The Impact of Actuator Device Design on Metered Dose Inhaler (MDI) In Vitro Performance

AAM 2020: GRx+Biosims Complex Workshop

Session 4: Device Considerations for Complex Drug-Device Combination Products

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Disclaimer

- *Views expressed in this presentation 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.*
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Introduction

- FDA Generic Drug User Fee Amendments (GDUFA)-funded research (U01FD004943):[1,2,3] investigation of how **formulation factors** along with **actuator design** **influence in vitro product performance for mometasone furoate (MF) suspension-based MDIs**.
  - **Delivered Dose (DD)**
  - **Aerodynamic Particle Size Distribution (APSD)**
    - **Fine Particle Dose less than 8 µm, 5 µm or 2 µm (FPD<8µm, FPD<5µm, FPD<2µm)**
  - **Spray Pattern (SP)**
    - **Ovality and Area**
  - **Plume Geometry (PG)**
    - **Angle and Width**

[1] Bielski, Elizabeth, et al. *2019 APPS PharmSci 360 Annual Meeting*, AAPS ePoster Library. Bielski E. 11/05/19; 280985; T0930-01-04

[2] Bielski, Elizabeth, et al., *Respiratory Drug Delivery 2020;* 2020, 3: 497-502.

[3] Dhapare, Sneha, et al., *Respiratory Drug Delivery 2020*; 2020, 3: 503-508.

Methods: MF MDI Formulations and Actuator Variants

Mometasone Furoate (MF) Formulations Factors*			
Formulation	MF 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

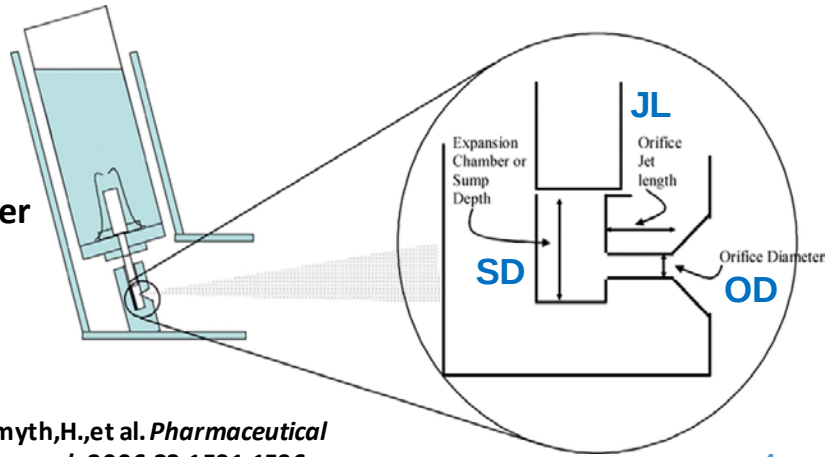
* Actual results, not targets

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

EtOH: Ethanol
OA: Oleic Acid

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

OD: Orifice Diameter
JL: Jet Length
SD: Sump Depth



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Smyth,H.,et al. *Pharmaceutical Research*,2006,23:1591-1596.

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>.[1]
  - ***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#**	**MediumP**	**0.2**	**2**
OPC*	**70#**	**MediumP**	**0.2**	**2**
VCU*	**70#**	**MediumP**	**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, <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.

Bielski, Elizabeth, et al., *Respiratory Drug Delivery 2020;* 2020, 3: 497-502.

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
  - *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%

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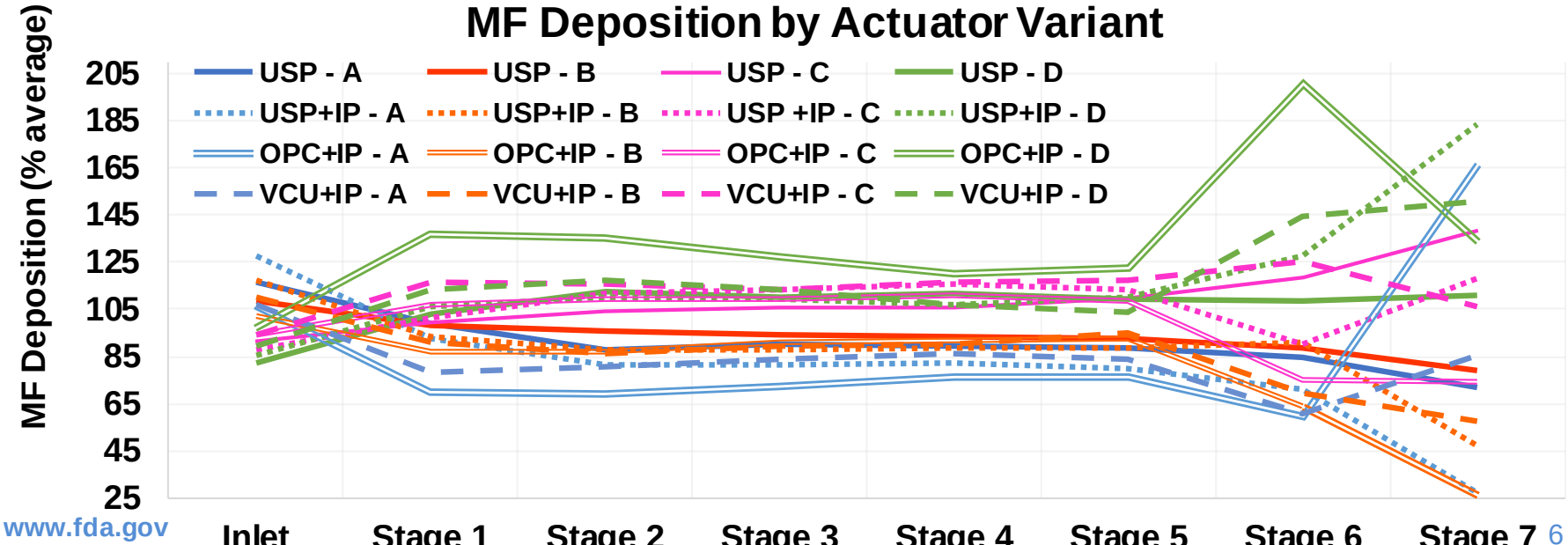
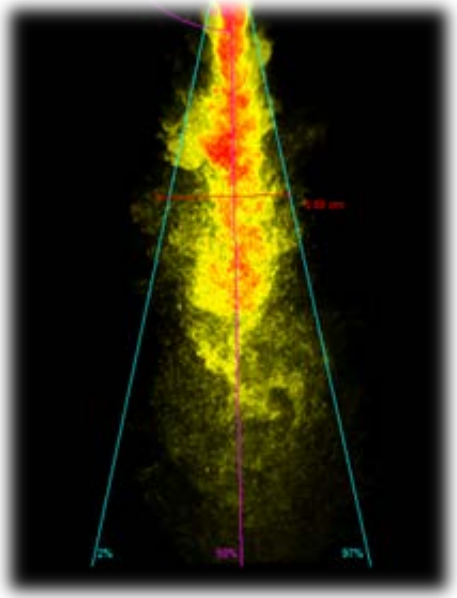


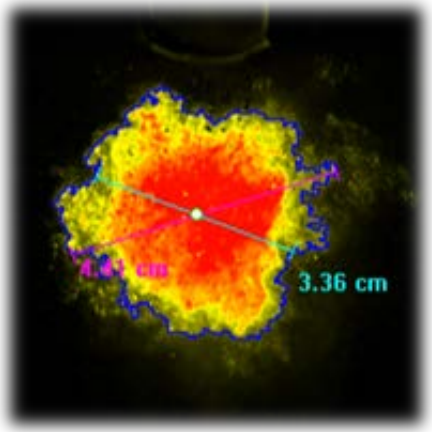
Methods: Spray Pattern (SP) and Plume Geometry (PG)

- **SP and PG method:**
  - Laser-based Envision Pharma R&D System (Oxford Lasers Ltd, Oxon, UK)
  - Automated pneumatic actuation
  - 6 cm distance from the actuator mouthpiece
- **SP measurements:**
  - ***Ovality and Area***
- **PG measurements:**
  - ***Angle and Width***



Plume Geometry

Spray Pattern



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Results: SP and PG – Actuator Variants

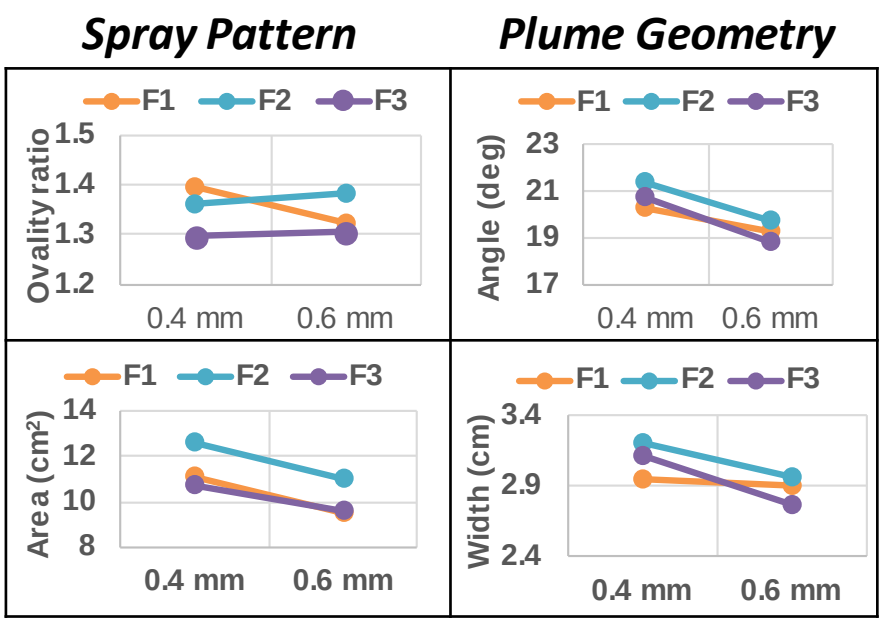
ANOVA p-values for Spray Characteristics

Formulation or Actuator Parameter	Spray Characteristic p-value			
	Ovality	**Area**	**Angle**	**Width**
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.

- **OD had no statistical effect on SP and PG**
- **SD influenced SP ovality and PG angle**
- **JL most significant influence on SP and PG**
  - *SP Area, PG Angle, and PG Width*
- **JL increased from 0.4 mm to 0.6 mm led to a decrease SP area, PG angle and PG width**

Impact of Jet Length (JL) on SP and PG



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Conclusions

- ***Actuator parameters influenced the in vitro performance of MF MDIs***
  - Delivered Dose was **not influenced** by the different formulation factors or actuator variants.
  - **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.
    - Consistent across all MF MDI formulations and APSD testing conditions.
    - F2 more affected by change in OD → more critical for formulations with lower API PSDs (finer APIs).
  - **OD** had **no significant effect** on any of the spray characteristics (SP and PG) while **SD** also showed some significant effects on spray pattern ovality and plume geometry angle.
  - **JL** were found to have **most significant effect** on SP and PG measurements
    - JL increased from 0.4 mm to 0.6 mm led to a decrease SP area, PG angle and PG width for all formulations evaluated.
- ***This work demonstrates importance of actuator design along with formulation factors and their interactions to influence in vitro product performance.***


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