THE EFFECTS OF FORMULATION FACTORS AND ACTUATOR DESIGN ON METASONE FUROATE METERED DOSE INHALER PERFORMANCE

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Introduction

Metered dose inhalers (MDIs) are complex drug-device combination products widely used as portable delivery systems to treat a variety of pulmonary disorders including asthma and chronic obstructive pulmonary disease (COPD). A typical MDI (Figure 1) consists of a canister, a metering valve, and an actuator-mouthpiece.[1,2] The formulation within the cannister containing the active pharmaceutical ingredient (API) can be either the form of a solution (API dissolved in liquid propellant) or a suspension (API particles dispersed in liquid propellant) along with inactive ingredients (e.g., co-solvents and surfactants).[3]

Product performance for MDIs depends on a myriad of factors including formulation characteristics and device design. Formulation factors that can vary include physiochemical properties of the API, and the amount and nature of excipients.[2,4] MDI device geometry can vary including valve metering chamber volume, actuator nozzle orifice diameter, actuator sump depth and actuator orifice jet length.[2,4] Currently, the impact of formulation factors on MDI performance and its interaction with actuator design is not fully understood. Therefore, the purpose of this work is to investigate how formulation factors along with actuator parameters influence in vitro product performance for mometasone furoate (MF) MDIs.

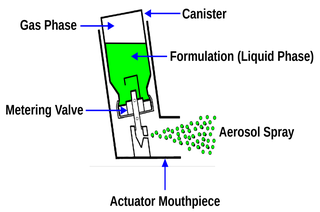

Figure 1. Schematic of a typical MDI.[2]

Methods

Formulation of MF MDIs: Three suspension-based MF MDIs were manufactured with changes in API particle size distribution (PSD D50) (Figure 2), oleic acid (OA, surfactant), and ethanol content (EtOH, cosolvent) (Table 1) in HFA-227 propellant. Each of the three MF MDI formulations were characterized for API content, ethanol content, oleic acid content, and moisture content.

Table 1: Formulation characteristics of MF MDIs.

MF Formulation Characteristics			
Formulation	API PSD D50 (μm)*	EtOH (% w/w)	OA (% w/w)
#1	1.69	0.52	0.0043
#2	1.10	2.10	0.0151
#3	1.69	1.30	0.0104

* PSD (Particle Size Diameter) D50: Particle diameter at 50% in the cumulative distribution (median diameter)

Figure 2. Scanning Election Microscopy images of MF API.

Actuator variants: Four actuator variants (Figure 3) differing in orifice diameter (OD), jet length (JL), and sump depth (SD) were encompassed in the analysis to evaluate formulation-actuator interactions (Table 2).

Table 2: Actuator variant parameters.

Actuator Parameters			
Actuator Variant	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

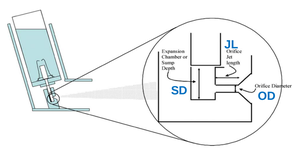

Figure 3. Design of MDI actuator orifce.[5]

In Vitro Characterization:
The MF MDIs (all 12 combinations of 3 formulations and 4 actuators) were characterized and evaluated by a variety of in vitro tests (below) to assess product performance. Statistical analyses on the data (ANOVA) were conducted to determine the effects of formulation factors and actuator design.

Delivered Dose (DD) was based on the mass deposited in a CareFusion AirLife EU303 filter (F) following the method described in USP <601>.

Aerodynamic Particle Size Distribution (APSD) was evaluated using a Next Generation Impactor (NGI) with an USP induction port (IP) with coated cups and back-up filter (CareFusion AirLife EU303) added after the micro-orifice collector (MOC). *NGI Delivered Dose (NGI DD)* was determined as the sum of drug collected by the NGI (IP to F). Calculations of Fine Particle Fraction (FPF<8μm, FPF<5μm, FPF<2μm) included linear interpolation of the cumulative distribution function normalized to NGI DD. *Fine Particle Mass (FPM < 8μm, FPM < 5μm, FPM < 2μm)* was calculated by multiplying the mass deposited on NGI with the FPF.

Ex-Anatomical Throat Mass was evaluated using a medium size oropharyngeal consortium (OPC) throat model with mass collected on a CareFusion AirLife EU303 filter.

All these in vitro characterization tests (DD, APSD, and Ex-anatomical Throat Mass) were run at a flow rate of 30 L/min.

Results

APSD Parameters by Formulation Changes

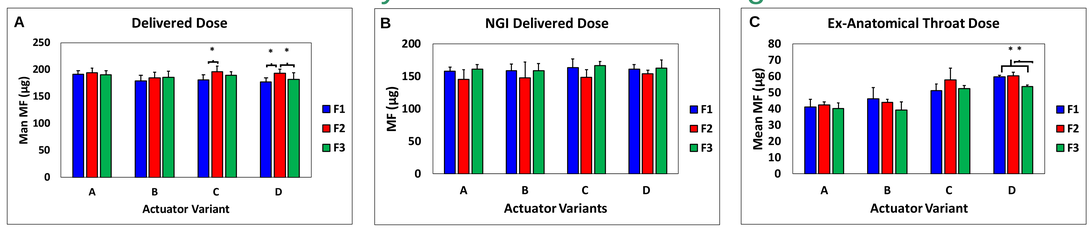

Figure 4. (A) DD, (B) NGI DD, and (C) Ex-Anatomical Throat Mass for 3 formulations and 4 actuator variants (mean ± STD, *p<0.05, ANOVA: Tukey's Multiple Comparison Test); MF: Mometasone Furoate, F1: Formulation #1, F2: Formulation #2, and F3: Formulation #3.

- *Statistical differences in formulations were seen in DD and Ex-Anatomical Throat Mass, but not in NGI DD, using the same actuator variant.*
- *Statistical differences in formulations were most apparent in DD and Ex-anatomical Throat Mass with use of actuator variant D.*

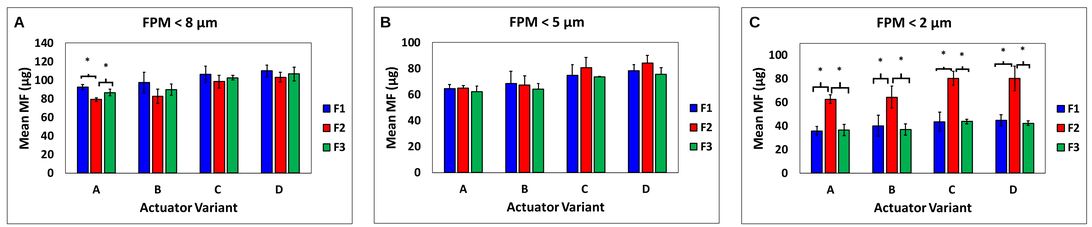

Figure 5. (A) FPM < 8μm, (B) FPM < 5μm, and (C) FPM < 2μm for 3 formulations and 4 actuator variants (mean ± STD, *p<0.05, ANOVA: Tukey's Multiple Comparison Test); MF: Mometasone Furoate, F1: Formulation #1, F2: Formulation #2, and F3: Formulation #3.

- *Statistical differences in formulations were seen in FPM < 8 μm and FPM < 2 μm, but not in FPM < 5 μm, using the same actuator variant.*
- *No statistical changes were seen between Formulation #1 and Formulation #3 for FPMs, which suggests that OA and EtOH concentrations may not significantly impact FPM.*
- *A lower API PSD in Formulation #2 mostly likely accounts for increased extra fines (FPM < 2 μm).*

APSD Parameters by Actuator Changes

Table 3. Results (p-values) from ANOVA assessing effects by actuator dimensions, by parameter and formulation. Statistically significant p-values < 0.05 are marked red.

Parameter	Formulation	OD	JL	SD
Delivered Dose	#1	0.0636	**0.0273**	0.1985
	#2	0.1802	0.1202	0.3408
	#3	0.5464	0.0784	0.6124
NGI Delivered Dose	#1	0.4532	0.9195	0.7832
	#2	0.6162	0.6683	0.8402
	#3	0.4068	0.6043	0.9246
Ex-Anatomical Throat Mass	#1	**0.0025**	**0.0386**	0.5076
	#2	**0.0001**	0.4214	0.8669
	#3	**0.0001**	0.8960	0.5721
FPM < 8 μm	#1	**0.0207**	0.3881	0.9072
	#2	**0.0003**	0.2621	0.8686
	#3	**0.0006**	0.2767	0.8773
FPM < 5 μm	#1	**0.0352**	0.4065	0.9582
	#2	**0.0014**	0.4166	0.8930
	#3	**0.0012**	0.4145	0.9969
FPM < 2 μm	#1	0.1338	0.5056	0.7079
	#2	**0.0072**	0.9037	0.8084
	#3	**0.0199**	0.5332	0.5507

- *Jet length (JL) and sump depth (SD) had no statistical significant effects on any of the assessed APSD parameters (the two p-values < 0.05 for JL may be considered random findings due to multiplicity).*
- *Orifice diameter (OD) had no effect on the DD, but it had a strong effect on the plume exiting the throat (Ex-Anatomical Throat Mass and FPMs)*
- *The results were very consistent between formulations, indicating that these effects (and lack thereof) are formulation independent. The size of the significant effects might however differ between formulations (see Table 4).*

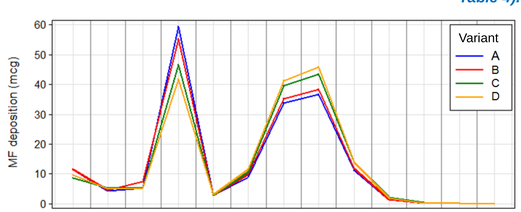

Figure 6. Mean MF deposition by actuator variant on the NGI; AD: Adaptor, ST: Stem, ACT: Actuator, IP: induction Port, S1-S7: Stage 1- Stage 7; MOC: micro-orifice collector F: Filter

OD was the most influential actuator characteristic for MF deposition on the NGI. Smaller OD (actuators C and D) allowed for increased deposition on stages S3 and S4, and decreased deposition on the IP.

Table 4. Least Square (LS) Means (μg) for each actuator dimension and factor level, by parameter and formulation. Statistically significant effects are marked red.

Parameter	Formulation	Orifice Diameter		Jet Length		Sump Depth	
		0.35 mm	0.48 mm	0.4 mm	0.6 mm	1.2 mm	1.5 mm
Delivered Dose	#1	179.1	185.5	**178.3**	**186.3**	184.4	180.2
	#2	194.8	189.6	189.1	195.3	194.0	190.4
	#3	185.8	187.8	183.7	190.0	186.0	187.6
NGI Delivered Dose	#1	162.5	158.1	160.0	160.6	159.5	161.1
	#2	151.4	146.7	151.0	147.1	150.0	148.1
	#3	164.7	159.9	160.8	163.8	162.0	162.6
Ex-Anatomical Throat Mass	#1	**55.4**	**43.7**	**52.9**	**46.2**	50.5	48.6
	#2	**59.0**	**43.1**	52.0	50.0	51.2	50.8
	#3	**53.0**	**39.7**	46.4	46.2	46.9	45.8
FPM < 8 μm	#1	**108.2**	**95.0**	103.7	99.5	101.3	101.9
	#2	**100.9**	**80.9**	92.9	88.8	91.1	90.6
	#3	**104.8**	**88.3**	98.3	94.7	96.8	96.3
FPM < 5 μm	#1	**79.3**	**68.9**	75.9	72.3	74.0	74.2
	#2	**84.1**	**67.4**	77.2	74.2	76.0	75.5
	#3	**77.1**	**65.4**	72.3	70.2	71.2	71.2
FPM < 2 μm	#1	9.0	7.7	8.6	8.1	8.2	8.5
	#2	**17.1**	**13.2**	15.3	15.1	15.0	15.3
	#3	**9.0**	**7.6**	8.1	8.5	8.2	8.5

- *The statistically significant effects by OD were in the range of 14-37%*, with larger results for the smaller OD of 0.35 mm.*
- *The numerically strongest effect was seen on the Ex-Anatomical Throat Mass (range of 27-37%*).*
- *The results are consistent between formulations but with a clearly stronger effect on Formulation #2 (range of 25-37%*) as compared to Formulation #1 (range of 15-27%*) and Formulation #3 (range of 14-34%*). This may indicate that design and control of the spray OD is more critical for suspension-based MDIs with finer APIs.*

* Calculation as follows: [(LS mean of smaller parameter - LS mean of larger parameter) / (LS mean of larger parameter) x 100%].

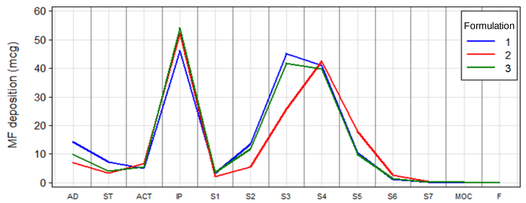

Figure 7. Mean MF deposition by formulation on the NGI; AD: Adaptor, ST: Stem, ACT: Actuator, IP: induction Port, S1-S7: Stage 1- Stage 7; MOC: micro-orifice collector F: Filter .

- *Formulation #2 had significantly extra fine particle mass (FPM < 2 μm) compared to Formulations #1 and #3, allowing for differences in MF deposition on the lower NGI stages and suggesting that lower API PSD in Formulation #2 may influence MF deposition.*
- *Increase in MF deposition on IP and decrease on adaptor and stage S3 were seen for Formulation #3 compared to Formulation #1 suggesting that ~ 2-fold increase in OA and EtOH may inhibit MF deposition.*

Conclusions

- Statistical differences in formulations were seen in DD and Ex-Anatomical Throat Mass and were most apparent when using Actuator Variant D.
- Formulation #2 had significantly extra fine particle mass (FPM < 2μm) compared to Formulations #1 and #3, allowing for increased MF deposition on the lower NGI stages, which is most likely due to lower API PSD in Formulation #2.
- The influence of OA and EtOH warrant further investigation to understand their specific impacts on MF MDI aerosol performance.
- JL and SD had no effect on MF MDI aerosol performance within the ranges studied.
- OD had no effect on DD but a strong effect on plume exiting the throat (FPMs and Ex-Anatomical Throat Mass) and is formulation independent.
- The change in OD led to statistical significant effects in FPMs and Ex-Anatomical Throat Mass, ranging 14-37%* for all formulations. OD had stronger effect on Formulation #2 compared to Formulations #1 and #3, which indicates that control of OD may be more critical for formulations with finer APIs (lower API PSD).
- Overall, formulation factors and actuator design have shown to influence in vitro product performance of suspension-based MF MDIs. The possible effects of varying these characteristics must be studied on a case-by-case basis.
- Results from this work allow for improvement in quality by design (QbD) approaches to streamline MDI drug product development (both brand-name products and their generic counterparts) and provide insights on how to control MDI drug product performance parameters to achieve a desired performance profile.

References

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