

Spray pattern: A rapid and sensitive early development tool for respiratory drug products

Utilizing spray performance measurements to accelerate OINDP development

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Introduction

Spray pattern and plume geometry have long been established as required tests for orally inhaled and nasal drug product (OINDP) characterization. Furthermore, these tests are important indicators of aerosolization, spray performance and subsequent bioavailability (BA) of the delivered drug.¹ The industry guidelines for metered dose inhalers from the United States Food and Drug Administration (US FDA) state that, "Various factors can affect the spray pattern and plume geometry, including the size and shape of the actuator orifice, the design of the actuator, the size of the metering chamber, the size of the stem orifice of the valve, the vapor pressure in the container, and the nature of the formulation."² Understanding these effects becomes essential to successful drug development and approval.

Establishing bioequivalence (BE) in generic drug development using these and other tests has proven to be challenging.³ Moreover, innovation companies can utilize spray pattern to design new products with performance parameters that are difficult to match. Often in generic product development, investigation into the spray performance begins too late in the process given the importance of these measures. Understanding the relationship between the device and formulation and their effect on spray performance is a critical step in obtaining reproducible performance or achieving bioequivalence. Failure to gain this understanding can result in a costly redesign and a delay in product approval.

Spray pattern is a highly sensitive and rapid measurement technique, which makes it an ideal tool early in product development. This sensitivity provides an opportunity to fully understand the interactions between a large number of factors related to device design, formulation and patient usage. Obtaining this product information is essential in achieving proper drug delivery and performing successful BA/BE studies.

The present study was designed to examine spray pattern against changes in the sump design for pressurized metered dose inhaler (pMDI) products, specifically orifice diameter, orifice length and sump chamber depth parameters (Figure 1). These parameters were found, in a previous study, to have the most significant effects on spray performance.⁴ The results here corroborate the previous study's findings and demonstrate how small variations in sump design, as well as variability introduced by other factors (canister, valve, formulation), drive significant changes in spray pattern area. Proveris Scientific's SprayVIEW[®] measurement system can detect these small changes. This type of analysis gives valuable insight about various factors to control during the product development stage for both generic and new reference products.

Materials and methods

Materials

All spray pattern measurements were performed on two reference pMDI products: ProAir[®] HFA (Teva) and Ventolin[®] HFA (GlaxoSmithKline). Two specific actuators (one for each product) were custom-designed to hold the canister and sump component fixture. Eight different sump components were developed to reflect the three-parameter, two-level design of experiment from Smyth, et al. as shown in Table 1.⁴ The actuator's sump component was designed to be modular so all eight sumps could be replaced and tested. The actuator design maintained a horizontal spray but did not include a mouthpiece, in order to isolate the effects of the sump components. This design also removes a variable that can affect spray performance. Figure 1 highlights each of the three parameters varied: orifice diameter, orifice length and chamber depth. The sump components were machined from black delrin with high precision tolerance ($\pm 5\%$), using CNC (computer numerical control) machining technique.

Measurements and method parameters

Spray pattern measurements were performed using a SprayVIEW® system (Proveris Scientific, Marlborough MA, US). This non-impaction measurement system uses a laser light sheet and high-speed digital camera to collect images. Viota® software (Proveris Scientific) was used to quantify the time-averaged composite image for spray pattern at 30 mm distance from the edge of the orifice. Spray pattern measurements are visualized as the cross-sectional area perpendicular to the axis of the spray. (Figure 2) Key measurements include D_{\max} and D_{\min} (maximum and minimum diameter through center of gravity), ovality and area, averaged over time or assessed at individual time points.

For each product, ten spray pattern measurements were taken from each canister for each of the eight sump design components. Three canisters from each product were tested. Area and ovality spray pattern results were evaluated. Identical shaking and actuation parameters (shake duration/angle, actuation velocity/acceleration, hold time) were used throughout the study. These parameters were derived from an ergonomic study to be consistent with average patient usage of these products. The laser and camera settings were also kept identical for all canisters from each product. All data were statistically analyzed using JMP® software (SAS Institute, Inc., Cary, NC, US).

Spray pattern area throughout the life of the canister was evaluated for both ProAir and Ventolin to ensure consistency through actuations. The data showed that, with consistent shaking and spray interval conditions, there were no large fluctuations in spray pattern area throughout the lives of the canisters (ProAir relative standard deviation (RSD) = 7.68%; Ventolin RSD = 12.02%).

Results and discussion

Device component design effects on spray pattern area

Spray pattern is sensitive to the way devices are actuated (stroke length, hold time, actuation velocity), formulation properties, actuator design and pump/valve selection.⁶ The following experiments look at pMDI spray performance differences in formulations and actuator sump design.

Results of comparisons between ProAir and Ventolin. ProAir and Ventolin contain the same active pharmaceutical ingredient (API) of albuterol sulfate, however, they have different formulations (API + propellant + excipients). The left side of Figure 3 illustrates the variability of the combined results from all eight sumps. Formulation and/or metering valve can impact spray pattern area results, as Ventolin had greater variability (standard deviation (SD) = 19.88) compared to ProAir (SD = 13.33). Despite the formulation differences, both products show similar trends in spray pattern area across all eight sump components (see the trend lines through the mean spray pattern area on the right side of Figure 3).

Table 1

Actuator sump design features; three parameter factors at two levels.²

Sump ID#	Orifice Diameter (mm)	Orifice Length (mm)	Chamber 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

Figure 1

Diagrams of the sump component, its details and design parameters.

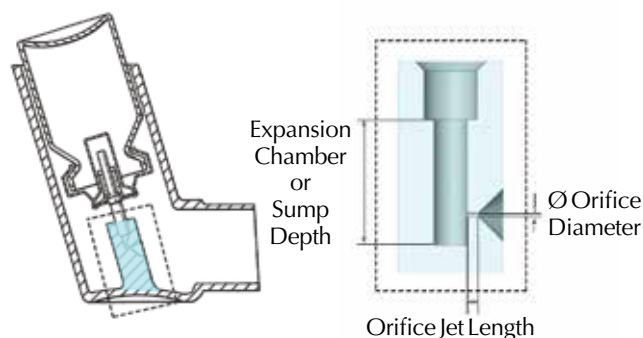


Figure 2

Representative spray pattern measurements from a SprayVIEW® system. The image highlights a typical spray pattern from a pressurized metered dose inhaler (pMDI).

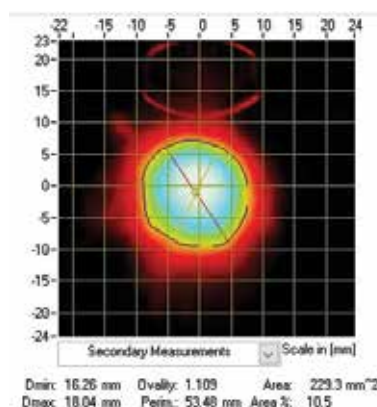


Figure 3

Spray pattern area results by product type. ProAir (blue) and Ventolin (red) show similar results in overall mean area (left portion of graph) and trends across the eight sump designs (right portion of graph).

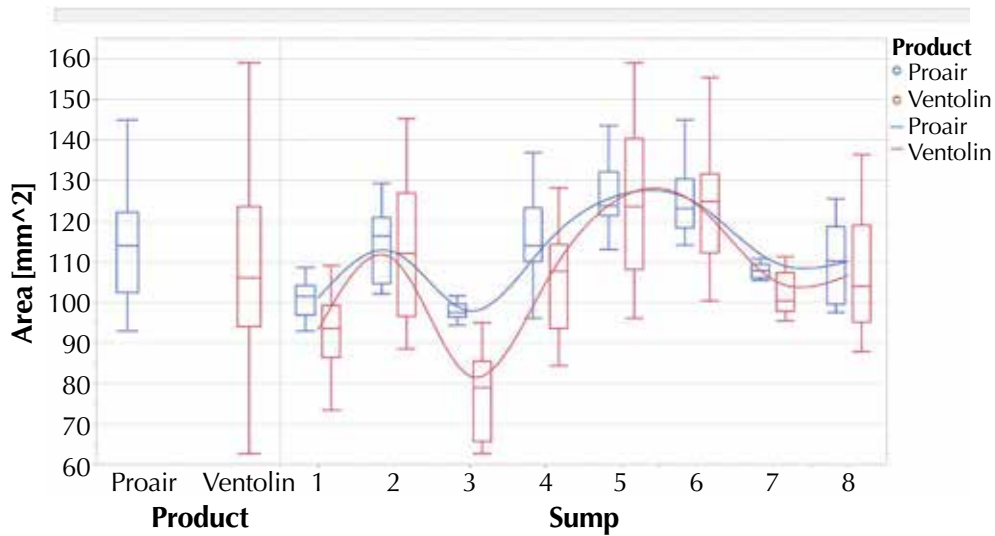
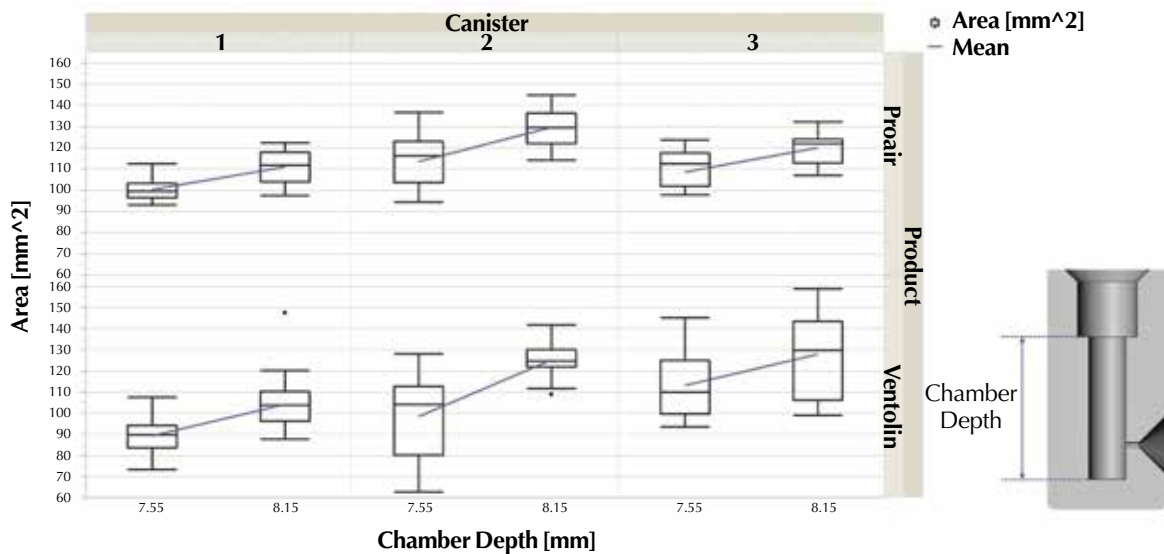


Figure 4

Effect of chamber depth on spray pattern area by product and canister, comparing ProAir (top) and Ventolin (bottom) at two different chamber depths (7.55 mm and 8.15 mm) across three canisters.



Screening spray pattern area for different formulations and device parameters can help optimize a combination product. Developers can make reference products difficult to replicate by having highly reproducible spray performance that is limited to a minimal number of possible sump designs. Conversely, generic pharmaceutical developers can use these screens to find a best match to those reference products.

Effect of individual parameters on spray pattern area.

Each of the three sump component parameters (orifice diameter, orifice length, chamber depth) individually drive changes in spray pattern area (all p values <0.0001). When the parameter effects are sorted, chamber depth shows the most prominent effect on spray pattern area. As shown in Figure 4, an increase in the spray pattern

area was observed at the higher chamber depth compared to the lower chamber depth across both products and each of the three canisters. The average percent difference for the increase that chamber depth had on spray pattern area was 10.44% for ProAir and 17.07% for Ventolin. Screening specific device components using spray pattern can inform developers about parameters that have the largest effects and facilitate focus on the most crucial design elements to control.

Interaction between sump design parameters. With single parameters showing significant effects on spray pattern, the next studies examined how combinations of parameters interacted to affect spray performance. To simplify understanding of the interaction between sump component parameters, only ProAir is described in the

Table 2

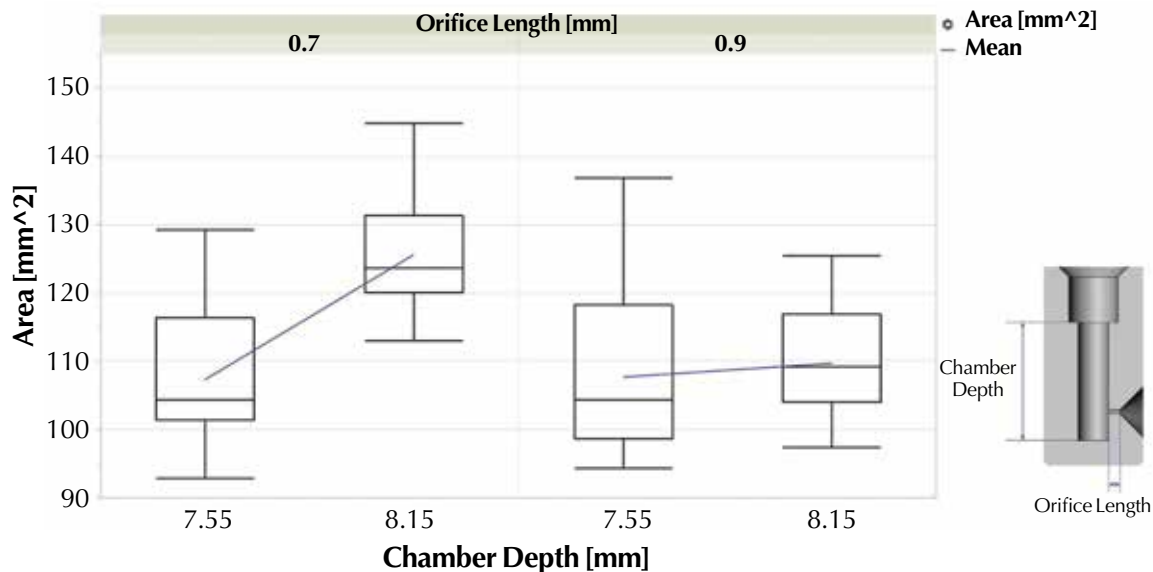
Effect on spray pattern area, examining individual sump component parameters compared against the other two parameters sequentially.

(Significant values with $p < 0.05$ are highlighted in bold.)

Parameter		p value	
		Chamber depth	Orifice diameter
Orifice length	0.7	<0.0001	0.0101
	0.9	0.8663	<0.0001
		Chamber depth	Orifice length
Orifice diameter	0.25	<0.0001	<0.0001
	0.31	0.1020	0.003
		Orifice diameter	Orifice length
Chamber depth	7.55	<0.0001	0.8703
	8.15	0.6792	<0.0001

Figure 5

Changes in orifice length differentially influence the effect of chamber depth on spray pattern area results. At the shorter orifice length (left), changes in chamber depth significantly affect the spray pattern area compared to the dampened effect of chamber depth at a longer orifice length (right).



following analysis. Each individual sump component parameter was compared against the other two component parameters sequentially to examine the effect on spray pattern area, as described in Table 2. A standard least squares fit model in JMP software was used for the analysis. The coefficients are sorted estimates with spray pattern area as the variable and chamber depth, orifice length and orifice diameter as model effects. The significance is set at p value < 0.05 . For example, at an orifice length of 0.9 mm (row 2 in Table 2), the variability in chamber depth does not have a statistically significant effect on spray pattern area. Conversely, orifice diameter

does have a statistically significant effect on spray pattern area, with a p value < 0.0001 .

Averaging all three canisters, at the shorter orifice length (0.7 mm), changes in chamber depth significantly affected the spray pattern area: the mean area at 7.55 mm was 107.26 mm² and at 8.15 mm was 125.57 mm², a 15.73% difference. At the longer orifice length (0.9 mm), the effect of chamber depth on spray pattern area was reduced with only a 1.87% difference, as shown in Figure 5. Further analysis revealed that this dampened effect correlated to changes in orifice diameter.

Figure 6

Orifice diameter and orifice length both influence the effect of chamber depth on spray pattern area. For the larger orifice length (right), an increase in chamber depth has a positive effect on spray pattern area at the smaller orifice diameter (top), compared to a negative effect on spray pattern area at the larger orifice diameter (bottom).

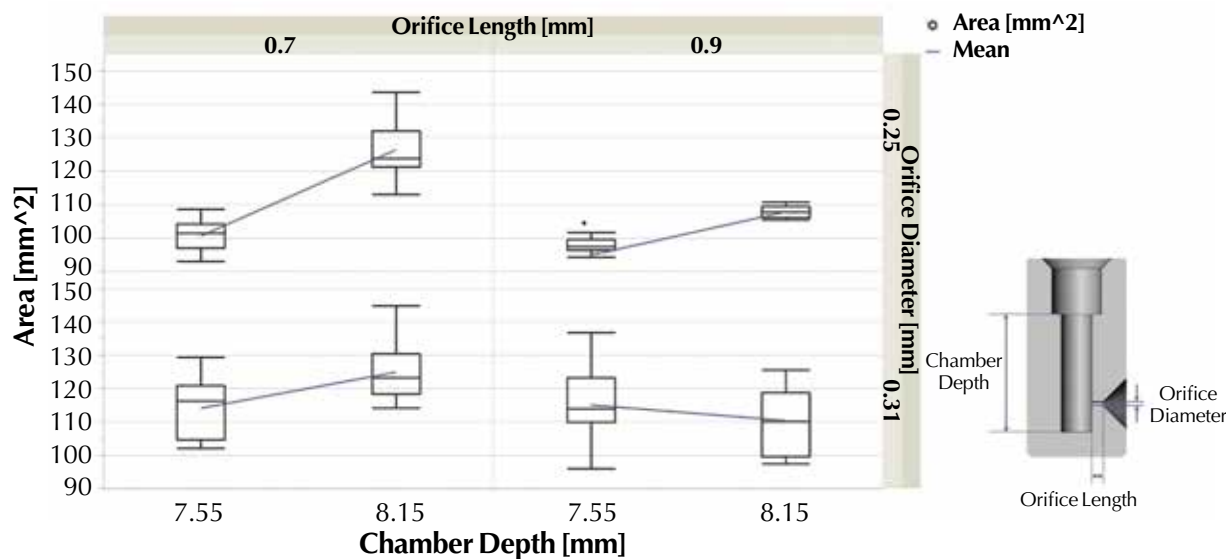
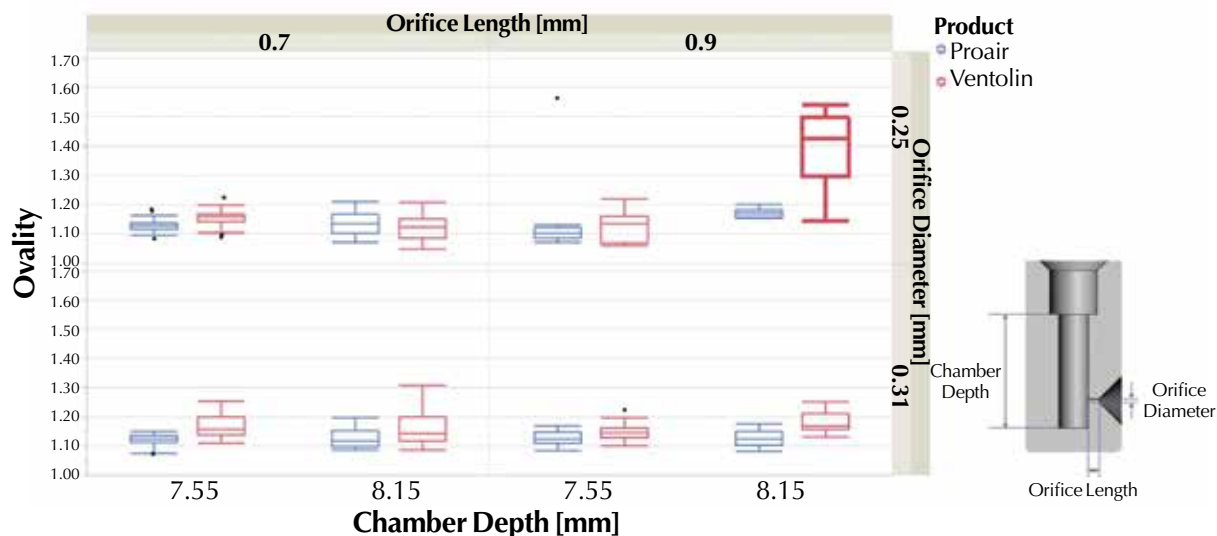


Figure 7

Effect of chamber depth, orifice length and diameter on spray pattern ovality by product. At a longer orifice length, smaller orifice diameter and longer chamber depth, Ventolin shows large ovality variation compared to the other sump component configurations.



When the effect of the orifice diameter (the third parameter) was examined, it was observed that, at the larger orifice length (0.9 mm), the chamber depth had a differential effect on spray pattern area. An increase in chamber depth had a positive effect in spray pattern area at the smaller orifice diameter, compared to a negative effect at the larger orifice diameter, as shown in Figure 6. These results illustrate a complex relationship between various components in these devices. This finding suggests that selecting device design parameters should be done carefully, with a large amount of data and an in-depth analysis to maximize the chances for successful BA/BE results.

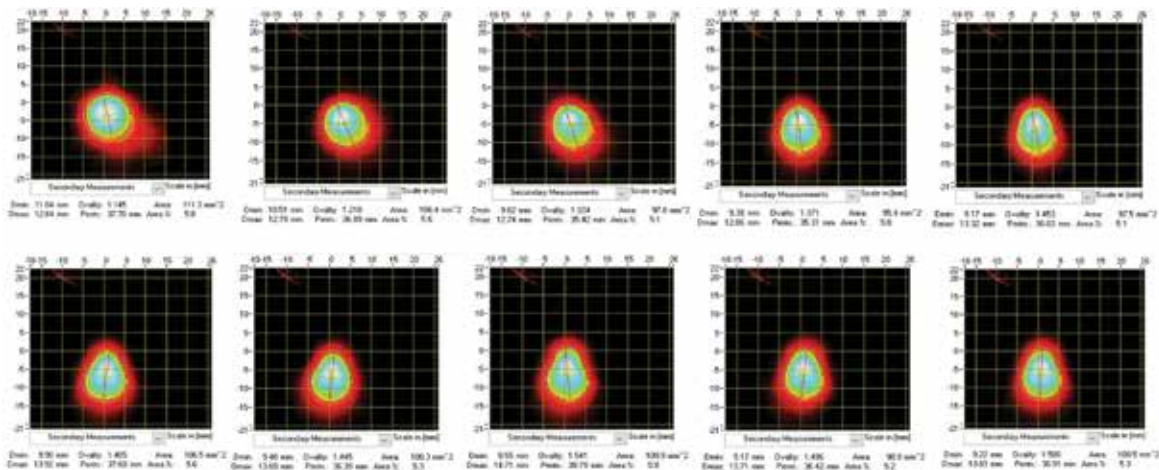
Additional spray pattern parameters illustrate device and formulation interactions

Spray pattern ovality. The FDA defines spray pattern ovality as “The ovality ratio is D_{\max} divided by D_{\min} . The perimeter of the true shape: D_{\max} (longest diameter) and D_{\min} (shortest diameter) that pass through the COG [center of gravity] and extend to the perimeter of the true shape.”⁵

A large variation in spray pattern ovality was observed when testing with a smaller orifice diameter, larger orifice length and larger chamber depth (sump #7) for Ventolin as shown in Figure 7. However, ProAir did not show as much variation in the same conditions. This

Figure 8

Ventolin spray pattern changes over successive shots in sump #7. The shape of the spray pattern changes from more circular during early shots to more oval in later shots.



could be due to formulation differences between the two products.

The Ventolin variability was confirmed by observing the spray pattern images of successive shots using sump #7. As shown in Figure 8, the shape of spray pattern changed throughout the ten sprays (from circular to oval). Sump #7 often became clogged during successive testing and needed to be cleaned more frequently. This finding shows that spray pattern ovality is a good indicator for sump blockage from a potentially incompatible formulation/device pairing when developing a new reference or generic product. It could also assist in establishing a device cleaning protocol for the patient.

Spray pattern intensity vs. time. Spray pattern variation over time can be visualized by recording the light intensity in the field of view throughout the entire data collection period. This measurement is useful for obtaining a more complete characterization of spray performance throughout the full duration of the actuation event. The upper portion of Figure 9 shows an example of a spray pattern image and intensity vs. time graph for Ventolin in sump #2. The spray began at approximately 50 milliseconds (ms), developed, and completed at approximately 300 ms. The majority of the formulation was expelled between 50 ms and 150 ms.

In comparison, the lower portion of Figure 9 shows an example spray pattern image and intensity vs. time graph for Ventolin in sump #3. Although the shape of the spray pattern was relatively circular, sump #3 expelled a spray of longer duration with non-uniform intensity compared to sump #2, which expelled more efficiently in a spray of shorter duration. This sump design did not exhibit any blockage, but the combination of design parameters still appears to have had a significant impact on flow. This shows that the intensity vs. time analysis can effectively monitor spray pattern variation over time and provide another sensitive mea-

sure for spray performance. This test could be used as a good indicator for formulation and device pairing compatibility and other design considerations. Further experiments will be necessary to determine whether these flow differences have any impact on bioavailability, as well as on other spray performance parameters such as particle size.

Conclusions

These results confirm the findings from Smyth, et al. that spray pattern area is sensitive to changes in individual parameters (orifice length, diameter, chamber depth) and “can yield information regarding the nature of aerosol generation from pMDIs.”⁴ This study has gone further, to show interactions between various parameters within the sump design of the pMDI actuator. This makes spray pattern a very useful tool during device design and product development, which can help lead to successful BA/BE studies.

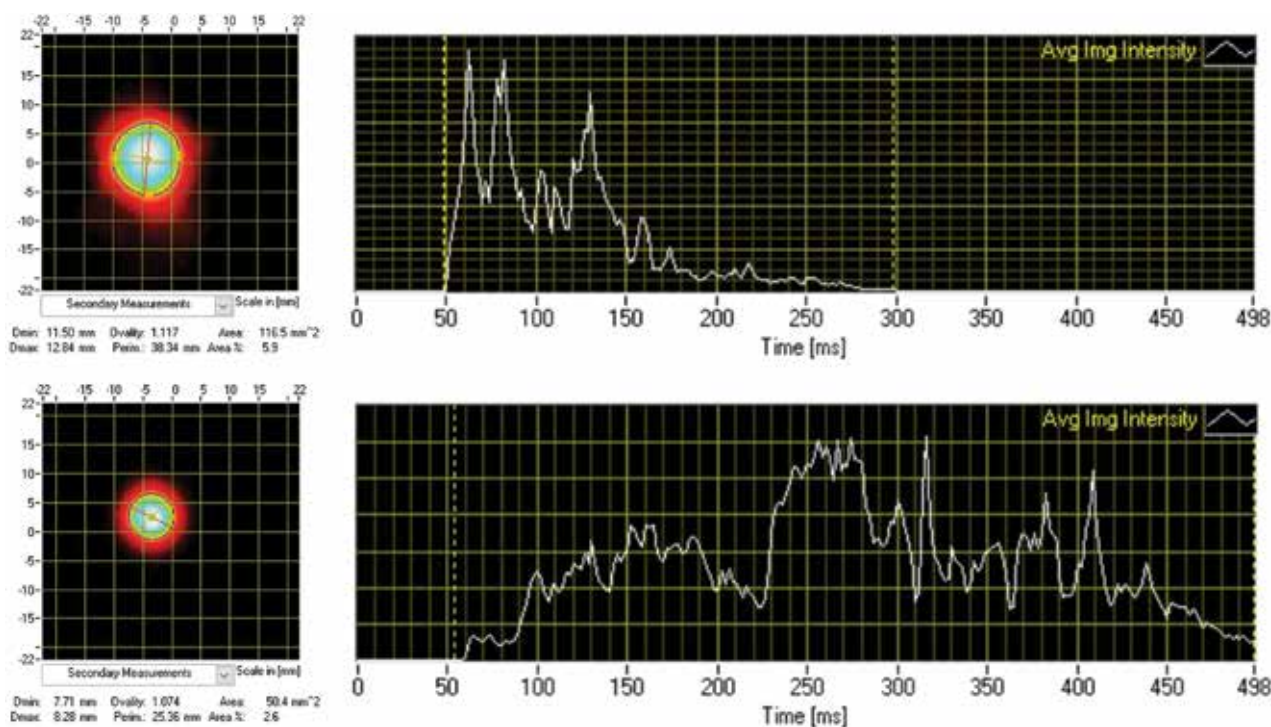
Sump design has a robust and reproducible effect on the nature of spray pattern, independent of formulation factors, as observed by the similar spray pattern area trend across sumps for ProAir and Ventolin. The effect of formulation factors is evident from differences in the spray pattern area values and variability between the two products.

Multiple characteristics of spray pattern, such as ovality and time-based intensity measurements can reveal subtle performance defects and design limitations. Smyth, et al. found that the “elliptical ratio... was shown to be insensitive to changes induced in actuator geometry.” These results show that a combination of formulation properties and actuator design can have an impact on spray pattern ovality, whether it be direct or indirect.

This study has been a small example of the value that spray pattern can have as a tool, and a means for providing rapid results early in reference or generic product

Figure 9

Examples of spray pattern image and intensity vs. time graphs for Ventolin in sump #2 (top) and sump #3 (bottom).



development. This type of analysis can be applied to other aspects of product development not examined in this study, such as valve, canister and mouthpiece design or formulation components, as well as to other types of devices including nasal spray products.⁷ Additional studies will be necessary to look at the relationship of spray pattern to other measures, such as deposition and particle size, as suggested by Smyth, et al.⁴

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