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Research Paper

Spray Pattern Analysis for Metered Dose Inhalers: Effect of Actuator Design

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Purpose. This study was conducted to identify the device factors influencing spray pattern and particle size to gain a more complete understanding of spray plume measurements.
Methods. A statistically designed experiment was used to investigate the influence of three actuator features (orifice diameter, expansion chamber depth, and orifice length) on spray pattern and particle size profiles. Custom-built actuators were manufactured and analyzed with laser light sheet illumination methods for spray patterns and laser diffraction for particle size analysis.
Results. In addition to orifice size, spray patterns were significantly influenced by the actuator orifice length and sump depth. Particle size analysis of the plumes generated from actuators used in these studies showed that all actuator features (orifice size, length, and sump depth) were significant factors influencing particle size.
Conclusions. The performance of propellant-based metered dose inhaler aerosols seems to be significantly related to sump depth and orifice length, in addition to orifice size. Rational design of propellant-based metered dose inhalers should therefore consider these variables in addition to formulation strategies and simply modifying orifice diameter.

KEY WORDS: aerosol plume; actuator; laser diffraction; pMDIs; spray pattern.

INTRODUCTION

Spray pattern and geometry analyses of propellant-based metered dose inhalers (pMDIs) have been performed for many years, but remains unproven as predictors of inhaler efficacy and quality. The relationship of spray pattern and efficacious delivery of drug to the lung is unsubstantiated. However, spray pattern measurements have been used as a quality control test to qualitatively evaluate the performance of actuators and drug products intended for administration via the respiratory route. Despite use for quality purposes, spray pattern measurements vary widely in method of quantification and degree of subjectivity. Efforts by regulatory agencies to ensure uniform test methods for pMDI and dry powder inhaler (DPI) products have resulted in the publication of a draft guidance document (1). It has been suggested that spray pattern analysis has a role in development, but is of limited value for routine drug product evaluation (2). This viewpoint is based on observations that spray pattern measurements vary significantly, and are insensitive to minor changes in formulation or components. Thus, there is some conjecture over the value of spray pattern measurements even as a quality control tool.

Nozzle design has been shown to have a significant impact on the characteristics of sprays (3). However, most studies focusing on atomization through different nozzle geometries have delivered low or nonvolatile liquid sprays. The operation and design of pMDIs are significantly different from other spray delivery systems as characterized by the following: (1) formulations containing high vapor pressure hydrofluoroalkane (HFA) propellants; (2) spray generation using small metered volumes of pressurized propellant; (3) small target particle size ranges, typically between 1 and 5 μm in diameter. Empirical data, cited in the literature, is of limited value for prediction and assessment of inhaler spray performance. In recent studies, spray patterns demonstrated dependence on the actuator spray orifice diameter (4). However, this dependence was not linear, and it was concluded that actuator orifice size is unlikely to be the single determinant of spray patterns (4).

The purpose of this study was to identify device factors influencing spray pattern and particle size to gain a more complete understanding of spray plume measurements. It was proposed that systematic evaluation of spray pattern measurements will yield information regarding the nature and characteristics of aerosol generation. A design of experiment (DOE) was planned where three actuator design features

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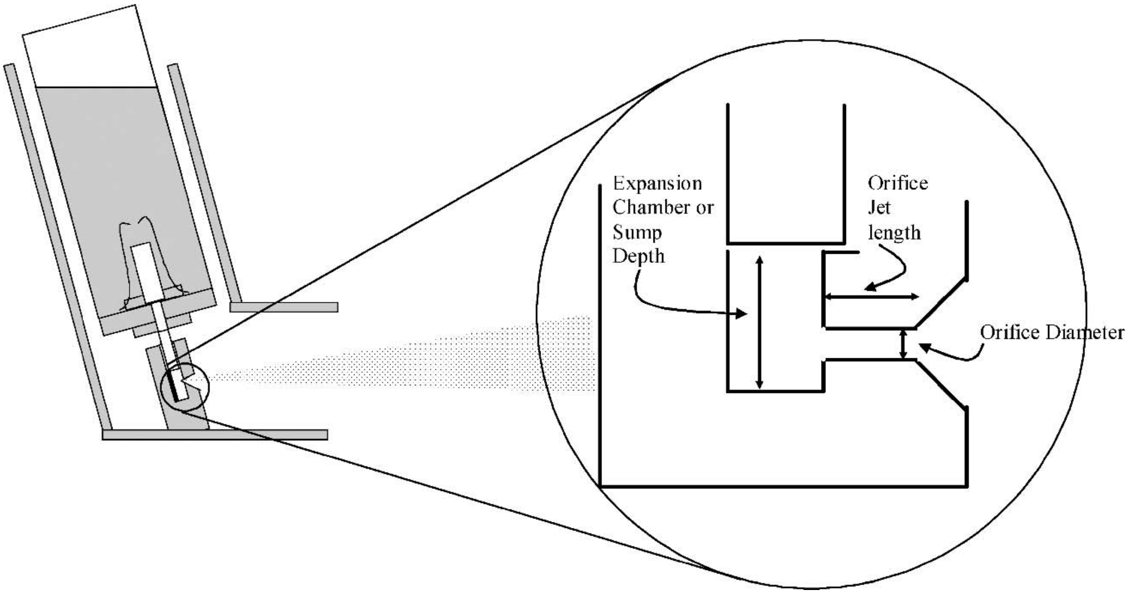

Fig. 1. Schematic of the basic design of the pMDI actuator orifice.

were selected for investigation: orifice diameter, sump depth, and orifice length. Spray pattern and particle size profiles were measures of the effects of device design features.

METHODS AND MATERIALS

Materials

A single batch of placebo solution pMDIs containing HFA 134a and ethanol were used in all studies (Flunisolide HFA; Forest Laboratories, New York, NY, USA). Canisters and valve components were identical for each pMDI system used (Forest Laboratories). Actuators were custom-manufactured to different specifications to span the ranges required for the experimental matrix. These parameters are outlined in Fig. 1.

Figure 1 illustrates the design features of the pMDI actuator that were modified. These three factors were varied at two levels in the investigations, yielding a matrix of eight different types of actuators. Each of these design factors was at values of typical geometries in marketed products. All other variables were held constant throughout the studies. The inhaler position, exit angles, and actuator materials (one-piece polypropylene) were all identical between measurements. The actuators were produced with high precision by injection molding manufacture methods. Internal geometries of the actuators were determined by using destructive and nondestructive methods and design parameters were observed to have tolerances of no more than ±5% of target values (Table I).

Spray Pattern Measurements

Spray pattern analysis was performed by using SprayView™ system (Image Therm Engineering, Sudbury, MA, USA). This instrument combines a laser light sheet with a high-speed digital camera to collect spray pattern images. Image software and spray pattern analysis algorithms were used to quantify several parameters of the pMDI spray pattern. Using this instrument, time averaging of collected images was performed to build a composite spray pattern. A total of nine responses were evaluated:

- Spray pattern major axis measurement and standard deviation
- Spray pattern minor axis measurement and standard deviation
- Spray pattern inclination angle and standard deviation
- Spray pattern elliptical ratio and standard deviation
- Inclusion ratio (goodness-of-fit measure)

Measurement details are fully described in an accompanying paper (4).

Particle Sizing

Particle sizing was performed by using a Malvern 2600c laser diffraction instrument with a custom-built trigger-timer

Table I. Individual Actuator Design Features. Three Factors at Two Levels (mm)

Actuator Identification #	Orifice Diameter (mm)	Orifice Length (Jet length) (mm)	Expansion Chamber Depth (Sump depth) (mm)
1	0.25	0.7	7.55
2	0.31	0.7	7.55
3	0.25	0.9	7.55
4	0.31	0.9	7.55
5	0.25	0.7	8.15
6	0.31	0.7	8.15
7	0.25	0.9	8.15
8	0.31	0.9	8.15

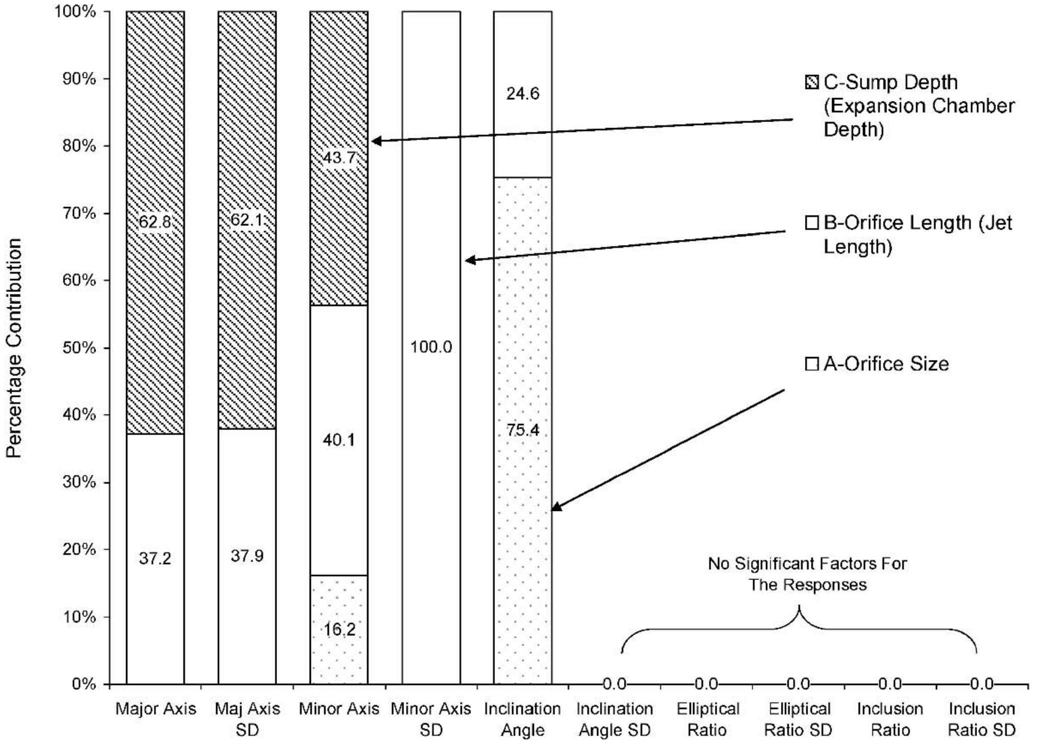

Fig. 2. Spray pattern measurement dependence on the actuator geometry features. The contribution of each device parameter on the spray pattern measures is shown as a statistically based percentage (percent of variance).

device. Each individual particle size measurement was a composite of three actuations. The laser diffraction patterns were converted to particle size distributions by volume, using the Fraunhofer theory as previously described (5).

Statistical Analysis

Experiment design was planned, randomized, and analyzed by using Design-Expert® software (Stat-Ease® Inc.,

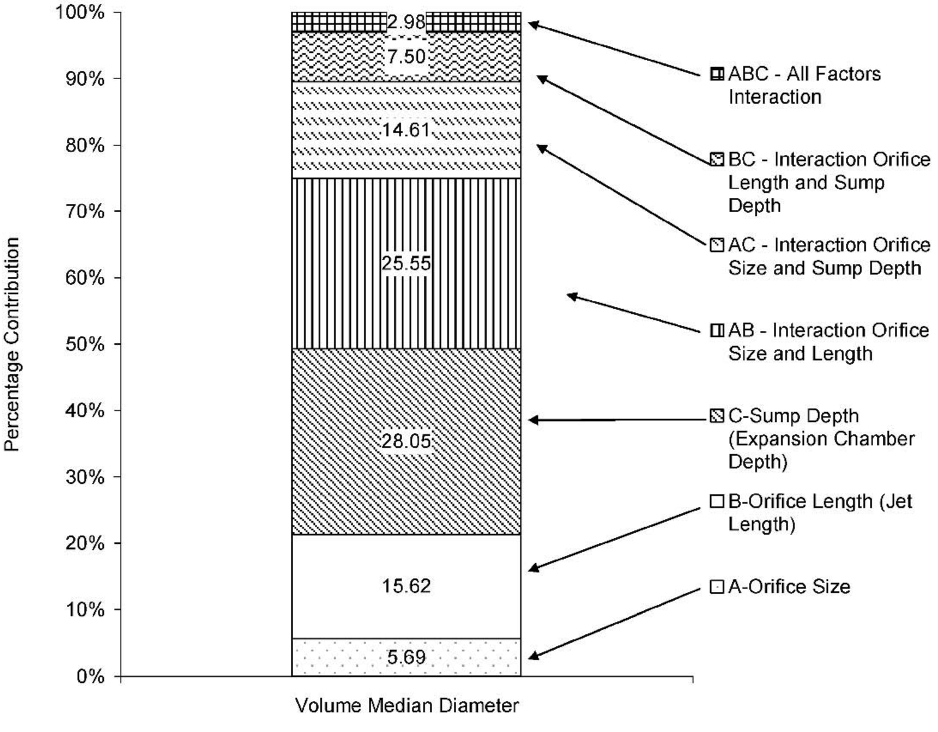

Fig. 3. Relative contributions of actuator design factors (and their associated interaction terms) to the particle size measured by laser diffraction particle sizing experiments.

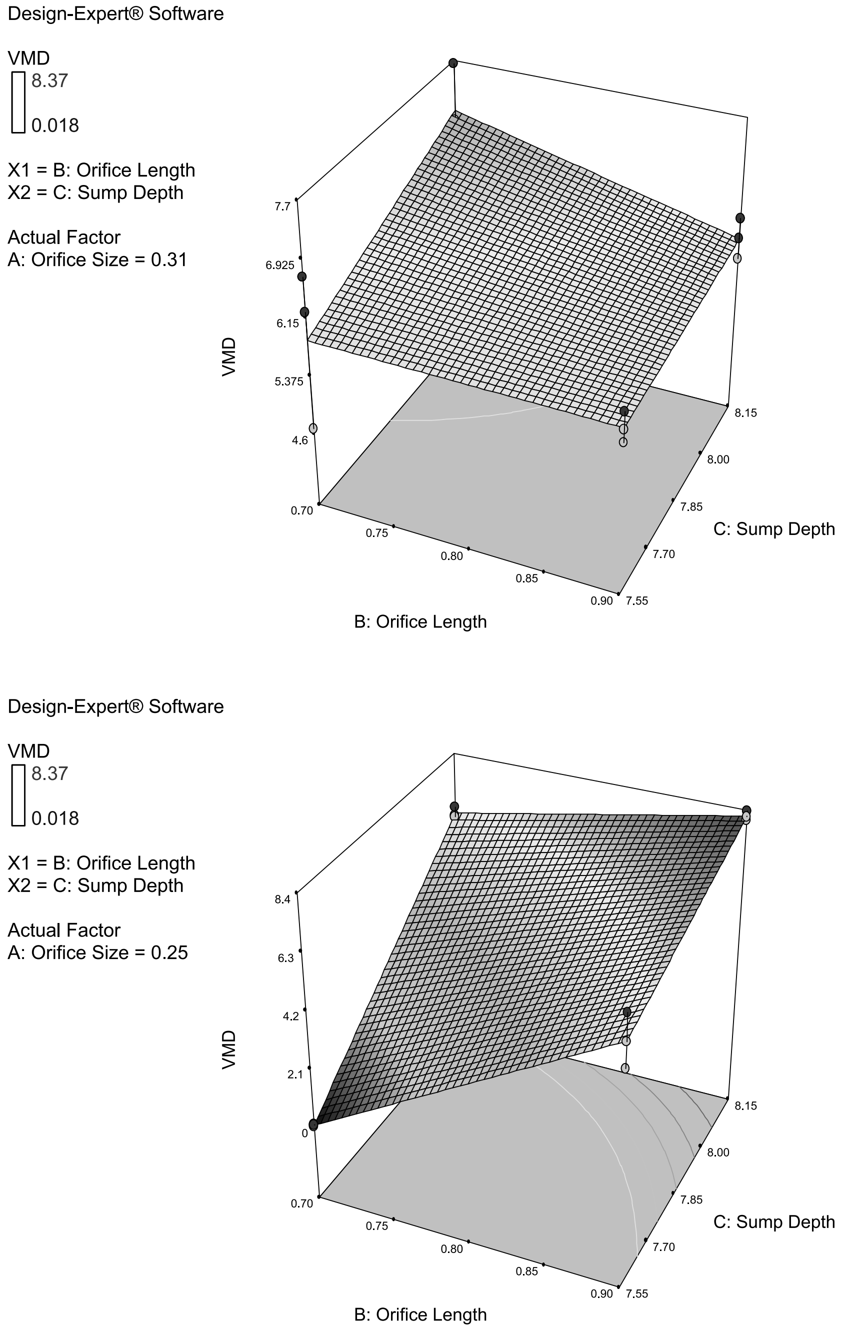

Fig. 4. The influence of orifice length and sump depth on the VMD when the orifice size was at 0.31 mm (upper graph) and at 0.25 mm (lower graph).

Minneapolis, MN, UAS). The factorial design was as follows: three factors, two levels, full factorial. Half-normal plots were analyzed for significant effects. No data transformations were required for statistical analysis. The sum of squares of the effects were used in the ANOVA analysis and the "percent contribution" of each effect was calculated.

RESULTS AND DISCUSSION

Spray Patterns

Figure 2 summarizes the statistical analysis of actuator geometry on main spray pattern measures. All three device parameters had significant effects on several spray pattern measurements. Notably, the orifice size had minimal influence on a number of standard quality measures: elliptical ratio, major length, and minor length of the spray pattern. These three measures are specifically noted in the FDA draft guidance document as key variables for spray pattern quantification (1). Spray pattern axis measurements were dependent on sump depth (contributions to: major axis = 63%; minor axis = 44%) and jet length (contributions to: major axis = 37%; minor axis = 40%) with little dependence on orifice diameter. Within the parameters of this study, device changes had no significant influence on elliptical ratios. Furthermore, the goodness of fit of the ellipse to the spray pattern image was also not influenced by device modifications. Significantly, statistical analysis demonstrated there were no interactions between the device factors for any of the pattern measurements. This may be important for prediction and control of spray pattern from knowledge of device design parameters.

Sump depth was the primary feature affecting the pattern shape (spray pattern major axis and minor axis were determined as 63 and 44%, respectively, by the sump depth). Orifice length was a secondary feature affecting the spray pattern shape (37 and 40% contributions to the major and minor axes, respectively). Within this model, the orifice diameter largely determined the inclination angle of the pattern (75% by orifice diameter and 25% by sump depth). This observation requires further evaluation as inclination angle may be relative to the distance from the actuator to the point of measurement of the spray pattern. The ellipticity ratio varied from 1.10 to approximately 1.20 with no apparent correlation to changes in the device features. Sump depth and jet length are features of actuators that are not typically measured or considered for pMDI performance, but clearly show significant influence on spray pattern formation in these studies.

From these analyses, it seems that major and minor axis lengths are more sensitive measures of actuator nozzle geometry than the elliptical ratio. The elliptical ratio is likely to have decreased sensitivity to device changes because it is the ratio of major length and minor length, and these individual measures were influenced by the same device parameters.

Particle Size

These studies represent the first detailed analyses of the effects of actuator nozzle design on particle size characteristics of the spray emitted from a pMDI. Previously published reports have focused only on orifice diameter as a primary device factor that can be used to modify the performance of typical pMDIs (6–14). However, in addition to spray plume characteristics, particle size can also be significantly influenced by actuator characteristics other than orifice diameter (Fig. 3). Unlike in the spray pattern analyses, particle size changes detected by laser diffraction were sensitive to all device changes. Contributions to changes in particle size were significantly altered by changing sump depth and orifice length, in addition to orifice diameter. These results demonstrate the complexity of interactions within the actuator design that have significant effects on particle size. To our knowledge, this has not been previously reported.

Volume median diameter is a statistical measure of the average droplet size in a spray plume, such that 50% of the volume of sprayed material is composed of droplets smaller in diameter than the volume median diameter (VMD). VMD was minimized by decreasing the following factors:

1. Orifice size
2. Orifice length
3. Sump depth

However, these device factors did not contribute independently to particle size distributions, and there were significant interactions between them:

4. Decreasing orifice size decreased the VMD only when the orifice length was decreased

5. Similarly, decreasing orifice size only decreased the VMD when the sump depth was decreased

6. In addition, changing the orifice length did not have any significant effect when the sump depth was at its maximum value

These effects were identified as statistically significant ($p < 0.05$) and the direction of the effect was quantified.

The influence of actuator nozzle changes on particle size are summarized in the two graphs presented in Fig. 4. In the system used in these studies, VMD could be modulated from 8.1 to 0.2 μm depending on the combination of orifice size, orifice length, and sump depth. Formulation and orifice size changes have historically been the most useful parameters for controlling particle size output from pMDIs (e.g., in equivalence studies between chlorofluorocarbon-based and HFA-based products, or between innovator pMDIs and generic pMDIs) (10,15). From previous observations it seems that particle size modulation using actuator design may be greater than previously thought (10), and may be achieved by considering orifice length and sump depth. Given the complexity of the interacting factors, design of experiments yielding surface response curves may be the most efficient method of determining the actuator design parameters for the desire particle size. The span of the particle size distributions was not evaluated in the statistical design but ranged from narrow distributions (span = 1.3) to broad distributions (span = 20).

The influence of design parameters on droplet formation and particle size is relatively unknown. Some aspects associated with the atomization of metered volumes of superheated liquid propellants have been investigated (16–23). The discharge from the actuator orifice has been shown to be choked and mass-limited (17). As the propellant begins to exit the atomization orifice incipient cavitation occurs, and liquid propellant is dispersed with rapidly growing bubbles (23). It can also be shown that this bubble growth occurs in turbulent flow regimes (16,22). Dunbar *et al.* developed the model illustrated in Fig. 5 for discharge from a pMDI actuator. From this analysis, the creation of an eddy behind the orifice is a response to the presence of the actuator sump. In addition, bubble growth from this region is proposed to extend into the orifice periodically, as measured by using phase-Doppler spray analysis, and therefore suggests that both orifice length and sump are important factors in spray formation.

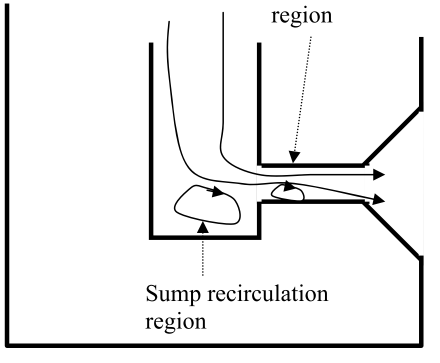

Fig. 5. Schematic diagram of the proposed fluid dynamics within the actuator orifice during the generation of an aerosol.

CONCLUSIONS

The purpose of this study was to identify which device features influence spray pattern measurements. It was proposed that spray pattern measurements can yield information regarding the nature of aerosol generation from pMDIs. Statistical experimental design showed that, in addition to orifice size, spray patterns are significantly influenced by the actuator orifice length and sump depth. Particle size analyses of the plumes generated from custom test actuators showed that a multitude of actuator geometry features (orifice size, orifice length, and sump depth) also significantly influenced particle size.

Because spray pattern measurements are sensitive to changes in the actuator design, they may be useful in product testing. However, the elliptical ratio, a quantity suggested to be of importance in the FDA guidance document, was shown to be insensitive to changes induced in actuator geometry. The major axis, minor axis, and the angle of rotation were more appropriate and sensitive measures of spray patterns. The linking of spray patterns to efficacy measures or upper airway deposition has not yet been demonstrated in the literature, but would provide additional motivation for performing routine analysis of pMDI actuators by using pattern measurements. Moreover, it seems that particle size analysis may be more sensitive to actuator design changes. Lung deposition has well-established relationships with particle size and therefore, with our current understanding, the latter seems to be a preferred analytical method.

In terms of design of actuators, important observations were made with regard to the importance of previously unstudied actuator design parameters. The performance of pMDI aerosols seems to be significantly related to sump depth and orifice length in addition to orifice size. Rational design of pMDIs should therefore consider these variables in addition to formulation strategies and simply modifying orifice diameter.

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