

CONCLUSION

The APSD of three experimental MDI configurations was measured using the NGI with and without utilizing static controls. The three MDI configurations had different formulations but used the same valve, canister, and actuator. For each formulation evaluated, there was a statistically significant reduction in USP throat deposition and corresponding increase in the ISM when static controls were used during testing. While the use of static controls had a significant impact on the mass of drug reaching the impactor, it did not impact the aerodynamic size distribution of the drug particles reaching the impactor. The HFA-227 BUD suspension formulation had the greatest difference between test results from tests with and without static controls. For this formulation, the average USP throat deposition varied by 15% between the testing conditions. The average USP throat deposition for the other two formulations (HFA-134a BDP solution and HFA-134a AS suspension) were impacted by the use of static controls, but to a lesser degree. This may be due to the formulation differences or because the actuator configuration used was not optimized for these formulations and resulted in high deposition in the USP throat. These results demonstrate that electrostatic effects can lead to meaningful variability in cascade impactor test results. Static controls should be considered when developing cascade impactor test methods for MDI products in order to eliminate variability in test results.

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