MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 8, pp. 865–876, 2003

RESEARCH PAPER

Influence of the Metering Chamber Volume and Actuator Design on the Aerodynamic Particle Size of a Metered Dose Inhaler

Julianne Berry, Ph.D.,* Susan Heimbecher, Ph.D., John L. Hart, Ph.D., and Joel Sequeira, Ph.D.

Schering Plough Research Institute, Kenilworth, New Jersey, USA

ABSTRACT

Presented in this work are the results of a study designed to investigate the impact of the valve metering chamber volume and actuator design on the aerodynamic particle size distribution (PSD) of a suspension metered dose inhaler (MDI) containing propellant HFA-227. It was hypothesized that the valve metering volume and the actuator design in the MDI could influence the PSD of the emitted dose since it would affect the aerosol spray dynamics. The PSD results from this study, measured using cascade impaction, revealed that samples containing an actuator intended for oral delivery (rectangular mouthpiece and orifice diameter of ≈0.5 mm) produced a higher fine particle dose (FPD) than those containing an actuator intended for nasal delivery (circular nosetip and orifice diameter of ≈1 mm). In addition, the drug PSD profile was shown to be more sensitive to differences in the particle size of the suspended material when the oral actuator was used compared to when the nasal actuator was used. The valve metering chamber (25 vs. 63 μL volume) did not appear to have a major effect on the product aerodynamic PSD or the droplet size. These results demonstrate the importance of actuator design and orifice size in determining the aerodynamic PSD of an MDI.

Key Words: Cascade impaction; Laser diffraction; Particle size; Metered dose inhaler; Actuator; Valve.

*Correspondence: Julianne Berry, Ph.D., Schering Plough Research Institute, 2000 Galloping Hill Road, Building K-11-2, Mailstop J-5, Kenilworth, NJ 07033, USA; Fax: (908) 740-2802; E-mail: julianne.berry@spcorp.com.

DOI: 10.1081/DDC-120024182
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

INTRODUCTION

A metered dose inhaler (MDI), the most commonly used device for delivering drugs to the respiratory tract in the treatment of pulmonary diseases such as asthma,[1–3] is comprised of the formulation, a metering valve, container (can), and actuator. For suspension formulations, which make up most marketed products, micronized drug is suspended in a propellant/surfactant mixture. The MDI formulation is administered to the patient as an aerosol spray containing fine droplets, formed by the atomization of the liquid phase of the formulation.

The atomization mechanism is thought to result from the evaporation of the propellant within the actuator nozzle[4] and is highly dependent on the propellant vapor pressure and actuator spray orifice dimensions.[5–10] The amount of fine particles in the spray is shown to be inversely proportional to the orifice diameter of the actuator and proportional to the square root of the vapor pressure of the formulation.[9,10]

The aerodynamic particle size distribution (PSD) of the MDI is a critical parameter that needs to be carefully controlled since it determines where the aerosol will deposit in the respiratory tract and is closely linked to the efficacy of the delivered medication.[11–13] Medications used for local treatment of the lung, i.e., beta-2 agonists for bronchodilation or corticosteriods for the reduction of inflammation caused by asthma, generally target the size range of 2–5 μm. The delivery of particles to the lung that are not within the 2–5 μm range can lead to high oropharyngeal deposition (if much larger than 5 μm)[12–13] as well as local and systemic side effects.[12–14]

Due to the importance of controlling the particle size of the delivered dose of MDIs, this study was initiated to evaluate the influence of valve metering chamber volume and actuator design on the aerodynamic PSD of a suspension aerosol. It was hypothesized that the aerodynamic PSD is affected by the spray volume and the actuator design since both of these parameters control the nature of the emitted aerosol spray.

The focus of the study was to evaluate the aerodynamic PSD of an MDI formulation containing hydrofluoroalkane (HFA)-227 using 25 and 63 μL metered valves and actuators designed for oral and nasal delivery. The design features of the nasal actuator allow the production of a larger droplet size compared with the oral actuator (i.e., larger orifice diameter and smaller diameter nosetip), which is intended to target the emitted spray to the nasal cavity. An MDI containing an HFA propellant was selected as the model formulation for this work since, due to the imminent phase out of chlorofluorocarbon (CFC) propellants,[14,15] it was considered to be representative of future MDIs.

MATERIALS AND METHODS

Preparation of Samples

A single batch of a suspension product containing micronized drug substance, surfactant, alcohol (i.e., ethanol), and propellant HFA-227 was manufactured according to a standard method for the preparation of aerosol products. In this process, the bulk drug concentrate (drug, oleic acid, ethanol) was continuously mixed throughout the course of manufacturing. The manufacturing process consisted of filling the drug concentrate from the bulk suspension into a 14 mL aerosol can, which was subsequently fitted and crimped with a standard prototype metering valve for HFA formulations (either 25 μL or 63 μL version). The propellant was then pressure filled into the can through the metering valve.

For this study, MDI samples were filled within 30 min of preparing the drug concentrate (beginning of fill), and then at 48 h (end of fill). The conditions of the manufacturing process were selected in order to increase the propensity for particle size growth of the suspended drug substance over the 48 h filling time. Independent studies of this formula/process have shown long mixing times (>24 h) to result in an increase in the particle size of the suspended drug. The drug concentrate suspension, however, was uniform throughout the extended filling process as confirmed by the assay of the drug content per can.

Particle growth during manufacturing has been attributed to the partial solubility of the drug in the concentrate and the ensuing Ostwald Ripening, although particle agglomeration could also explain this phenomenon. Microscopic evaluation (scanning electron microscopy using a Hitachi S-3500 N, Hitachi high technologies, Gaithersburg, MD, 5 kV accelerating voltage) of this batch showed, qualitatively, that samples from the end of filling generally contained larger size drug particles than those from the beginning.

The test samples were divided into the following four categories: Prototype 1 (63 μL valve, oral actuator), Prototype 2 (63 μL valve, nasal actuator),

Prototype 3 (25 μL valve, oral actuator), Prototype 4 (25 μL valve, nasal actuator). Each prototype included samples taken from both the beginning and the end of fill.

Except for the volume of the metering chamber, the 63 and 25 μL valves used in this study were identical with respect to design. However, the nasal and oral actuators used in this study differed in both the orifice and mouthpiece/nosetip diameters. The orifice diameters of the oral and nasal actuators are about 0.5 and 0.1 mm, respectively. The mouthpiece of the oral actuator, which is rectangular in shape, is about 15×20 mm. The nosetip of the nasal actuator is circular in shape and has a diameter of about 8 mm. A photograph of each of these actuators is given in Fig. 1.

Cascade Impactor Testing

For all prototype/fill time combinations, the particle size was evaluated using cascade impaction, the method required by the Food and Drug Administration (FDA) for size classification of MDIs. This methodology, well documented in the literature,[16–18] provides a measurement of the PSD of the droplets associated with the drug.

The Mark II Andersen Cascade Impactor (1 AFCM Non-Viable Ambient Particle Sizing Sampler, 28 L/min flow rate, Graseby-Andersen, Smyrna, GA) was used to obtain the PSD of the aerosol spray droplets associated with drug. A 1 L glass entry port was employed in place of the United States Pharmacopeia (USP) throat since studies in this laboratory have shown it to be more sensitive to changes in particle size profiles. Each sample was fitted with the appropriate actuator, primed, and then tested per validated cascade impaction methodology.

The drug was recovered from the cascade impactor stages and accessories in an appropriate high-performance liquid chromatography (HPLC) grade solvent, and the concentration was determined by HPLC with spectrophotometric detection. The mass of drug on each stage or accessory was divided by the total amount collected to give the dose percentage for each part of the apparatus. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were estimated based on the USP method.[18] The fine particle dose, also calculated, is defined as the percent of the dose ≤4.7 μm.

In order to evaluate the reproducibility of the method, the variability of trials (cascade impactor determinations) was established both within a can and between cans for the beginning of fill samples of Prototype 1. For this experiment, four trials were performed with the first can (Can 1) and then a single trial, each, was performed with a second and third can (Cans 2 and 3). The cascade impactor aerodynamic PSD profiles for the four trials of Can 1 and the single trials of Cans 2 and 3, appear similar (i.e., residual standard deviation (RSD) ≤5% for impactor recovery, fine particle dose, MMAD, and GSD). Based on the reproducibility of the aerodynamic

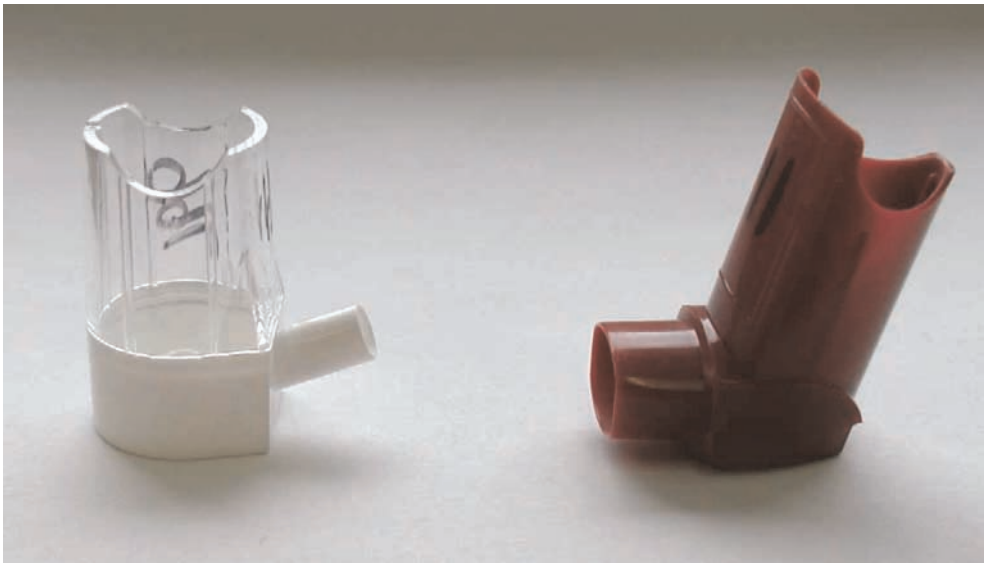

Figure 1. Side view of nasal actuator (left) and oral actuator (right).

PSD observed with initial samples of Prototype 1, it was decided that testing would be performed only in duplicate for other prototype/fill time combinations (i.e., two samples × one trial each sample).

Sympatec Testing

For the beginning of fill samples of all prototypes, the particle size was also evaluated using laser diffraction, a more exploratory method (i.e., not required by the FDA) for size classification of MDIs. This methodology, which is described in the literature,[19–21] provides a nondiscriminatory measurement of the distribution of the droplets associated with the drug as well as the droplets that are not associated with drug (i.e., contain propellant alone or with other non-volatile ingredients).

The Sympatec HELOS Compact, model KA with a R2 helium-neon laser (0.25–87.5 microns) was used to obtain the PSD, referred to as the volume size distribution (VSD), of the aerosol spray droplets (Sympatec, GmbH, Windox Software 3.0, Clausthal-Zellerfeld, Germany). A special adapter for which MDI actuation could be performed automatically was attached. According to this method,[19–21] a detector with 31 channels is used to measure the diffraction pattern caused by the presence of particles in the path of the laser beam. The measurement begins after the first few spray droplets pass through the laser beam and stop when the spray decays below a detectable level. Fraunhofer diffraction is used as the mathematical theory for assigning the measured diffraction intensity to the particle size and frequency. The diameter of the diffraction ring is inversely proportional to the size of the particles, while the distribution of the light energy in the diffraction pattern is associated with the particle quantities. All particles present in the measured cross section transmit scattered light to create the diffraction pattern. The software converts the light scattering information to a VSD, i.e., the volume distribution of particles present in individual size classes.

The VSD profiles were obtained at a spray distance of 10 cm (measured from the actuator mouthpiece). It was estimated that droplets emitted at this distance, the approximate distance from the mouth to the back of the throat, would provide a good representation of the product that enters the cascade impactor. For all prototypes, five sprays were sampled from each of two cans.

RESULTS

Cascade Impaction

Drug Recovery

The total drug recovered (i.e., percent of label claim) in the cascade impactor, including all stages and accessories, was ≈20–25% lower for the nasal

Table 1. Percent of label claim (LC) recovered in the Anderson cascade impactor.

Prototype	Valve metering volume (μL)	Actuator design	Filling time	% LC of active recovered,[a] mean (range)
1[b]	63	Oral	Beginning	106 (101–110)
			End[c]	101 (99.8–103)
			Average	104
2	63	Nasal	Beginning	81.8 (81.5–82.0)
			End[c]	81.7 (81.6–81.8)
			Average	81.8
3	25	Oral	Beginning	101 (93.0–108)
			End[c]	94.1 (93.3–95.0)
			Average	97.6
4	25	Nasal	Beginning	75.3 (70.9–79.6)
			End[c]	77.4 (75.0–79.8)
			Average	76.4

[a]Described in the experimental section, $N = 2$.
[b]$N = 6$.
[c]48 h filling time.

Table 2. Percent recovery from the emitted dose on the Anderson cascade impactor stages and accessories.

Prototype #	Valve metering volume (μL)	Actuator design	Filling time	% Drug recovered from dose[a], mean (range)		
				On impactor stages	On entry port	On casings
1[b]	63	Oral	Beginning	85.1 (82.1–87.0)	9.3 (7.5–12.4)	5.6 (5.2–6.0)
			End[c]	85.2 (84.9–85.4)	7.4 (6.7–8.1)	7.5 (7.0–7.9)
			Average	85.2	8.4	6.6
2	63	Nasal	Beginning	57.5 (57.3–57.6)	39.0 (38.4–39.6)	3.6 (2.8–4.3)
			End[c]	57.9 (54.6–61.2)	38.8 (35.2–42.3)	3.3 (3.1–3.6)
			Average	57.7	38.9	3.5
3	25	Oral	Beginning	83.9 (81.7–86.1)	9.8 (8.1–11.5)	6.4 (5.8–6.9)
			End[c]	87.4 (85.1–89.6)	6.4 (4.5–8.2)	6.3 (5.9–6.6)
			Average	85.7	8.1	6.4
4	25	Nasal	Beginning	62.6 (58.6–66.6)	28.9 (27.7–30.0)	8.5 (5.7–11.4)
			End[c]	61.6 (61.0–62.3)	33.6 (33.0–34.3)	4.7 (4.7–4.7)
			Average	62.1	31.3	6.6

[a]Described in the experimental section, $N = 2$.
[b]$N = 6$.
[c]48 h filling time.

samples than for the oral samples (Table 1). This result is consistent with independent experiments from this laboratory that compared the amount of drug that was lost to nasal vs. oral actuators (and was therefore unavailable for delivery to the cascade impactor). In these experiments, drug recovery from nasal actuators was approximately 20% of the dose whereas, for the oral actuators, 5% or less of the dose was recovered.

On the other hand, the amount of drug recovered in the impactor does not appear to be affected by the size of the valve metering chamber (Table 1). The impactor recoveries for the oral samples containing the 63 and 25 μL valves were comparable and within 10% of label claim (Prototypes 1 and 3, Table 1). Similarly, the impactor recoveries for the nasal samples, containing the 63 and 25 μL valves, are also comparable and within 80% ± 10% of the label claim (Prototypes 2 and 4, Table 1).

For each of the prototypes, the total drug recovery was also unaffected by batch manufacturing time. This was shown by the comparable drug recovery results for the beginning and end of fill samples (Table 1).

Impactor Stage Recovery

There was no significant effect seen between the 63 μL vs. the 25 μL valve in the % dose recovered from the impactor stages relative to that on the entry port. This is shown by the comparable results for the % dose collected for Prototypes 1 vs. 3 and Prototypes 2 vs. 4 (Table 2).

The graphical presentation of the % of drug recovered in the impactor stages (aerodynamic PSD profiles for the beginning of fill of Prototypes 1–4, Fig. 2) also illustrates the relative insensitivity of the particle size to the valve metering chamber. The shape of the aerodynamic PSD profile produced by the oral samples containing the 63 μL valve is similar to that of the oral samples containing the 25 μL valve (Prototypes 1 and 3, respectively, Fig. 2). Likewise, the shape of the aerodynamic PSD profile produced by the nasal samples containing the 63 μL valve is similar to that of the nasal samples containing the 25 μL valve (Prototypes 2 and 4, respectively, Fig. 2).

However, significant differences were seen with the oral vs. the nasal actuator in the % dose recovered from the impactor stages relative to the entry port. Although no difference was seen for the amount of drug on the casings (Table 2), the difference in % recovery between the impactor and the entry port is greater than 75% for the oral actuator samples (Prototypes 1 and 3, Table 2) while, for the nasal actuator samples this difference is only about 25% (Prototypes 2 and 4, Table 2).

The higher recovery on the cascade impactor seen for samples with oral actuators is also illustrated

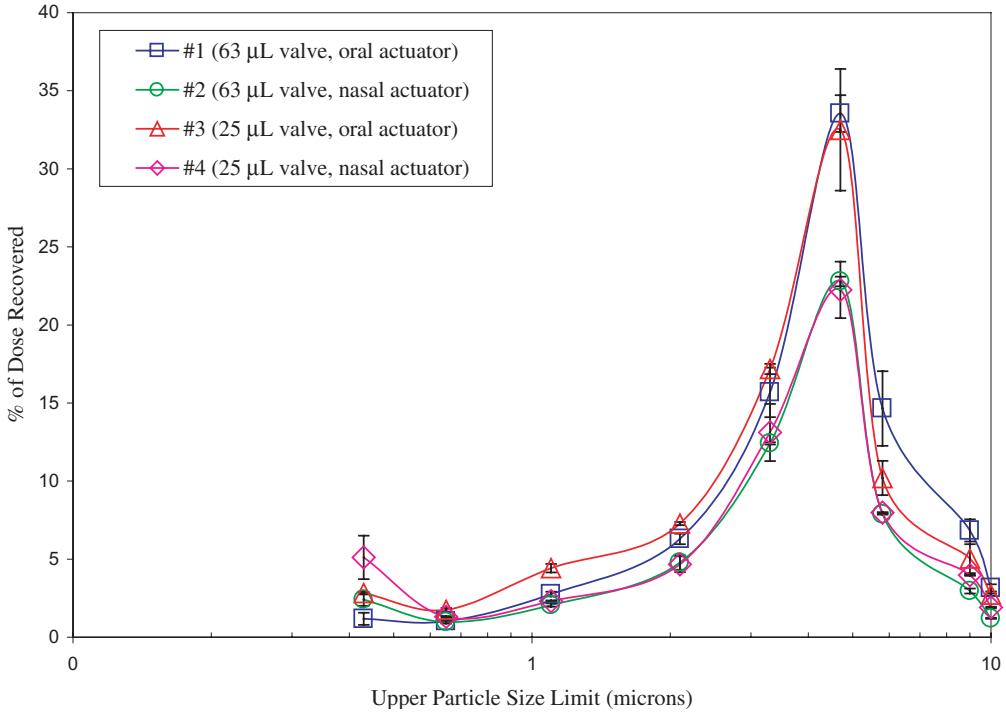

Figure 2. Andersen cascade impactor PSD profiles for prototypes 1–4 (beginning of fill).

in Fig. 2. In this figure, the % dose recovered on the cascade impactor for the oral samples (Prototypes 1 and 3) is shown to be substantially higher than the % dose recovered for the nasal samples (Prototypes 2 and 4).

These results (Table 2, Fig. 2) demonstrate that the % of dose ≤ 10 microns (i.e., the dose recovered from the impactor stages) is greater for the oral samples than for the nasal samples, regardless of the valve used. In addition, the results in Table 2 show that the % dose on the impactor stages, entry port, and casings is similar for the beginning and end of fill samples and, thereby, independent of batch manufacturing time for the prototypes tested.

Aerodynamic Particle Size Distribution

The % fine particles, or the % of drug obtained from particles ≤ 4.7 microns, is equivalent to the sum of the % collected on stages 3–7 + filter. For the beginning of fill samples, the % fine particles is approximately 26% higher for the oral samples than for the nasal samples and appears to be independent of the valve metering chamber (Table 3).

Interestingly, although a reduction in the % fine particles from beginning to the end of the batch is observed for all of the prototypes, this reduction appears to be attenuated for the nasal samples (Table 3). For the oral samples, the % fine particle difference from the beginning to the end of the batch is approximately 2.6 times greater than that for the nasal samples (Table 3).

The cascade impactor aerodynamic PSD profiles shown in Fig. 3 for the 63 µL valve prototypes illustrate graphically how the profiles are changing from beginning to the end of the batch for the oral samples compared with the nasal samples in the ≤ 10 micron particle size region. This profile (Fig. 3) shows that the shift to larger particle size for the oral samples is of a greater magnitude than that of the nasal samples. The same trend is observed for the 25 µL valve prototypes.

The results for the distribution of drug on the impactor stages and filter when expressed as the mass median aerodynamic diameter (MMAD) again point out that the particle size increase for the beginning to end of filling is smaller for the nasal samples as compared with the oral samples. Although all prototypes showed a corresponding increase in MMAD from the beginning to the end of the batch, the increase in the oral samples was approximately 2.3 times larger than that of the nasal samples (Table 3).

Table 3. % Fine particles, MMAD and GSD.

Prototype #	Valve metering volume (μL)	Actuator design	Filling time	% Fine particles (≤ 4.7 μm), mean (range)	MMAD[a,b] (μm), mean (range)	GSD,[1,2] mean (range)
1[c]	63	Oral	Beginning	60.5 (58.0–63.0)	3.13 (2.97–3.27)	2.13 (2.07–2.22)
			End[d]	43.3 (42.6–44.0)	3.98 (3.86–4.09)	2.32 (2.28–2.36)
			Difference[e]	−17.2	+0.85	+0.19
2	63	Nasal	Beginning	45.4 (45.4–45.4)	2.54 (2.53–2.54)	2.21 (2.18–2.24)
			End[d]	38.9 (35.2–42.6)	2.94 (2.84–3.03)	2.36 (2.34–2.38)
			Difference[e]	−6.5	+0.40	+0.15
3	25	Oral	Beginning	66.0 (63.8–68.1)	2.63 (2.62–2.64)	2.26 (2.22–2.29)
			End[d]	50.3 (49.7–51.0)	3.45 (3.36–3.53)	2.48 (2.46–2.49)
			Difference[e]	−15.7	+0.82	+0.22
4	25	Nasal	Beginning	48.8 (44.8–52.7)	2.40 (2.31–2.48)	2.51 (2.48–2.53)
			End[d]	42.4 (41.1–43.7)	2.74 (2.70–2.77)	2.59 (2.54–2.63)
			Difference[e]	−6.4	+0.34	+0.08

[a]Estimated based on USP method.
[b]$N = 2$.
[c]$N = 6$.
[d]48 h filling time.
[e]The difference in results obtained at the 48 h timepoint vs. those at the initial timepoint.

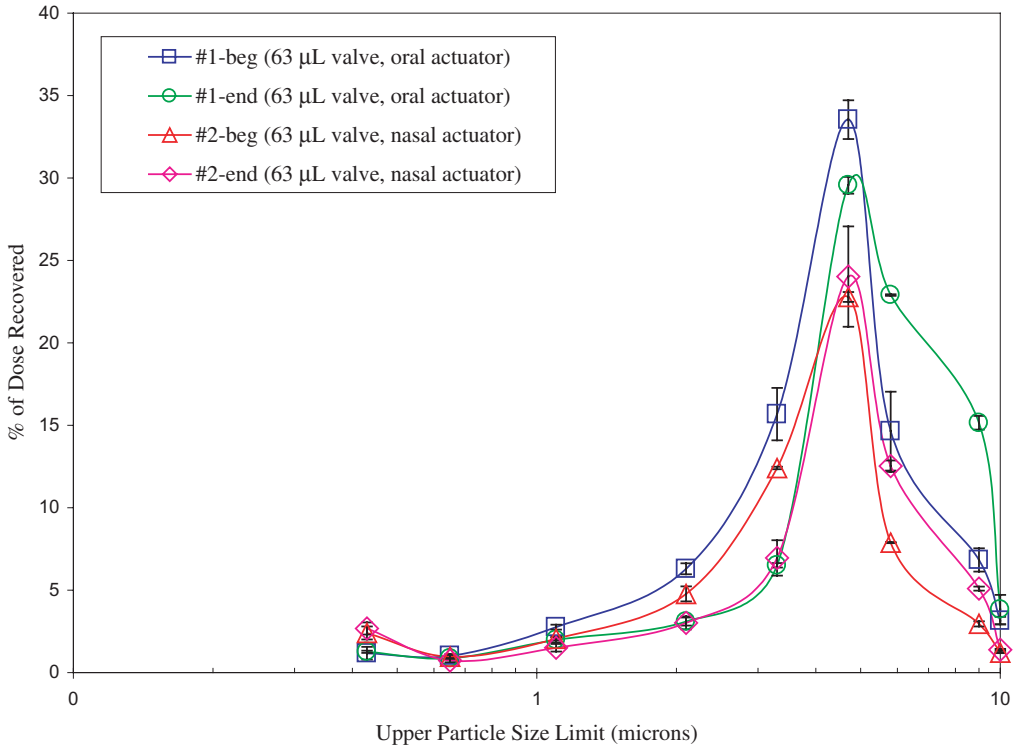

Figure 3. Andersen cascade impactor PSD profiles for prototypes 1 and 2 (beginning and end of fill).

Furthermore, the MMAD showed a reduction with a decrease in valve metering chamber size that was most apparent with the oral actuator (e.g., beginning of fill results; Table 3). The effect of the valve metering chamber on MMAD was, in fact, the only effect that was seen for the 63 µL vs. the 25 µL valve in this study.

The MMAD values in Table 3 are slightly lower for the nasal samples compared with the oral samples. Although the lower MMAD of the nasal samples suggests a smaller particle size for these prototypes, the MMAD alone does not determine the overall particle size. Previous data for the nasal samples (higher entry port and lower % fine particles, Tables 2 and 3) suggest that the overall particle size of the nasal samples is actually larger than the oral samples. However, it may be that for the nasal samples the larger particles settle in the entry port, but the fraction entering the impactor are actually finer than that produced by the oral samples.

The geometric standard deviation (GSD) values of drug distribution on the impactor stages was also evaluated. As shown in Table 3, no significant trend was seen with either the actuator type, valve metering chamber size, or with the time of batch manufacture (i.e., with beginning vs. end of fill samples).

Particle Size by Sympatec

The volume size distribution (VSD) profiles of the emitted spray droplets obtained by Sympatec at the 10 cm spray distance show smaller droplet sizes for the oral samples compared with the nasal samples (Fig. 4). These results are consistent with the higher fine particle dose observed with the oral samples, i.e., the production of smaller droplets is expected to lead to a higher % of fine particles. On the other hand, no significant difference in the VSD profiles was seen between the 63 and 25 µL valve prototypes with either actuator (Fig. 4). This result is also consistent with the cascade impactor results whereby the % fine particles was not affected by the valve metering chamber.

The droplet sizes for 10, 50, 90, and 99% of the particles in the emitted spray (designated as X 10, 50, 90, and 99, respectively) given in Table 4, also illustrate the smaller droplet size of the oral samples compared with the nasal samples. These results show

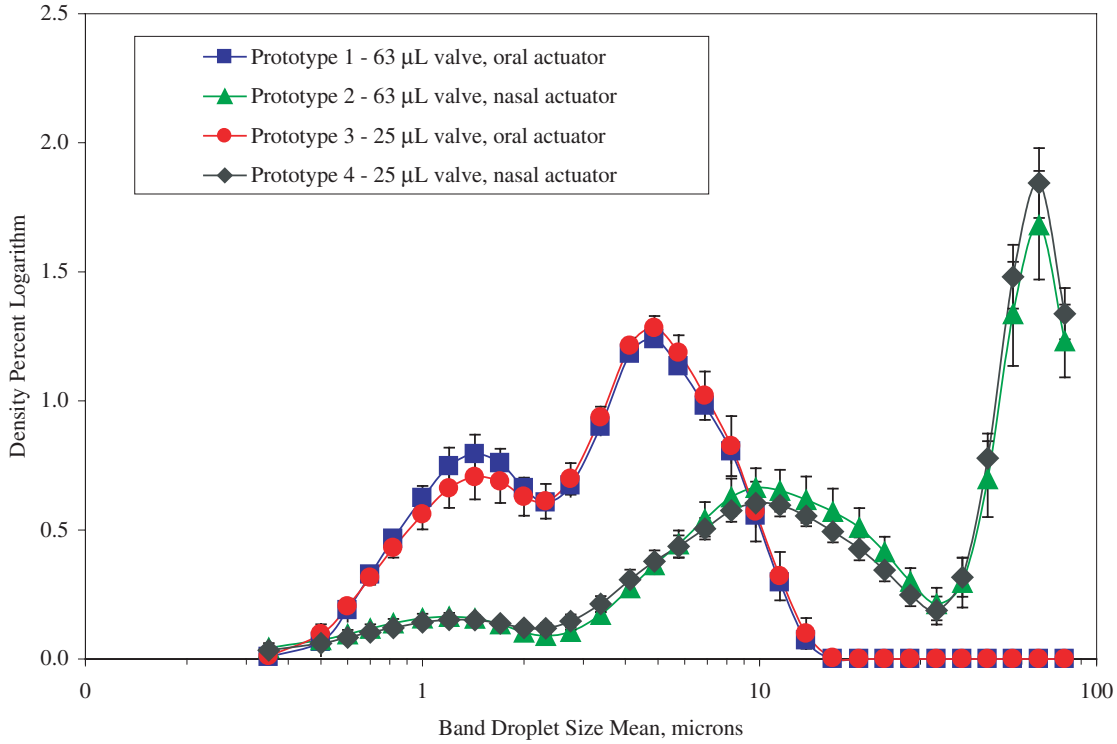

Figure 4. Sympatec VSD profiles for prototypes 1–4 at 10 cm spray distance (beginning of fill).

Table 4. Sympatec laser diffraction results at 10 cm spray distance[a,b].

Prototype #	Valve metering volume (μL)	Actuator design	Volume distribution (μm), mean ± SD			
			×10	×50	×90	×99
1	63	Oral	0.97 ± 0.04	3.49 ± 0.12	8.18 ± 0.22	12.1 ± 0.22
2	63	Nasal	2.38 ± 0.57	20.1 ± 4.5	72.8 ± 1.3	86.0 ± 0.2
3	25	Oral	0.90 ± 0.06	3.13 ± 0.09	7.84 ± 0.24	12.2 ± 0.2
4	25	Nasal	2.65 ± 0.48	22.5 ± 4.6	73.7 ± 0.8	86.1 ± 0.1

[a]Described in the experimental section, samples taken from beginning of fill.
[b]$N = 10$ (2 samples, 5 trials per sample).

that the droplet size of the nasal samples is approximately seven times larger than that of the oral samples (Table 4).

DISCUSSION

Impact of Actuator Design

It is apparent from this study that the dimensions of the actuator play a major role in determining the characteristics of the resultant MDI aerosol spray. The cascade impactor and Sympatec results show that the oral actuator (0.5 mm orifice diameter and 15×20 mm rectangular mouthpiece) produces a higher % of fine particles and smaller droplets than that of the nasal actuator (1 mm orifice diameter and 8 mm diameter nosetip). Thus, the design features of a small orifice combined with large mouthpiece or nosetip (Fig. 1) allow a higher % of the dose to exit the actuator and deliver a spray with a smaller aerodynamic particle size.

These results are consistent with earlier findings in which a small orifice diameter in the actuator led to the production of smaller drug particles in both suspension formulations[6,22] and solution formulations.[10,23,24] In addition, particle size reduction due to a decrease in the actuator orifice has been shown to lead to a higher concentration of respirable particles.[10,23–25] These findings are also in agreement with a study using laser diffraction in which a rank-order relationship between the actuator orifice diameter and the droplet size of the resulting spray was established.[26]

The significance of the actuator in these studies is not surprising in that the transformation of the formulation as a bulk liquid to small droplets occurs at the actuator orifice.[5,9] Furthermore, droplet size is controlled by the actuator diameter[5,9,17] whereby a small actuator orifice leads to the production of smaller droplets due to greater constriction at the nozzle. The evaporation of the resulting droplets will also occur more rapidly as droplet size is reduced due to more efficient convection from air molecules.[17]

In addition, in the case of suspension formulations, the reduction in the PSD seen with a decrease in orifice diameter has also been attributed to the deaggregation of suspended material.[27] It is thought that a smaller orifice will produce more flow constriction and, in this way, lead to greater shear of the drug formulation through the nozzle.[27]

The fact that the nasal actuator shows a higher entry port deposition than the oral actuator (Table 2) also appears to be related to the larger size of the actuator orifice. This effect can be explained by two different mechanisms. First, it has been found that a larger orifice results in an increase in the spray force[28] and this, in turn, could lead to a greater ballistic effect of the spray with a corresponding increase in entry port (or throat) deposition. Alternatively, the larger droplets produced by a larger actuator orifice might be expected to settle out of the spray and onto to the entry port faster than smaller droplets, also causing larger drug particles to settle in the entry port.

The dimensions of the mouthpiece or nosetip also affect the spray characteristics. The spray plume is thought to consist of larger, faster moving droplets surrounded by smaller, slower moving droplets that are dispersed in the periphery of the plume.[5] Thus, a reduction in the size of this opening (mouthpiece or nosetip) could cause a higher percentage of small droplets to adhere to the actuator. This, in turn, would result in a higher proportion of larger, higher velocity particles exiting the actuator, a greater percentage of the spray impacting the entry port and, a reduction in the dose that is collected on the impactor stages. In this

way, the narrow nosepiece of the nasal actuator may contribute to the higher percentage of large particles seen for the nasal samples.

Impact of Valve Metering Volume

Based on the results in this study, the metering volume does not appear to have as strong an impact on the spray characteristics as the actuator design. The cascade impactor results for the 25 and 63 μL valve prototypes show similar aerodynamic PSD profiles (Tables 1–3, Fig. 2) and, the droplet sizes as measured by Sympatec (VSD), are similar for the two different valve metering volumes (Table 4, Fig. 4).

However, it has been proposed that a smaller spray volume will have a higher fine particle fraction and, thereby, a higher respirable mass. This is based on the hypothesis that, as a result of more efficient evaporation and greater impact of drag forces, a lower spray volume will produce a greater number of small particles with lower velocity.[8,29,30] This effect may explain why the MMAD (Table 3) is slightly reduced for the 25 μL valve compared with the 63 μL valve using the oral actuator. Nevertheless, since the % fine particles (Table 3) and aerodynamic PSD and VSD profiles (Figs. 2 and 4) are relatively independent of the metering volume, it is assumed that the spray plume characteristics are similar for the valves used in this study.

Recent studies have also demonstrated a similarity of plume characteristics for different spray volumes. Using HFA-based formulations and a variety of particle sizing techniques including cascade impaction, time-of-flight, and laser diffraction, it was shown that PSD profiles were not influenced by the metering chamber volume.[31,32] In addition, it has been reported that for both CFC and HFA propellants, the spray force does not change as a function of the valve metering volume.[28] This further suggests that there are similarities in the properties of the spray produced with different volume sprays.

Device Sensitivity to Particle Size Changes

As described in the materials and methods section, a manufacturing process was selected such that the particle size of the suspended drug substance would increase from the initial, beginning samples, to the end samples which were filled after 48 h. As expected, all the MDI samples did show an increase in particle size over time. However, samples containing the oral actuator showed a much larger particle size difference between the beginning and end samples than prototypes containing the nasal actuator (Fig. 3). This effect can be explained based on the sensitivity of the cascade impactor to sprays emitted using oral vs. nasal actuators that are very different in design.

Aerosol spray droplets are separated by cascade impaction based on an apparent particle size (MMAD) in which the measured droplets can be composed of different solid to liquid ratios. In this way, droplets with similar MMAD values could contain solid particles of different sizes. It is noteworthy that the ratio of droplet size to drug particle size is significantly larger for sprays from the nasal actuator, e.g., the spray droplet size median (X50) of the nasal actuator samples is ≈20 μm (Table 4) whereas, for the solid, suspended drug, the particle size median is close to 1 μm. On the other hand, the spray droplet size median (X50) of the oral samples is ≈3 μm (Table 4) or about seven times smaller than that of the nasal samples. Thus, it is postulated that particle size changes in the suspended solid are more difficult to detect for the nasal prototypes, in which small particles are carried within very large droplets. It is for this reason that the difference in % fine particles and MMAD is smaller for the beginning vs. the end nasal samples. Conversely, for the oral prototypes, the contribution of the suspended solid can be expected to significantly contribute to the overall droplet size. In this case, cascade impaction testing, as reflected by the % fine particles and MMAD values, is more sensitive to changes in particle size of the suspended solid.

CONCLUSION

The actuator design (i.e., orifice diameter, mouthpiece geometry) plays a major role in determining the drug PSD of the product. In this study, the nasal actuator, as compared to the oral actuator, was shown to produce a larger droplet size (approximately 7×) and a correspondingly larger aerodynamic drug particle size. In addition, the samples fitted with nasal actuators had less total drug recovery and less sensitivity to particle size changes of the solid suspension. Hence, any change in the actuator design has the potential to lead to changes in both total drug recovery and in the particle size profile. Conversely, the valve metering volume did not appear to have a major effect on either the droplet size or the drug particle size profile.

ACKNOWLEDGMENTS

The authors would like to thank Slavka Libovicova-Tarzian, Angela Fahey, and Lukeysha Kline for their assistance in conducting the analytical testing.

REFERENCES

1. Dolovich, M. Characterization of medical aerosols: physical and clinical requirements for new inhalers. Aerosol Science and Technology **1995**, *22*, 392–399.
2. Elvecrog, J. Metered dose inhalers in a CFC-Free future. Pharmaceutical Technology Europe **1997**, *9* (1), 52–55.
3. Keller, M. Innovations and perpectives of metered dose inhalers in pulmonary drug delivery. International Journal of Pharmaceutics **1999**, *186*, 81–90.
4. Dunbar, C.A.; Watkins, A.P.; Miller, J.F. *Characterization of the pMDI Spray using Numerical Methods*. Proceedings of ICLASS **1997**, August 18–22, 876–883.
5. Dunbar, C.A. Atomization mechanisms of the pressurized metered dose inhaler. Particulate Science and Technology **1998**, *15* (3–4), 253–271.
6. Polli, G.P.; Grim, W.M.; Bacher, F.A.; Yunker, M.H. Influence of formulation on aerosol particle size. Journal of Pharmaceutical Sciences **1969**, *58* (4), 484–486.
7. Moren, F. Drug deposition of pressurized inhalation aerosols I. Influence of actuator tube design. International Journal of Pharmaceutics **1978**, *1*, 205–212.
8. Kim, C.S.; Trujillo, D.; Sackner, M.A. Size aspects of metered dose inhalers. American Review of Respiratory Disease **1985**, *132* (1), 137–142.
9. Clark, A.R. The physics of aerosol formation by MDIs—limitations of the current approach. Journal of Biopharmaceutical Sciences **1992**, *3* (1/2), 69–76.
10. Brambilla, G.; Ganderton, D.; Garzia, R.; Lewis, D.; Meakin, B.; Ventura, P. Modulation of aerosol clouds produced by pressurized inhalation aerosols. International Journal of Pharmaceutics **1999**, *186* (1), 53–61.
11. Dolovich, M.B.; Ruffin, R.E.; Roberts, R.; Newhouse, M.T. Optimal delivery of aerosols from metered dose inhalers. Chest 80 (suppl) **1981**, 911–915.
12. Meyer, K.C.; Auerbach, W.R. Drug delivery to the lung. In *Polymeric Site-Specific Pharmacotherapy*; Domb, A.J., Eds.; John Wiley and Sons: New York, 1994; 347–367.
13. Pritchard, J.N. The influence of lung deposition on clinical response. Journal of Medicine **2001**, *14* (1), S19–S26.
14. Leach, C.L.; Davidson, P.J.; Boudreau, R.J. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. European Respiratory Journal **1998**, *12*, 1346–1353.
15. Matthys, H. Chlorofluorocarbon-free aerosol therapy in patients with pulmonary airflow obstruction. Respiration **1996**, *63* (3), 321–324.
16. Milosovich, S. Particle size determination via cascade impaction. Pharmaceutical Technology **1992**, *16*, 82–86.
17. Johnsen, M.A. Properties of aerosol particles. Spray Technology and Marketing **1992**, *2* (8), 46–55.
18. United States Pharmacopeia 25, General Chapter 601 (2001), 1969–1980.
19. Ranucci, J. Dynamic plume-particle size analysis using laser diffraction. Pharmaceutical Technology **1992**, *16*, 108–114.
20. Witt, W.; Rothele, S. Laser diffraction–unlimited? Part. Syst. Charact. **1996**, *13* 280–286.
21. Le Brun, P.P.H.; de Boer, A.H.; Gjaltema, D.; Hagedoorn, P.; Heijerman, H.G.M.; Frijlink, H.W. Inhalation of tobramycin in cystic fibrosis. International Journal of Pharmaceutics **1999**, *189* (2), 205–214.
22. Steckel, H.; Muller, B.W. Metered-dose inhaler formulation of fluticasone-17-propionate micronized with supercritical carbon dioxide using the alternative propellant HFA-227. International Journal of Pharmaceutics **1998**, *173*, 25–33.
23. Warren, S.J.; Farr, S.J. Formulation of solution metered dose inhalers and comparison with aerosols emitted from conventional suspension systems. International Journal of Pharmaceutics **1995**, *124*, 195–203.
24. Evans, R.M.; Farr, S.J.; Armstrong, N.A.; Chatham, S.M. Formulation and in vitro evaluation of pressurized inhalation aerosols containing isotropic systems of lecithin and water. Pharmaceutical Research **1991**, *8* (5), 629–635.
25. Newman, S.; Pitcairn, G.; Steed, K.; Harrison, A.; Nagel, J. Deposition of fenoterol from pressurized metered dose inhalers containing hydrofluoroalkanes. Journal of Allergy and Clinical Immunology **1999**, *104* (6), S253–257.

26. Ranucci, J.A.; Cooper, D.; Sethachutkul, K. Effect of actuator design on metered dose inhaler plume particle size. Pharmaceutical Technology **1992**, *16*, 84–92.
27. Vervaet, C.; Byron, P.R. Drug-surfactant-propellant interactions in HFA-formulations. International Journal of Pharmaceutics **1999**, *186*, 13–30.
28. Gabrio, B.J.; Stein, S.W.; Velasquez, D.J. A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers. International Journal of Pharmaceutics **1999**, *186* (1), 3–12.
29. Moren, F. Drug deposition of pressurized inhalation aerosols II. Influence of vapour pressure and metered volume. International Journal of Pharmaceutics **1978**, *1*, 213–218.
30. Newman, S.P.; Moren, F.; Pavia, D.; Corrado, O.; Clarke, S.W. The effects of changes in metered volume and propellant vapour pressure on the deposition of pressurized inhalation aerosols. International Journal of Pharmaceutics **1982**, *11*, 337–344.
31. Williams, R.O., III; Liu, J.; Koleng, J.J. Influence of metering chamber volume and water level on the emitted dose of a suspension-based pMDI containing Propellant 134a. Pharmaceutical Research **1997**, *14* (4), 438–443.
32. Tiwari, D.; Goldman, D.; Malick, W.A.; Madan, P.L. Formulation and evaluation of albuterol metered dose inhalers containing tetrafluoroethane (P134a), a Non-CFC Propellant. Pharmaceutical Development and Technology **1998**, *3* (2), 163–174.