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# Spray Pattern Analysis for Metered Dose Inhalers I: Orifice Size, Particle Size, and Droplet Motion Correlations

**H. Smyth and A. J. Hickey**
School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina

**G. Brace**
Straightforward Solutions, LLC, Raleigh, North Carolina

**T. Barbour**
Bespak Inc., Apex, North Carolina

**J. Gallion**
Polyzen, Inc. Apex, North Carolina

**J. Grove**
AXON Corporation, Raleigh, North Carolina

**ABSTRACT** Factors that influence spray pattern measurements of pressurized, metered-dose inhalers have been evaluated. Spray patterns were correlated with changes in actuator orifice diameter, particle size profiles, and calculated estimates of particle-size dynamics of plumes during a spray. Spray patterns, regardless of actuator orifice size, were ellipsoid in the vertical direction. Measures of elliptical ratio, major axis, and minor axis were significantly influenced by orifice size in a non-linear fashion over the range of orifice sizes investigated. Spray patterns also correlated with particle size profile and spray geometry measurements. Spray distribution asymmetry may be related to droplet evaporation and sedimentation processes. However, the spray patterns did not appear sensitive to changes in gravitational force acting on the plume. Instead, it is postulated that elliptical spray patterns may have dependence on fluid dynamic processes within the inhaler actuator. Developing an understanding of these processes may provide a basis for developing spray pattern tests with relevance to product performance.

**KEYWORDS** Aerosol, actuator, laser diffraction, pMDI, respiratory drug delivery

## INTRODUCTION

Various test methods have been developed to evaluate the quality of aerosol products. These include dose delivery tests, vapor pressure, particle size analysis, dose content uniformity, moisture uptake, impurities and degradation, spray geometry, and spray pattern determinations (FDA, 1998). Spray pattern measurement has historically been used as a quality control test to qualitatively evaluate the performance of actuators and drug products intended for administration via the respiratory route. Several methods have been utilized for aerosol plume pattern and geometry evaluation. These include dye spray tests, thin layer chromatography, high speed flash photography, high speed video, and digital imaging (Benjamin et al., 1983; Lee et al., 1991; Keller et al., 1995; Cummings et al., 1998; ITFG/IPAC-RS Collaboration, 2001; Smyth et al., 2002). As a consequence, spray pattern tests have

Address correspondence to H. Smyth, College of Pharmacy, University of New Mexico, Albuquerque, NM 87108. E-mail: hsmyth@unm.edu

been developed that vary widely in methods of pattern quantification and levels of objectivity.

To ensure more uniform test methods for propellant-driven, metered-dose inhalers (pMDI) and dry-powder inhaler products, the U.S. Food and Drug Administration (FDA) published a draft guidance document in which spray pattern measurement is outlined for routine product analysis (FDA, 1998). The recommended test should include measures of the shape and size of the spray pattern. Several groups have suggested that spray pattern analysis has a role in development but is of limited value for routine drug product evaluation (ITFG/IPAC-RS Collaboration, 2001). This point of view 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 as a quality control tool.

A fundamental interpretation of the factors influencing spray plume properties has not yet been described in the literature. In addition, there is a remarkable absence of in vitro, or in vivo, studies linking spray pattern characteristics with inhaler performance. Under low evaporative conditions, spray patterns are a function of several performance factors, such as dispersion, penetration, cone angle, and radial distribution (Lefebvre, 1989). These factors are influenced by both the physicochemical properties of the liquid and atomizing conditions (e.g., nozzle design, pressures, flow conditions) (Lefebvre, 1989). From this phenomenological understanding, it is proposed, spray patterns can be used to obtain performance and quality information for pressurized metered dose inhalers (pMDIs).

The objective of these studies was to identify features of spray pattern analyses that correlate with changes in device parameters (orifice size) or with a known predictor of inhaler performance (particle size). These studies were complemented by theoretical approximations of droplet evaporation and motion due to gravity. Identification of spray pattern correlations with established pMDI features and performance variables may provide a basis for developing spray pattern tests with greater relevance to product performance.

## METHODS AND MATERIALS

### Materials

A single batch of placebo solution pMDIs containing HFA 134a and ethanol (Flunisolide HFA, Forest Laboratories, New York, NY) were used in all studies. Canisters and valve components (Flunisolide HFA, Forest Laboratories, New York, NY) were identical for each pMDI system used. Actuators were custom manufactured to different orifice size specifications using various sized orifice pins during the injection molding process. The orifice sizes of the manufactured actuators were determined using photomicrography.

### Actuator Characteristics

Eight different actuators with orifice sizes between approximately 0.25–0.30 mm were produced using injection molding. Photomicrographic inspection of the orifice of each actuator was performed, and it was confirmed that orifices were uniformly cylindrical.

### Spray Pattern Measurements

Spray pattern measurements were performed using the SprayView™ system (Image Therm Engineering, Inc, Sudbury, MA). 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. Spray patterns were quantified using standard parameters outlined in the FDA guidance document and those automatically provided by the imaging software and are indicated in Fig. 1 (elliptical ratio, major length, minor length, ellipse rotation, and inclusion ratio). The elliptical ratio is defined as the major length divided by the minor

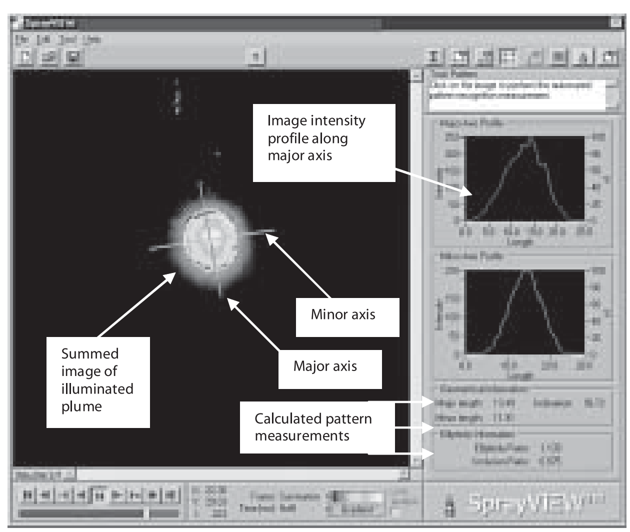


**FIGURE 1** Illustration of the Image Analysis Software Used to Calculate the Spray Pattern and Spray Geometry.

length. The major length is the longest length of the ellipse, while the minor length is the length that is drawn perpendicular to the major length. The inclusion ratio is defined as the total area of the pattern divided by the total area of the fitted ellipse. The ellipse rotation is calculated as the angle of rotation of the major length relative to a horizontal line. Time averaging of collected images was performed to build a composite spray pattern. The same image analysis parameters were employed for all measurements. The image noise threshold was adjusted to 50%. Summation was performed using the "manual" mode (excessive averaging of low concentrations of spray occurred at the end of an actuation during automatic mode). Summation was performed on images from the first frame where spray was detected to a predetermined point where intensity did not adversely influence the resolution of the averaged images (summation ended at half of the total number of frames collected for each spray). Thus, the number of frames used to determine the spray pattern was a function of the total number of frames collected. Spray pattern measurements were made at a predetermined distance from the actuator orifice (23.9 mm). In parallel studies the effect of spray direction (i.e., gravity) on the pattern was investigated by rotating the SprayView™ instrument such that plumes were directed downward (in the direction of gravity). Except where noted, the actuator was positioned horizontally for all spray pattern determinations. One-way ANOVA was performed on the data obtained from these studies, and differences were identified using post hoc least significant difference (Tukey) statistical analysis.

## Spray Geometry

Spray geometry measurements were performed using the SprayView™ system. The procedure was similar to that of obtaining spray patterns except that it was performed at a right angle to the orifice. Summation procedures and software settings were identical to those used for spray pattern measurements. Geometries were obtained from different vertical slices to evaluate the patterns of spray distribution at different widths within the plume.

## Particle Sizing

Particle sizing was performed by laser diffraction (Model 2600c, Malvern Instruments, Worcs., UK). The pMDI actuator was positioned at a constant distance from the detector lens (2.5 cm), at one of two distances from the laser beam (7 or 9 cm), and could be moved along the vertical axis to allow particle sizing of different heights of the spray plume. Droplet size distributions and volume diameters were collected using Malvern software.

## Sedimentation and Evaporation Estimates

Estimates of particle settling velocity and evaporation were performed for qualitative comparison with experimental observations. Settling velocities at high Reynolds numbers were calculated using an iterative method described by Baron and Willeke using the following equation (Baron & Willeke, 2001):

$$V_{TS} = \frac{\rho_p d^2 g}{18\eta} \tag{1}$$

where $V$ is the terminal settling velocity, $\rho$ represents the density of the particle, $d$ is the particle diameter, $g$ is the acceleration due to gravity, and $\eta$ is the viscosity of the air. Evaporation rates of pure HFA 134a droplets were estimated using a simplified model described by Finlay (2001). The evaporation rate was calculated using the following relationship:

$$\frac{d(d_p)}{dt} = \frac{4D_v M}{R\rho_p d_p}\left(\frac{p_\infty}{T_\infty} - \frac{p_d}{T_d}\right)\phi \tag{2}$$

where $\Phi$ is the Fuchs correction factor and is required for $d_p < 1$ μm, $D_v$ is the diffusion coefficient of the vapor, $M$ is the molecular weight of the liquid, $R$ is the gas constant, $\rho_p$ is the density of the liquid, $p_\infty$ and $T_\infty$ are the partial pressure and temperature away from the droplet surface, and $p_d$ and $T_d$ are the partial pressure and temperature at the droplet surface. The combined effects were plotted and compared to experimental observations. These approximations do not completely resemble the conditions present during experiments (e.g., droplets are composed of HFA 134a and ethanol) and are used for qualitative comparisons to observed plume behavior.

# RESULTS

## Spray Patterns

A summary of the spray pattern data obtained from each actuator is summarized in Table 1. A brief description of the method of calculation of spray pattern data is summarized by Figure 1. All spray patterns obtained were elliptical. Elliptical ratios, the ratio of the major length to the minor length of the fitted ellipse, ranged from 1.1 to 1.4.

The rotation of the ellipse obtained from the spray patterns was approximately 90 degrees. This degree of rotation was well-conserved with all actuators, including actuators with different orifice sizes ($p > 0.05$). Fig. 2 illustrates the rotation angle and the variability (standard deviation) from the mean. Reasons for the formation of oval/elliptical spray patterns have not been addressed in the pharmaceutical literature. Subsequent investigations described below probed some aspects of this phenomenon.

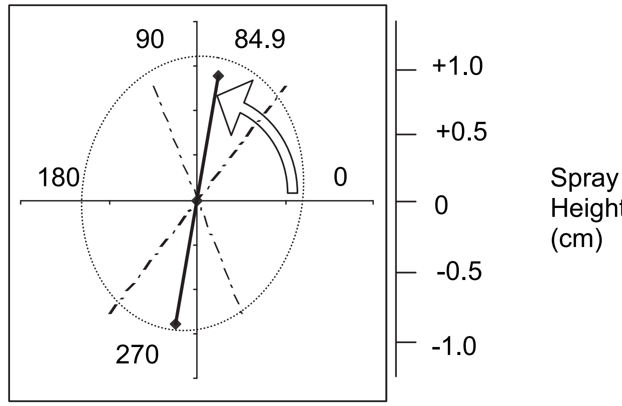


**FIGURE 2** **Spray Pattern Ellipse Rotation. (The average rotation of spray pattern ellipse is indicated by the solid line (84.9 degrees), the dashed lines indicate the standard deviation (16.9 degrees), and the dotted outline indicates the average ellipse.) (Data from eight actuators, *n* = 3 for each actuator; numbers are in degrees.).**

## Spray Pattern and Atomizing Orifice Size

The major measures of spray pattern (elliptical ratio, minor length, and major length) were plotted against the orifice size and are shown in Figs. 3–5, respectively. Differences in spray patterns were distinguishable between the eight actuators with different orifice sizes. Statistical analyses confirmed that differences were significant between the elliptical ratios and major and minor lengths generated by actuators with

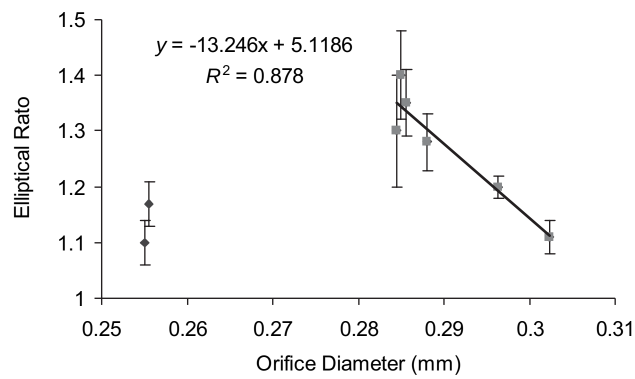


**FIGURE 3** **Plot of the Elliptical Ratio of the Fitted Ellipse Versus the Orifice Size of the Actuator.**

**TABLE 1** **Summary of Basic Spray Pattern Data Obtained Using Eight Different Actuators (from eight injection molding cavities with varying orifice sizes) (*n* = 4)**

| Orifice Diameter (mm) | Actuator ID | Eliptical Ratio | Standard deviation | Minor Length (mm) | Standard deviation | Major Length (mm) | Standard deviation |
|---|---|---|---|---|---|---|---|
| 0.255 | 6 | 1.1 | 0.04 | 14.1 | 0.32 | 15.55 | 0.36 |
| 0.2556 | 2 | 1.17 | 0.04 | 13.01 | 0.35 | 15.14 | 0.33 |
| 0.2844 | 5 | 1.3 | 0.1 | 13.32 | 0.42 | 17.34 | 1.32 |
| 0.285 | 1 | 1.4 | 0.08 | 12.83 | 0.13 | 18.02 | 1.12 |
| 0.2856 | 8 | 1.35 | 0.06 | 13.29 | 0.56 | 17.91 | 0.86 |
| 0.288 | 7 | 1.28 | 0.05 | 13.07 | 0.4 | 16.66 | 0.29 |
| 0.2964 | 3 | 1.2 | 0.02 | 12.32 | 0.34 | 14.83 | 0.28 |
| 0.3024 | 4 | 1.11 | 0.03 | 12.68 | 0.22 | 14.1 | 0.38 |

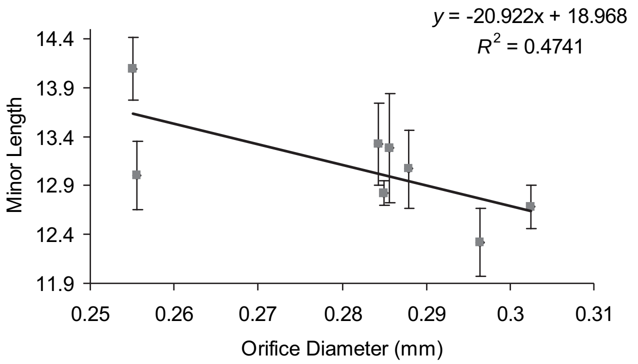


**FIGURE 4** **Plot of Minor Length of the Fitted Ellipse Versus the Orifice Size of the Actuator.**

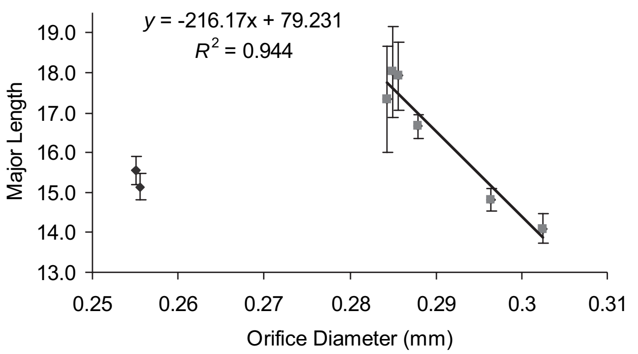


**FIGURE 5** **Plot of Major Length of the Fitted Ellipse Versus the Orifice Size of the Actuator.**

different orifice sizes ($p < 0.05$). Within certain ranges of orifice size (0.28–0.31 mm orifice size), a linear relationship with respect to spray pattern measurements (elliptical ratio, major or minor length) was fitted (regression line shown in figures). However, at smaller orifice sizes (orifice sizes < 0.28 mm), spray pattern measurements did not follow this relationship. The correlation of orifice size with major length was stronger than that with minor length (correlation coefficients 0.94 and 0.47, respectively). These linear correlations were facilitated due to the number of different orifice sizes we used in these investigations, giving a sufficient number of points in which least squares regression could be performed with confidence. As noted above, spray pattern rotation was not influenced by orifice size changes, and spray patterns were consistently rotated ~90 degrees vertically in all the test actuators ($p > 0.05$).

The correlation of orifice size to spray pattern measures indicates that the latter may be employed as a marker for performance. However, the utility for quality control is limited by the observation that the inverse linear relationship does not hold over the entire range of orifice sizes tested. A detailed investigation of actuator design feature effect on spray pattern is currently under investigation in our laboratories.

## Spray Pattern Correlation with Particle Size

The elliptical nature of the plume pattern was investigated using laser-diffraction particle sizing. Various regions of the spray plume were sampled so that droplet size profiles, as a function of height of the plume, could be constructed. This particle size analysis of pMDI plumes has not been reported previously using laser diffraction. The obscuration values (proportional to spray density in the laser sensing region) are shown in Fig. 6. The obscuration profiles across the plume match spray pattern measurements and demonstrate that droplet concentrations were highest at the center of the plume.

Particle size profiles are shown in Figs. 7 and 8 for two distances (7cm and 9 cm). At the 7-cm distance from the

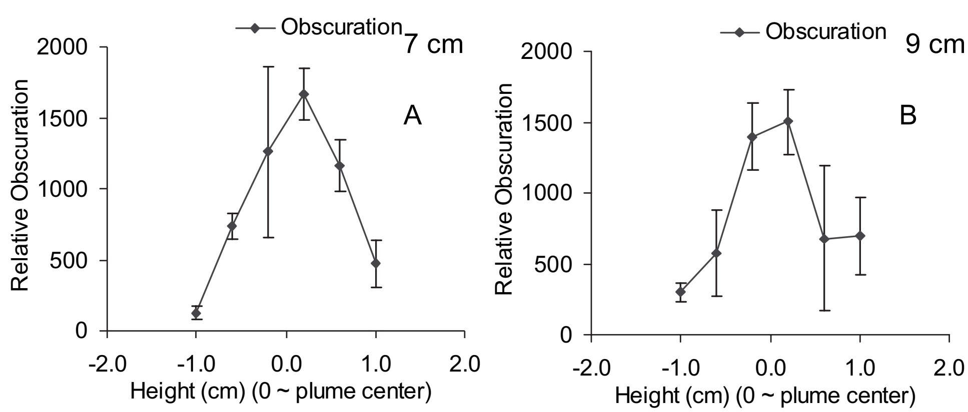


**FIGURE 6** **The Laser Obscuration Values Determined at 7 cm (left) and 9 cm (right) From the Orifice (*n* = 4, mean +/– standard deviation). (Spray height values correspond to vertical distances above and below the orifice location (height = 0) as illustrated in Fig. 2.).**

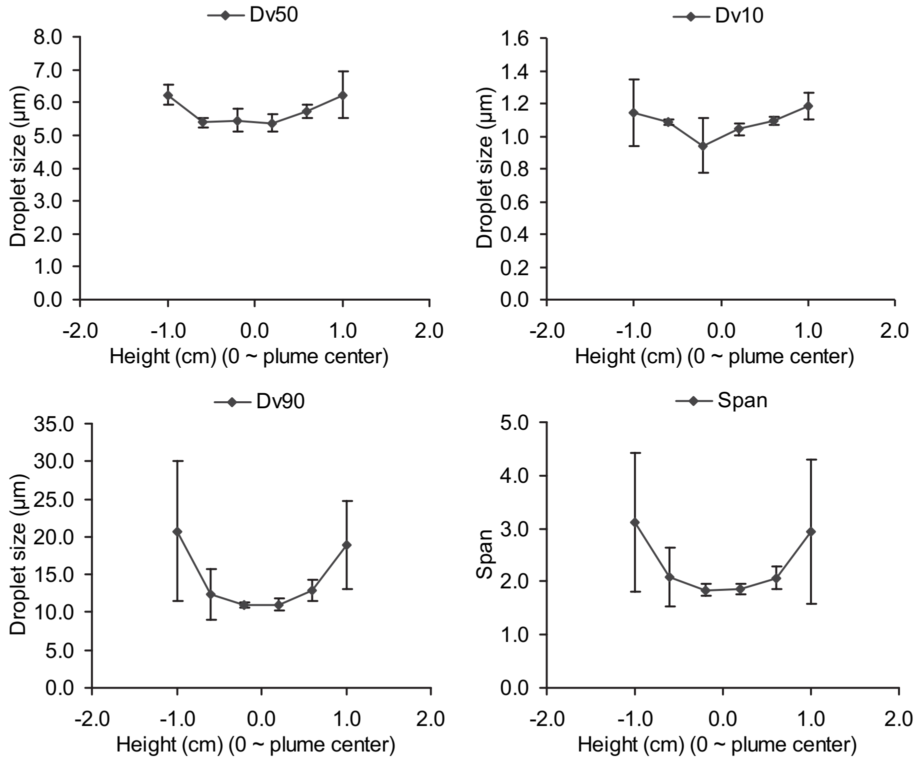


**FIGURE 7** **Vertical Particle Size Profile of Plume 7 cm From Orifice: (a) Volume Median Diameter, (b) 10th Percentile Volume Diameter, (c) 90th Percentile Volume Diameter, and (d) Span of Particle Sizes.**

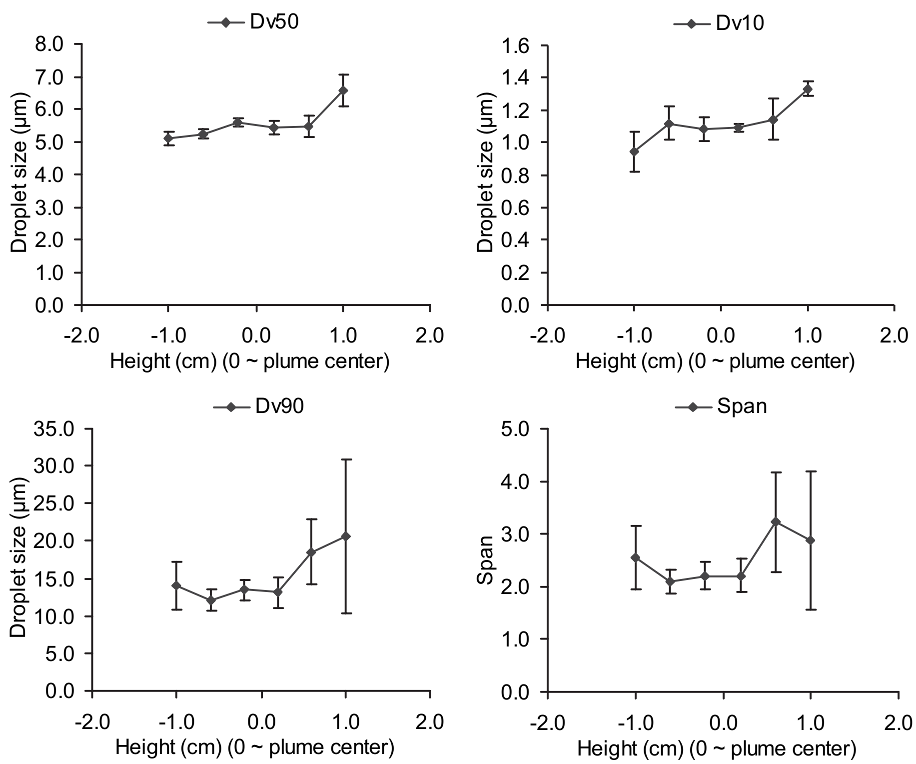


**FIGURE 8** **Vertical Particle Size Profile of Plume 9 cm From Orifice: (a) Volume Median Diameter, (b) 10th Percentile Volume Diameter, (c) 90th Percentile Volume Diameter, and (d) Span of Particle Sizes.**

orifice (Fig. 7), the particle size profiles for the plume were characteristically u-shaped and symmetrical. Particle size profiles showed that the DV10, DV50, and the DV90 all increased toward the edges of the plume and may be explained by the Kelvin effect, where preferential evaporation of smaller droplets at the edges occurs (Hinds, 1999). Particle size estimates became more variable (as indicated by standard deviation bars) at points farther from the center of the plume. This increased variability at the edge is due to decreased droplet concentrations that result in decreased accuracy of the particle size calculations (Fraunhofer calculations).

At 9 cm from the orifice, particle size profiles were asymmetric about the actuator orifice, and larger particle sizes were observed at lower portions in the plume (Fig. 8). The presence of larger droplets at lower parts of the plume has several implications and possible causes. This observation appears compatible with the spray pattern rotation measurements described in Fig. 2 above, where elongation is in the vertical direction. This also suggests that gravitational effects and sedimentation may be the basis of both of these observations. Thus, the hypothesis that gravitational forces and particle sedimentation cause demonstrable effects on spray patterns was further investigated.

## Spray Geometry Measurements

Spray geometry measurements were used as a complementary method in determining the general characteristics that result in asymmetrical and vertically oriented ellipsoid spray patterns. The analysis of spray geometry images showed asymmetrical image intensities along the vertical axis of the spray plume (Fig. 9). The image intensities were greater in the lower half of the spray image than in the top half. It is apparent that spray geometry measurements are more sensitive than spray pattern measurements in the detection of plume directional changes.

## Theoretical Estimates of Evaporation and Sedimentation and Effects of Gravity on Spray Analysis

Droplet evaporation in the aerosol plume downstream of the nozzle involves the coupling of droplet

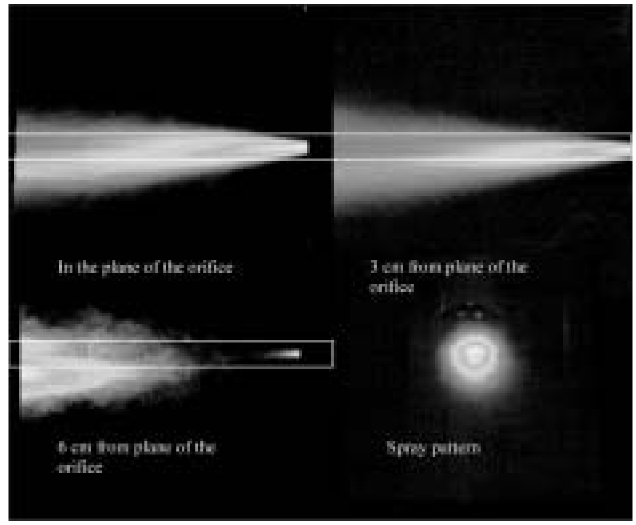


**FIGURE 9** **Example of Spray Geometry Measurement. (Measurements were performed at different distances from the plane of orifice (centerline of the plume).**

evaporation with the surrounding vapor, and vice versa (Hinds, 1999; Finlay, 2001). Finlay suggests that this coupling is largely a result of the sensitivity of droplet evaporation on the continuous phase temperature because droplet evaporation is relatively insensitive to the mass fraction of propellant in the air (Finlay, 2001). Consequently, the cooling of the air surrounding the droplets (caused by evaporation) rather than the presence of propellant vapor decreases evaporation rates. In the following analyses we have used droplet size ranges that correspond to the initial particle sizes produced at the actuator orifice (Dunbar et al., 1997; Dunbar, 1998). The upper limit appears high compared to the particle size data above, but it must be recognized that these experimentally determined values are from regions downstream of the orifice. Thus, significant droplet evaporation may have occurred prior to measurement via laser diffraction. The spray concentrations close to the orifice preclude particle sizing at this region. The time scales of these theoretical estimates are relevant to plume generation and actuation times (100–200 msec per actuation). Settling velocities were calculated, and estimates were combined with evaporation rates to yield Fig. 10. The modeling assumed the droplets were entirely composed of HFA 134a and were in a dry environment. Thus, this estimate is likely to underestimate droplet evaporation rates. Evaporation will depend on the location of the droplet in the plume, i.e., whether or not it is in a saturated vapor or cooled environment

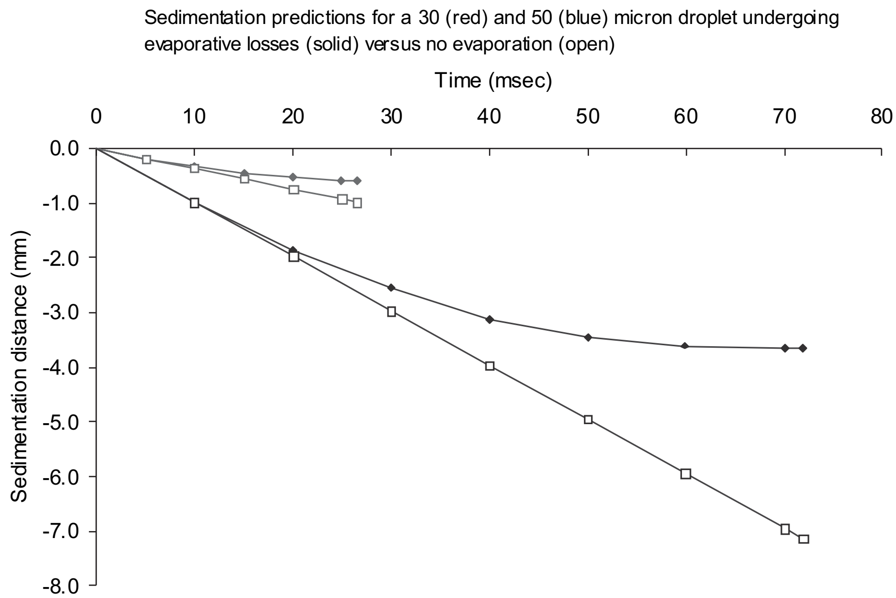


**FIGURE 10** **Sedimentation and Evaporation Processes Simultaneously Estimated for HFA 134a Droplets as a Function of Time.**

(middle of the plume) or if no decrease in evaporation rate occurred due to the rapid removal of vapor from the surface of the droplet. In Fig. 10 the curved line represents a combination of the evaporative and sedimentation processes. The straight line represents sedimentation without evaporation. The actual sedimentation values are located somewhere between these two lines because the droplets are evaporating into an environment that has some degree of cooling and significant concentrations of propellant vapor.

The effect of gravity on the nature of spray measurements was examined by analyzing plume geometry and spray pattern when sprayed perpendicular and parallel to the direction of gravity. Comparison of normal and downward sprays showed that no differences existed between spray patterns or geometries. There were no statistical differences between elliptical ratios (pattern measurements) or intensity profiles (geometry measurements) ($p > 0.05$). The theoretical estimates of droplet sedimentation distances in the presence of evaporation also corresponded to the asymmetrical spray patterns. These calculations estimated that larger droplets (10–50 μm) may sediment significantly with respect to the resolution of the spray pattern images (e.g., Fig. 9). However, the hypothesis that gravitational effects significantly influence spray pattern formation appears less likely based on directional spray analyses where no differences were detected ($p > 0.05$). Regardless of spray direction (perpendicular or parallel to gravity), spray pattern asymmetry remained constant. Thus, the effect of gravity on spray pattern appears minimal. In addition, visual inspection demonstrated that orifice shapes were uniformly cylindrical. Therefore, it is proposed that the mechanism resulting in asymmetrical and elliptical-shaped spray patterns are primarily related to nozzle geometry and the fluid dynamics within the actuator.

Correlations between larger particle sizes at lower portions of the plume (at 9-cm distances from the orifice) may still be a reflection of particle motion under the influence of gravity. However, spray pattern analyses were not sufficiently sensitive to detect these potential subtleties of droplet motion and regional changes in particle size distributions.

The utility of spray pattern analyses using the current methodologies may be a marker for actuator performance (fluid dynamic sensitivity, nozzle quality) rather than a measure of the aerosol plume quality at the level of particle size.

## CONCLUSIONS

Routine spray pattern analyses using a laser light-sheet method coupled with image analysis software revealed several interesting features. Ellipsoid and asymmetrical patterns were observed in the vertical direction. Pattern measurements were significantly influenced by orifice size. This relationship was not linear over the entire range of orifice diameters investigated. Asymmetrical spray patterns were consistent with regional differences detected using particle size analyses. Particle size measurements are typically performed without regard to location of the plume. This is the first report describing significant differences in particle size characteristics depending on the location of sampling using laser diffraction. Spray distribution differences may be related to droplet evaporation and sedimentation processes occurring after atomization. However, the spray patterns were not sensitive to changes in gravitational force acting on the plume. Instead, it is postulated that elliptical spray patterns may be dependent on fluid dynamic processes occurring due to propellant flow and atomization interactions within the inhaler actuator. This phenomenon requires further investigation.

By elucidating the mechanisms of plume formation, spray patterns may become a more useful tool in evaluating pMDIs. It is envisioned that spray pattern measurements may be used for quality control purposes, but much more sophisticated analysis is required.

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