The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler In Vitro Aerosolization Performance

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The Effects of Formulation Factors and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers

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Introduction

- Previous FDA Generic User Fee Amendments (GDUFA)-funded research (U01FD004943) on the quality by design (QbD) paradigm helped define design spaces for formulation factors to allow for similar aerodynamic performance for MDIs with different formulations.[1,2,3]

- The purpose of this work is to extend this research by investigation of how **formulation factors**, along with **actuator designs**, **influence in vitro product performance for mometasone furoate (MF) suspension-based MDIs**.

  - **Delivered Dose (DD)**
  - **Aerodynamic Particle Size Distribution (APSD)**
  - **Spray Pattern (SP)**
  - **Plume Geometry (PG)**

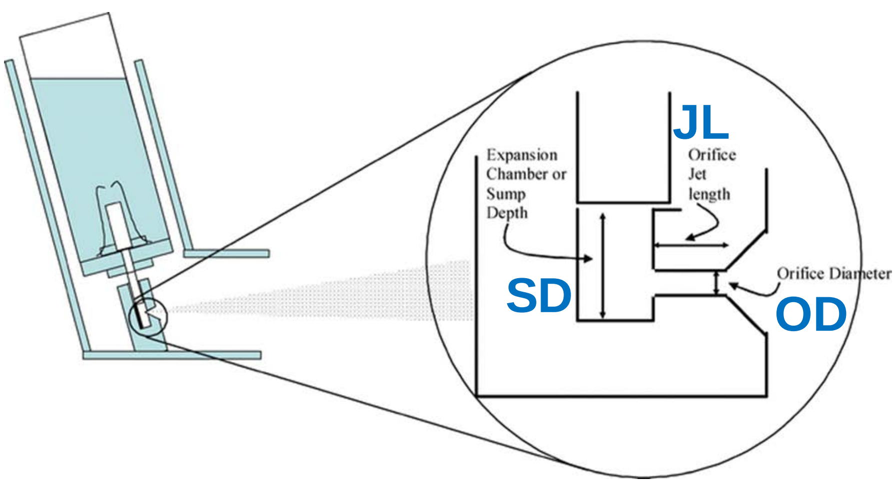
[1] Sheth, Poonam, et al. *The AAPS Journal*, 2017,19: 1396-1410.
[2] Sheth, Poonam, et al. *Respiratory Drug Delivery 2016,* 2016, 2: 285-290.
[3] Conti, D.S., et al., *2016 AIChE Annual Meeting*; November 14, 2016, San Francisco, CA, USA.

Methods: MF MDI Formulations and Actuator Variants

MF Formulations 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

* Actual results, not targets

** **D50**: the median diameter (the particle diameter at 50% in the cumulative distribution)



Actuator Variants			
Actuator	OD (mm)	JL (mm)	SD (mm)
A	0.48	0.6	1.2
B	0.48	0.4	1.5
C	0.35	0.6	1.5
D	0.35	0.4	1.2

Methods: DD and APSD

- **APSD Testing Conditions**
  – ***DD*** was based on the mass deposited in a CareFusion AirLife EU303 filter (F) following the method described in USP <601>.
  – ***APSD*** was evaluated using a Next Generation Impactor (NGI) (Copley Scientific) described in USP <601>[1] and the Table below.

APSD Testing Conditions

Induction Port or M-T Model	Flow Rate (L/min)	Inhalation Profile (IP)	Triggering Time Point (seconds)	Actuations per NGI run
USP	30	-	-	2
USP	70[#]	Medium[p]	0.2	2
OPC*	70[#]	Medium[p]	0.2	2
VCU*	70[#]	Medium[p]	0.2	2

* Medium sized mouth-throat (M-T) models: Oropharyngeal Consortium (OPC); Virginia Commonwealth University (VCU).

[#] Peak Inspiratory Flow (PIF) of 60 L/min.

[p] A medium IP based on the mathematical formula proposed by Byron *et al.*[2] and shape parameters by Longest *et al.*[3]

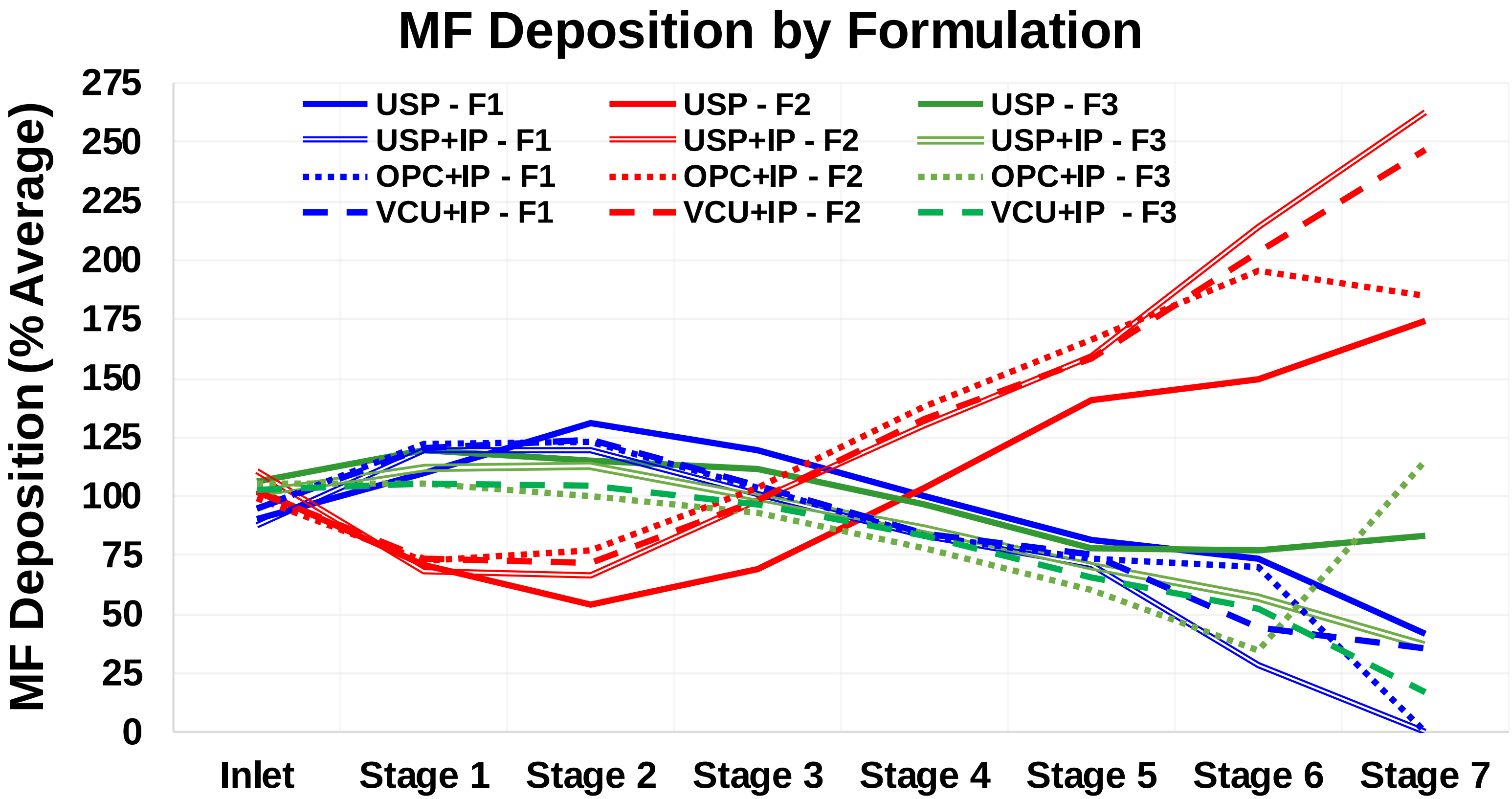
[1] United States Pharmacopeia and National Formulary. In <601> "Inhalation and Nasal Drug Products, Aerosols, Sprays, and Powders – Performance Quality Tests." *USP43-NF38*; 2018: 6819

[2] Byron, P.R., et al., *Respiratory Drug Delivery 2014,* 2014, 1: 295-302.

[3] Longest, P.W., et al., *Pharmaceutical Research,* 2012, 29: 1670-1688.

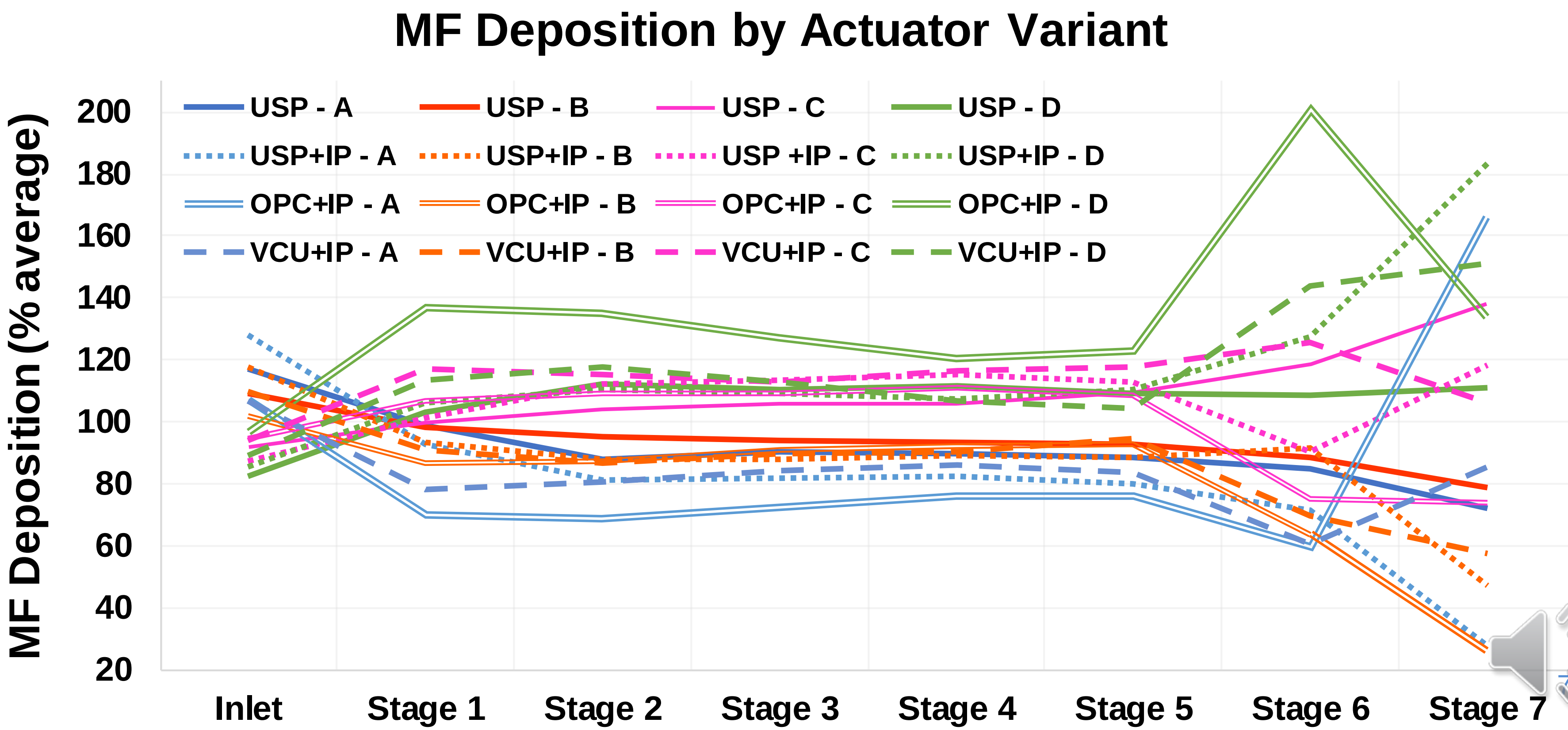
Results: APSD - Formulation

- **APSD by Formulation**
  - *Formulation has a statistically significant effect on FPD<2μm*
    - 1.6-2.2 times higher for F2 compared to F1 and F3
    - May be due to the smaller API D50 in F2
    - The result is consistent across all actuator variants and APSD testing conditions
  - *The direct influence of OA and EtOH could not be assessed due to limitations in experimental design*



Results: APSD – Actuator Variants

- **APSD by Actuator Variant**
  - *OD produced strongest Effects on FPDs*
    - Increased MF deposition for Actuators C and D compared to A and B
    - Consistent across all MF MDI formulations and APSD testing conditions
  - *The reduction of OD from 0.48 to 0.35 mm caused a significant increase in FPDs*
    - FPD<8µm: 14-53%; FPD<5µm 15-51%; FPD<2µm: 14-52%

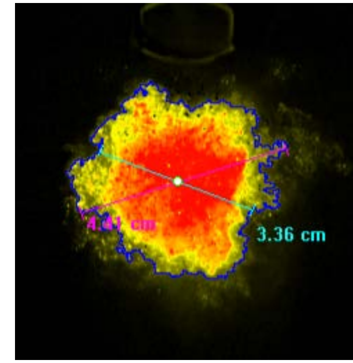


Conclusions: DD and APSD

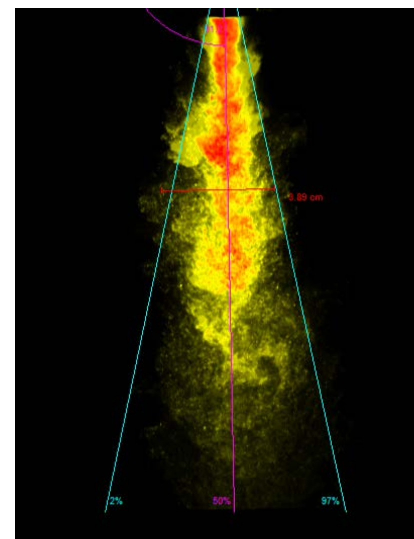
- *Different formulation factors and actuator parameters influenced the in vitro performance of suspension-based MF MDIs as demonstrated by the observed differences in FPD.*
  - *DD and NGI DD were **not influenced** by the different formulation factors or actuator variants.*
  - *The MF MDI **F2** produced **significantly more fine particle dose** **(FPD<2µm)** compared to F1 and F3, which can most likely be attributed to the smaller API D50 used in the F2.*
  - *Due to limitations in experimental design and number of formulations, the influence of **OA and EtOH warrants further investigation** to understand their impacts on the in vitro performance of MF MDIs.*
  - ***OD** had a strong effect on the MF particles exiting the USP induction port or M-T model (**smaller OD led to increased FPDs**), which was found to be formulation independent.*
- *The in vitro performance results across all APSD testing conditions*
  - ***Formulation**: **F2** being most influential compared to F1 and F3*
  - ***Actuator Design**: **OD** being most influential actuator parameter*

Methods: Spray pattern (SP) and Plume Geometry (PG)

- SP and PG measurements were made at 6 cm distance from the actuator mouthpiece using a laser-based Envision Pharma R&D System (Oxford Lasers Ltd, Oxon, UK) following automated pneumatic actuation
- Spray pattern measurements:
  - ***Ovality and Area***
- Plume geometry measurements:
  - ***Angle and Width***
- In total, twelve MF MDI formulation (F1, F2 and F3)-actuator (A, B, C and D) combinations were studied
- Correlation between **APSD-derived parameters** to each of the spray characteristics obtained in this study was attempted



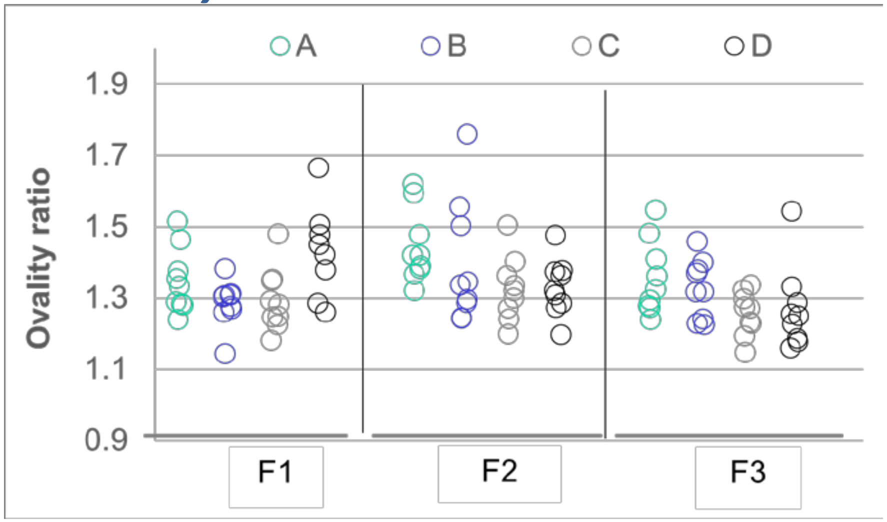
Example of a Spray Pattern measurement



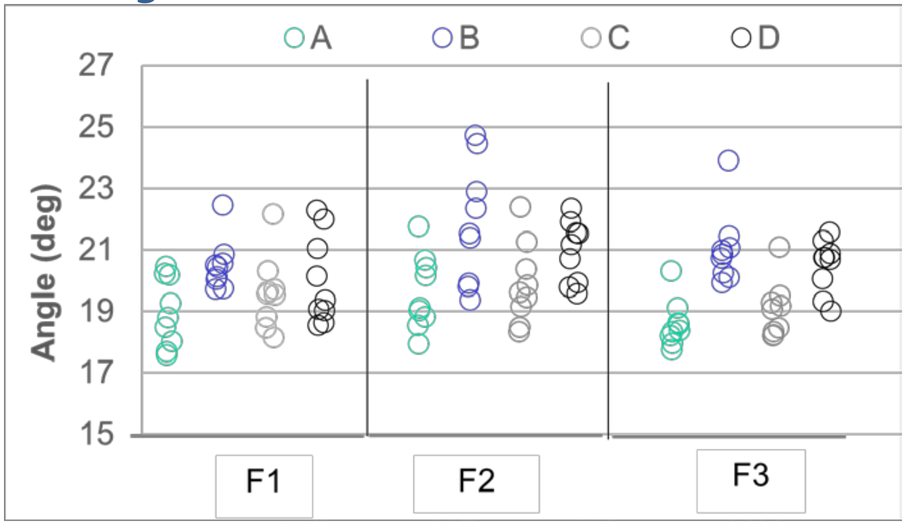
Example of a Plume Geometry measurement

Results: SP and PG

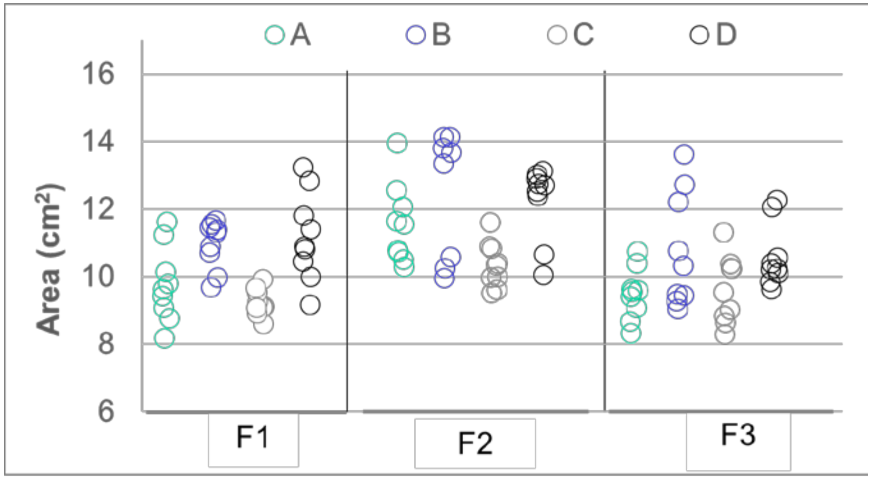
SP Ovality



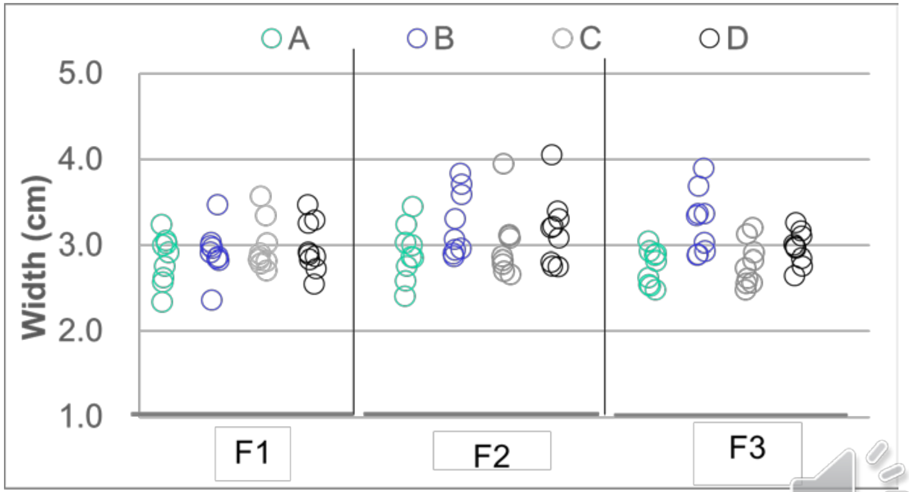
PG Angle



SP Area



PG Width

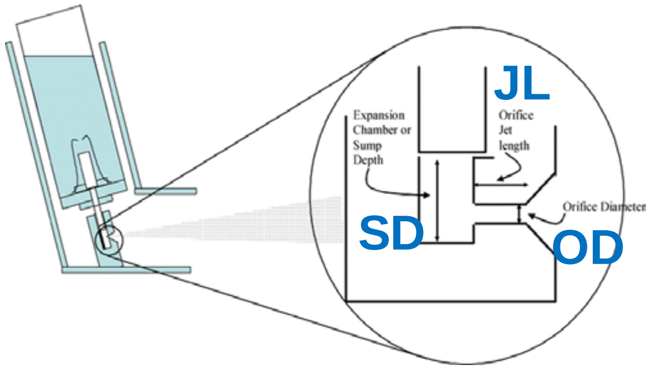


Results: SP and PG – Formulation and Actuator Variants

ANOVA p-values for each Spray Characteristic

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

Significant differences ($p<0.05$) are shown in red.



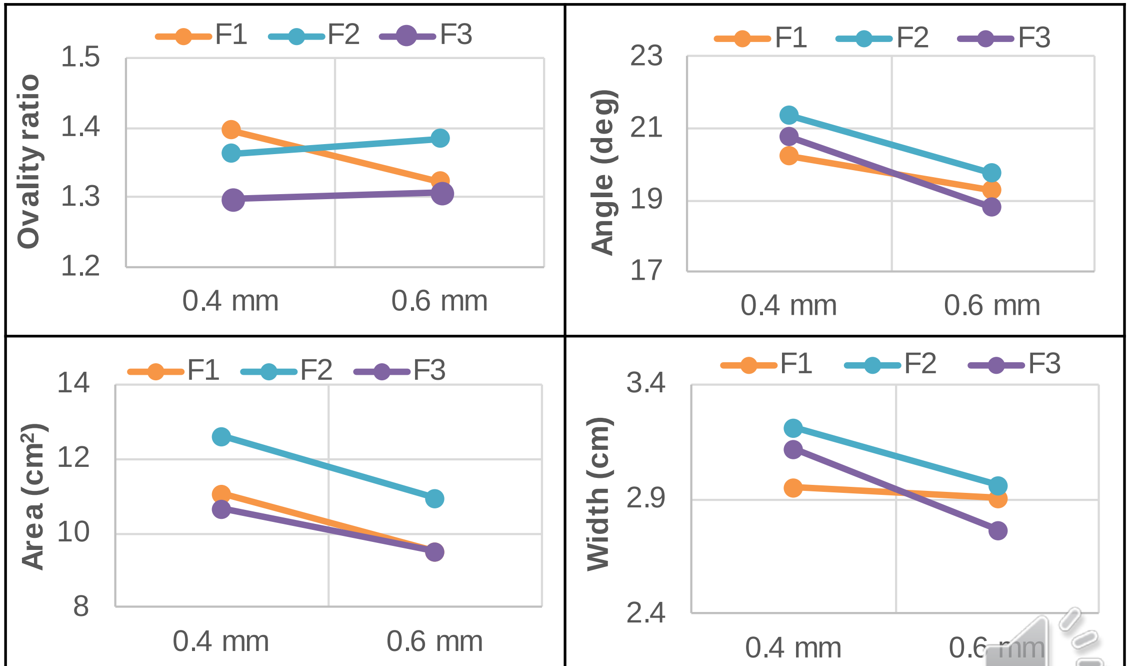
Proposed mathematical models along with the % of effects explained

$$\text{Ovality} = 1.524 + 0.222 \cdot OD - 0.076 \cdot OL - 0.205 \cdot SD$$
(**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**)



Results: SP and PG – Correlations with APSD Parameters

- ***Area*** *showed the highest correlation coefficient (|r|>0.6) to actuator deposition, DD and MMAD.*
- ***Actuator deposition*** *was also well-correlated with* ***angle*** *and* ***width*** *along with* ***area****.*
- *Relatively low values for Pearson's correlation coefficient were obtained for* ***FPD<5 µm*** *and* ***FPD<2 µm****.*
- *No significant correlation was seen between spray characteristics with other APSD parameters such as USP throat deposition and ISM.*

Correlation of Spray Characteristics to Actuator and Induction Port Deposition, and APSD Parameters.

APSD-derived Parameter	Spray characteristic $\|r\|$ value			
	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

Pearson's Correlation Coefficient ($|r|$) values greater than 0.6 are shown in red.

Conclusions: SP and PG

- *Formulations and actuator effects on spray characteristics:*
  - *MF MDIs manufactured with different API D50, OA and EtOH content were shown to influence **both** spray pattern and plume geometry characteristics.*
  - ***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.*
  - ***OD** had **no significant effect** on any of the spray characteristics.*
- *Correlations with APSD-derived parameters:*
  - *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-derived parameters** for the MF MDI formulations suggested that these measurements may be independent of each other.*

Overall Conclusions

- *The systematic investigations carried out in this study may enhance QbD approaches to streamline development of MDI products, including generics, and provide insights on how formulation factors and device parameters can be changed to achieve the desired in vitro performance.*

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