Effects of Formulation and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers (MDIs)

Sneha Dhapare[1], Elizabeth Bielski[1], Denise S. Conti[1], Oluwamurewa Oguntimein[1], Poonam Sheth[2], Mårten Svensson[3], Dennis Sandell[4#], Jüergen Bulitta[5], Günther Hochhaus[5]

[1]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA; [2]Recipharm, 511 Davis Drive, Suite 100, Morrisville, North Carolina 27560, USA. Present Address: AstraZeneca, Durham, NC, USA; [3]Emmace Consulting AB, Medicon Village, SE-223 81 Lund, Sweden; [4]S5 Consulting, Ekvägen 8, SE-275 62 Blentarp, Sweden; [5]Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA. [#] *In Memoriam, October 29, 2020.*

Abstract

Background: Spray pattern and plume geometry analyses are used in the product quality and in vitro bioequivalence assessment of MDIs but their utility in detecting changes in formulation is poorly understood. **Purpose**: To better understand the utility of spray shape tests, this study systematically investigated the effects of formulation and actuator variables on spray pattern (ovality and area) and plume geometry (angle and width) using suspension-based mometasone furoate (MF) MDIs. **Methods**: A total of 108 spray pattern and plume geometry measurements were made on MF MDI formulations and actuator variations as described in Bielski et al. Twelve formulation-actuator combinations were evaluated for spray pattern and plume geometry using a laser-based Envision Pharma R&D System. All measurements were performed at 6 cm distance from the actuator mouthpiece. The results for ovality, area, angle and width with different formulation-device combinations were analyzed by ANOVA using all MF MDI formulations as a fixed effect and actuator characteristics (Orifice Diameter, OD; Jet Length, JL; and Sump Depth, SD) as covariates. Correlations of spray shape characteristics with aerodynamic particle size distribution (APSD) parameters were attempted. **Results**: Different MF MDI formulations resulted in significant (p<0.05) effect on spray ovality, area and plume angle, but had no significant effect on plume width. OD had no significant effect on any of the 4 spray characteristics, which is contrary to observations with APSD. However, JL had significant effect on area, angle and width, while SD had significant effects on ovality and angle. Correlation attempts between actuator characteristics and spray properties showed that all – ovality, area, angle and width – increased with increasing SD, and decreased with increasing JL. Area showed the highest correlation (|r|>0.6) to actuator deposition, delivered dose and mass median aerodynamic diameter, while low values for Pearson's correlation coefficient (|r|<0.6) were obtained for fine particle dose (FPD<5 µm and FPD<2 µm). Actuator deposition was also well-correlated with angle and width along with area. **Conclusions**: Rational design and product development of generic suspension-based MDIs should consider the influence of both formulation and device changes on spray characteristics to achieve the comparable product performance to the branded products.

Introduction

Spray pattern and plume geometry analyses of metered dose inhalers (MDIs) are used in the assessment of drug product quality and in vitro bioequivalence of generic orally inhaled and nasal drug products.[1,2] These spray characteristics of MDIs are expected to be influenced by the formulation factors such as physiochemical properties of the active pharmaceutical ingredient (API), the amount and nature of excipients and device properties like actuator nozzle orifice diameter (OD), sump depth (SD) and orifice jet length (JL) (Figure 1).[3] However, a systematic study to assess the effect of formulation and device factors on spray pattern and plume geometry of MDIs has not been conducted. Moreover, the relationship between these two spray characteristics and the delivery of inhaled drugs to local sites of action in the lung, and subsequently efficacy, is unsubstantiated.

To better understand the spray characteristics of MDIs, this study systematically investigated effects of formulation changes (excipient levels and drug particle size distributions) and actuator variables (orifice diameter, jet length and sump depth) on spray pattern (spray ovality and area) and plume geometry (plume angle and width) using mometasone furoate (MF) suspension-based MDIs. Our goal was to probe the relationship between these spray characteristics and formulation and device parameters.

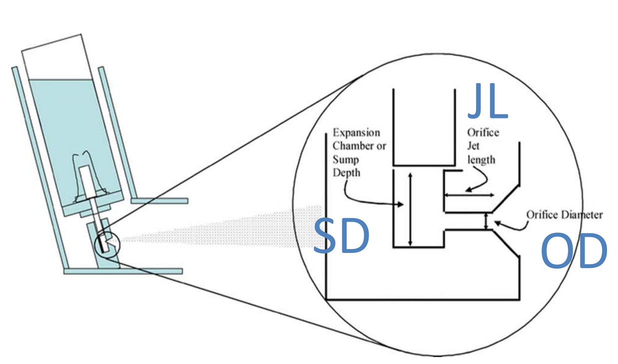

Figure 1: MDI actuator parameters schematic.[3]

Methods

MF MDIs: Based on Dulera® as a model system, three suspension-based MF (the API of interest) MDIs were manufactured with changes in API particle size (D50), oleic acid (OA, surfactant) and ethanol (EtOH, cosolvent) content (Table 1) in HFA-227 propellant. Four actuator variants differing in OD, JL and SD were also included in the study (Table 1).[4] The effects of each of these formulations and actuator variants on spray characteristics were evaluated.

Spray Pattern and Plume Geometry Measurements: Twelve formulation-actuator combinations (3 canisters for each combination x 3 replicate measurements on each canister) were evaluated for spray pattern and plume geometry using a laser-based Envision Pharma R&D System (Oxford Lasers Ltd, Oxon, UK) following automated pneumatic actuation. The motion of the pneumatic actuation of the MDI canister was 300 mm/sec and the canister was pressed down for 3 seconds before being released. All spray measurements were performed at 6 cm distance from the actuator mouthpiece. ***Spray pattern*** was measured by calculating ***ovality*** (the ratio of maximum and minimum diameter (Dmax / Dmin) of an axial cross-section of the plume) and ***area*** of the plume.

Methods

Table 1: MF MDI Formulation Factors and Actuator Variants Studied.

MF Formulation Factors			
Formulation	**API D50 (µm)***	**EtOH (% w/w)**	**OA (% w/w)**
F1	1.69	0.53	0.004
F2	1.10	2.15	0.015
F3	1.69	1.35	0.010
*D50 = the median diameter (the particle diameter at 50% in the cumulative distribution).			
Actuator Variants			
Actuator	**Orifice Diameter (OD, mm)**	**Jet Length (JL, mm)**	**Sump Depth (SD, mm)**
A	0.48	0.6	1.2
B	0.48	0.4	1.5
C	0.35	0.6	1.2
D	0.35	0.4	1.5

Plume geometry *was* measured by assessing **angle** and **width** of the plume. Envision Patternate Software (version 1.3.1) was used for these measurements and analysis of the spray pattern and plume geometry parameters, with the plume edge being defined in the software as "percent to include = 95%" of pixel intensity. Actuators were not cleaned between each actuation because review of preliminary study results indicated no meaningful shift in measured parameters with increasing actuation number within a single MF canister or reuse of the actuator. The MDIs were primed between tests with different actuators and between each spray, according to the labeling instructions. The results for ovality, area, angle and width with different formulation-device combinations were analyzed by ANOVA using all MF MDI formulations (F1, F2 and F3) as a fixed effect and actuator characteristics (OD, JL and SD) as covariates. A study determining the aerodynamic particle size distribution (APSD) of each of the 12 formulation-actuator combinations has also been carried out.[4] Correlation between APSD parameters obtained from the previous study (e.g., impactor stage mass (ISM), delivered dose (DD), fine particle dose (FPD), mass median aerodynamic diameter (MMAD), next generation impactor (NGI) stage deposition as well as actuator and USP throat deposition) to each of the spray characteristics obtained in this study was attempted.

Results and Discussion

Spray Characteristics of MF Formulations and Actuator Variants

- Different MF MDI formulations showed significant effects on spray pattern ovality ratio and area as well as plume geometry angle but did not a show significant effect on plume geometry width (Table 2). Overall, the observed effects were modest (Figure 2).
- The MF formulation F2 (smallest API D50 and highest EtOH and OA content) had the largest effect on spray pattern area and plume geometry angle of the three MF formulations evaluated (Figure 2).
- The change in actuator OD had no significant effects on any of the four spray characteristics. However, JL was shown to have significant effects on spray pattern area as well as plume geometry angle and width, while SD had significant effects on spray pattern ovality and plume geometry angle (Table 2).
- Correlation between actuator parameters and spray characteristics was determined. These showed that all spray characteristics – spray pattern ovality and area as well as plume geometry angle and width – increased with increasing SD and decreased with increasing JL.
- An increase in JL from 0.4 to 0.6 mm led to significant decreases in spray pattern area (10-15%), plume geometry angle (5-10%) and width (2-11%) for each of the three MF formulations studied (Figure 3).
- An increase in SD from 1.2 to 1.5 mm, on the other hand, significantly decreased spray pattern ovality (2-10%) but increased the plume geometry angle (5-10%).

Table 2: Summary of ANOVA p-values for each Spray Characteristic. Significant differences (p<0.05) are shown in red.

Formulation or actuator characteristic	Spray characteristic p value			
	Ovality	**Area**	**Angle**	**Width**
MF Formulation	0.0493	0.0000	0.0060	0.0733
OD	0.2499	0.0949	0.6904	0.9317
JL	0.5444	0.0000	0.0000	0.0006
SD	0.0155	0.5158	0.0180	0.1126

Results and Discussion

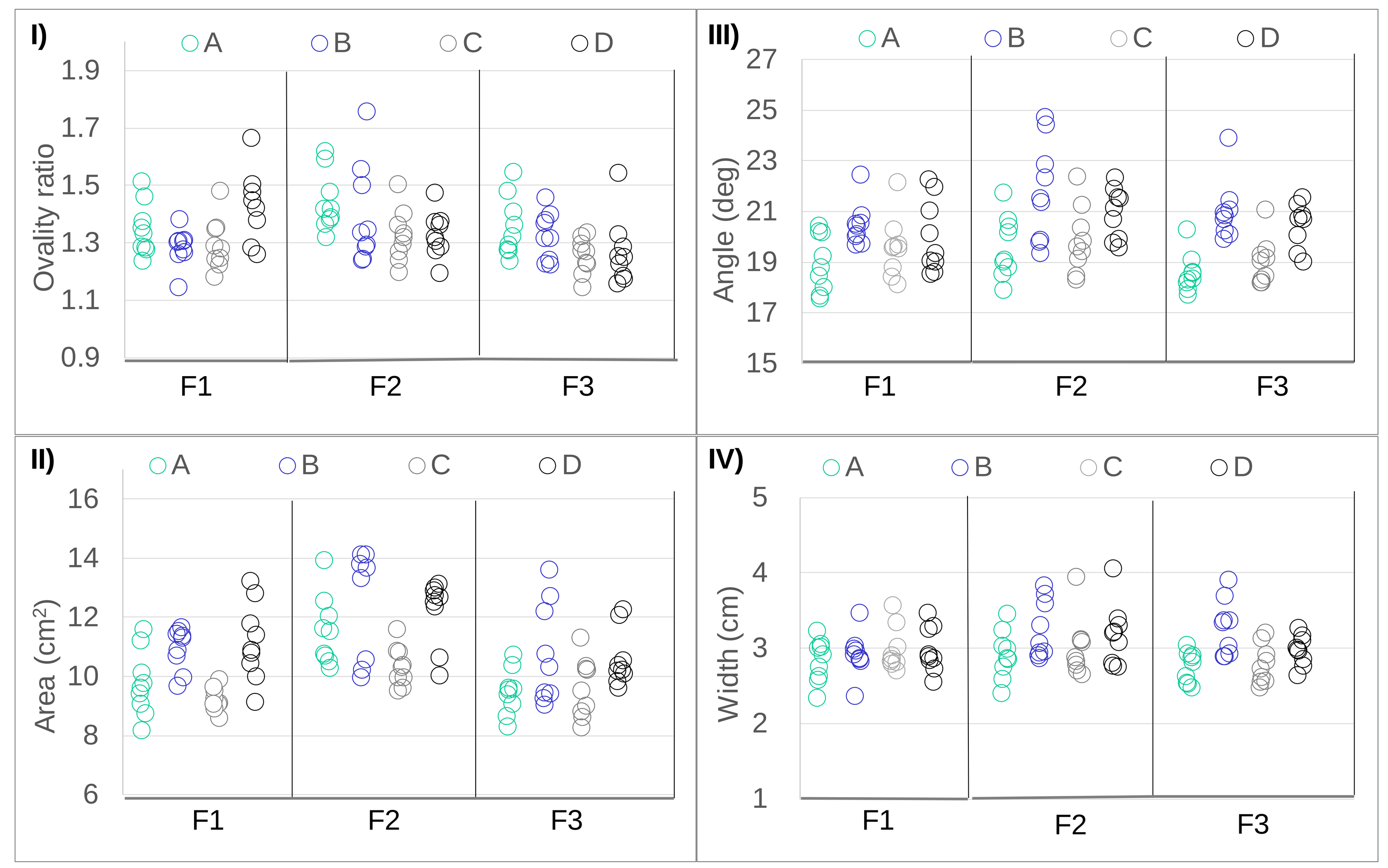

Figure 2: Spray Pattern Ovality Ratio (I) and Area (II) and Plume Geometry Angle (III) and Width (IV) for Three MF MDI Formulations (F1, F2 and F3) Combined with Actuator Variants (A, B, C and D).

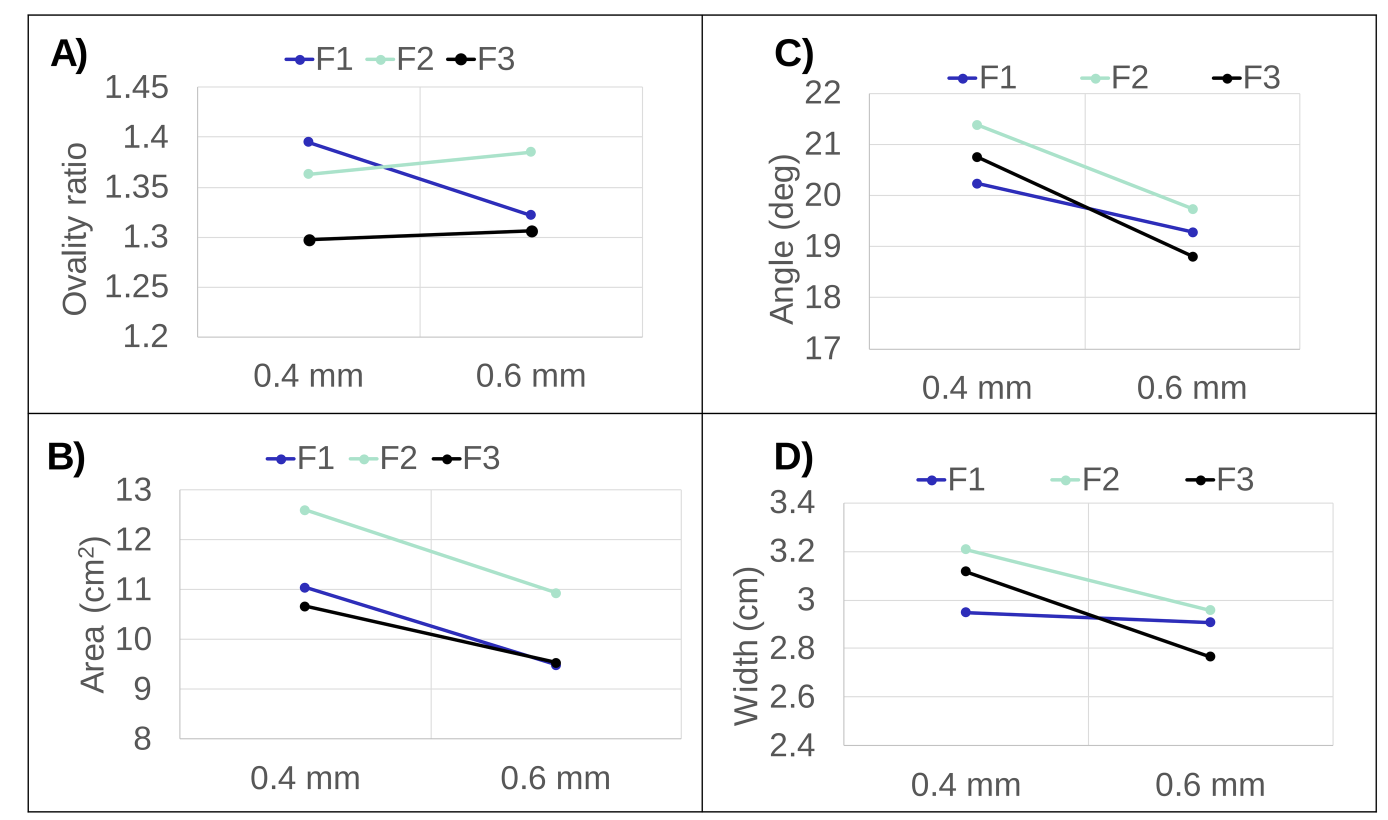

Figure 3: Average Change in Spray Pattern Ovality (A) and Area (B) and Plume Geometry Angle (C) and Width (D) of the Three MF MDI Formulations (F1, F2, F3) with Increase in Jet Length (JL) from 0.4 mm to 0.6 mm.

Correlation Between Spray Characteristics and APSD Parameters

Table 3: Summary of Correlation of Spray Characteristics to APSD Parameters. Pearson's Correlation Coefficient (|r|) values greater than 0.6 are shown in red.

APSD Parameter	Spray characteristic |r| correlation			
	Ovality	Area	Angle	Width
Actuator deposition	0.07	0.63	0.67	0.65
Induction port deposition	0.10	0.07	-0.11	-0.07
DD	-0.44	-0.65	-0.37	-0.40
ISM	-0.31	-0.41	-0.13	-0.17
FPD<2 µm	0.15	0.56	0.36	0.41
FPD<5 µm	-0.12	0.09	0.18	0.18
MMAD	-0.29	-0.65	-0.37	-0.41
Adapter	-0.09	-0.28	-0.23	-0.38
NGI Stage 1	-0.33	-0.68	-0.39	-0.41
NGI Stage 2	-0.28	-0.59	-0.30	-0.37
NGI Stage 3	-0.33	-0.62	-0.31	-0.37
NGI Stage 4	-0.05	0.16	0.22	0.23
NGI Stage 5	0.17	0.58	0.38	0.42
NGI Stage 6 - Filter	0.08	0.48	0.30	0.36

- Table 3 shows the correlation between the spray characteristics and APSD parameters: ISM, DD, FPD, MMAD, NGI stage deposition as well as actuator and USP throat deposition.
- Spray pattern area showed the highest correlation coefficient (|r|>0.6) to actuator deposition, DD and MMAD.
- Actuator deposition was also well-correlated with plume geometry angle and width along with spray pattern area. This may be attributed to the proximity of the actuator to the emerging MDI plume cone.
- Relatively low values for Pearson's correlation coefficient (|r|<0.6) were obtained for fine particle dose less than 5 and 2 µm (FPD<5 µm and FPD<2 µm, respectively).
- No significant correlation was seen between spray characteristics with other APSD parameters such as USP throat deposition and ISM.
- Meaningful correlation was also not seen with NGI stage deposition from Stage 1 to Stage 6-F for all of the spray characteristics.
- Based on the data analysis, mathematical models were developed to predict spray characteristics (ovality, area, angle and width) from actuator parameters (OD, JL and SD) for the three MF MDI formulations studied. The proposed models are listed below along with the % of effects explained:

$\text{Ovality} = 1.524 + 0.222 \cdot OD - 0.076 \cdot OL - 0.205 \cdot SD$ (12.1% explained)
$\text{Area} = 13.17 + 2.99 \cdot OD - 7.26 \cdot OL - 0.50 \cdot SD$ (45.6% explained)
$\text{Angle} = 20.8 + 0.70 \cdot OD - 7.59 \cdot OL + 1.81 \cdot SD$ (37.7% explained)
$\text{Width} = 3.024 + 0.037 \cdot OD - 1.074 \cdot OL + 0.325 \cdot SD$ (16.7% explained)

Conclusions

- MF MDIs manufactured with different API D50, OA and EtOH content were shown to influence both spray pattern and plume geometry characteristics.
- The MF MDI formulation with the smallest API D50 and highest OA and EtOH concentration had the largest effect on spray pattern area and plume geometry angle.
- Formulation factors and actuator JL were found to have most significant effect on spray pattern and plume geometry measurements, while actuator SD also showed some significant effects on spray pattern ovality and plume geometry angle. However, OD had no significant effect on any of the spray characteristics.
- Overall, spray pattern area was the only spray characteristic that showed good correlations to the APSD parameters (DD and MMAD) of the MF MDI formulations studied in this work.
- Actuator deposition was shown to correlate with all spray pattern and plume geometry measurements, except for spray pattern ovality.
- Lack of meaningful correlation between spray characteristics and APSD parameters for the MF MDI formulations suggested that these measurements may be independent of each other.
- Rational design and product development of branded and generic suspension MDIs should therefore consider the influence of both formulation and device changes on spray characteristics in order to achieve the desired MDI product performance.

References

1. FDA Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations (April 2018).
2. FDA Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation (July 2002).
3. Smyth, H., et al. (2006). *Pharmaceutical Research* 23(7): 1591-1596.
4. Bielski E. et al. (2020). *Respiratory Drug Delivery*. Volume 3, 2020: 497-502.

Acknowledgements

- Funding for this work was made possible, in part, by the U.S. Food and Drug Administration through Grant U01FD004943.
- Views expressed in this poster are from the authors only and do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.