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

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Abstract

Introduction: Metered dose inhalers (MDIs) have been utilized to treat a variety of lung disorders. The major influence on product performance for MDIs include key factors such as the physiochemical properties of the drug, the amount and type of excipients, and device properties. The influence of formulation factors and actuator design on MDI performance is not well understood. Therefore, the purpose of this work is to investigate how formulation factors along with actuator parameters influence the in vitro aerosol performance for suspension-based mometasone furoate (MF) MDIs. **Methods**: Three suspension-based MF MDI formulations were manufactured with changes in active pharmaceutical ingredient (API) particle size, oleic acid (surfactant) and ethanol content (cosolvent) relative to the levels of the commercial MDI product Dulera® (formoterol fumarate, mometasone furoate) Inhalation Aerosol. Four actuator variants similar to the Dulera® actuator design but differing in orifice diameter, jet length, and sump depth were included in the analysis. The MF MDIs were characterized, in vitro tests conducted, and data statistically evaluated to assess the impact of formulation factors, actuator design, and formulation-actuator interactions on aerosol performance. **Results**: Delivered dose (dose exiting the actuator) was not significantly affected by formulation or actuator variants. However, the formulation with lowest API particle size, and highest oleic acid and ethanol content had a statistically significant effect on fine particle dose less the 2µm (FPD<2µm; i.e., dose reaching the deep lungs), causing it to be 1.6-2.2 times higher when compared to the other two formulations, which may be due to the smaller API particle size within this formulation. Regarding actuator design, orifice diameter had a strong effect on the fine particle doses (FPDs, i.e., doses reaching different regions of the lung) for all formulations tested; a decrease in orifice diameter from 0.48 to 0.35 mm increased FPDs between 14-52% and most influential on the formulation containing the lowest API particle size. **Conclusions**: Overall, formulation factors and actuator design influenced the in vitro aerosol performance of suspension-based MF MDIs. Results from this work provide insights on how to modulate drug product parameters to achieve the desired in vitro aerosol performance for bioequivalence assessment.

Introduction

Metered dose inhalers (MDIs) are complex drug-device combination products widely utilized to treat a variety of pulmonary disorders including asthma and chronic obstructive pulmonary disease (COPD).[1,2] A typical MDI consists of a canister, a metering valve, and an actuator mouthpiece.[1,2] The formulation within the canister containing the active pharmaceutical ingredient (API) can be either 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 of MDIs depends on a myriad of factors such as the physiochemical properties of the API, the amount and nature of excipients, and device design.[2,4] Previous FDA Generic Drug 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.[4,5,6] The purpose of this work is to extend this research by investigation of how formulation factors, along with actuator designs, influence in vitro aerodynamic product performance for mometasone furoate (MF) suspension-based MDIs.

Materials and Methods

MF MDI Formulations: Three suspension-based MF MDI formulations (F1, F2, F3) were manufactured with differences in API particle size (D50) (Figure 1), oleic acid (OA, surfactant) and ethanol (EtOH, cosolvent) content in HFA-227 propellant (Table 1). Two formulations were predicted to have similar *in vitro* aerodynamic product performance based on a previous formulation design space evaluation,[6] and one would differ while still maintaining similar formulation levels to the commercial MF-containing MDI product Dulera®.

Table 1. 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

* Actual results, not targets

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

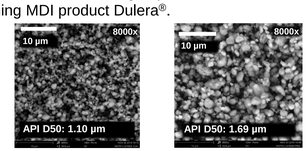

Figure 1. Scanning Election Microscopy images of MF API.

Actuator Variants: Four plastic actuator variants (Table 2) were purchased (RPC Formatec), which were similar to the Dulera® actuator design but differing in orifice diameter (OD), jet length (JL), and sump depth (SD) parameters (Figure 2).

Table 2. 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

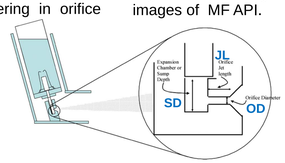

Figure 2. Design of MDI actuator parameters.[7]

In Vitro Characterization: ***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) (Copley Scientific) described in USP <601>[8] and Table 3. More realistic APSD testing was conducted using a medium inhalation profile (IP) generated by a breath simulator (F-SIG 6300 by AB FIA, Sweden). *NGI DD* was determined as the sum of API collected within the NGI (USP or M-T model to filter). 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 Dose (*FPD<8µm*, *FPD<5µm*, *FPD<2µm*) was calculated by multiplying the NGI DD with the FPF. All data were statistically evaluated by ANOVA (GraphPad Prism 7.0d Software). Means were considered statistically significant if $p < 0.05$.

Table 3. 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.*[9] and shape parameters by Longest *et al.*[10]

Results and Discussion

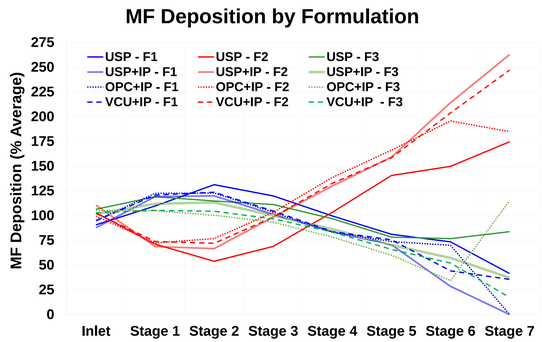

Figure 3. MF deposition (% average) on NGI stages by formulation (F1, F2 and F3) and APSD testing condition from all actuator variants. The % average for each APSD testing condition (e.g., USP+IP) = (mean MF deposition of each NGI stage by formulation) / (mean MF deposition of that NGI stage for all formulations) x 100%. USP: APSD testing using USP induction port and compendial method as described in USP <601>;[8] USP+IP / OPC+IP / VCU+IP: APSD testing using of IP with USP induction port or M-T model.

- ***DD (~180-200 µg) was not affected by formulation or actuator variants (not pictured).***
- ***NGI DD, FPD<8µm and FPD<5µm had some slight statistically significant changes between MF MDI formulations.***
  - ***Not consistent between actuator variants or APSD testing conditions.***
- ***Formulation had a statistically significant effect on FPD<2µm (Figure 3).***
  - ***1.6-2.2 times higher for F2 compared to F1 and F3.***
  - ***May be due to the smaller API D50 in F2 (Table 1).***
  - ***This result was consistent across all actuator variants and APSD testing conditions.***
- ***The direct influence of OA and EtOH content could not be assessed due to limitations in experimental design.***

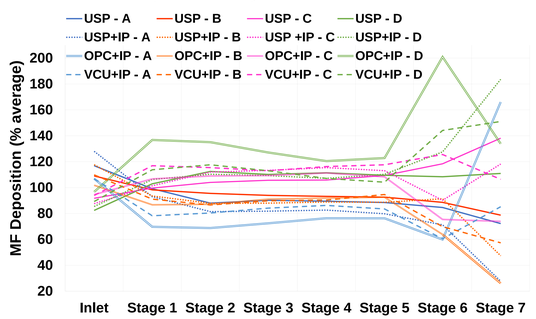

Figure 4. MF deposition (% average) on NGI stages by actuator variant (A, B, C, D) and APSD testing condition from all formulations. The % average for each APSD testing condition (e.g. USP+IP) = (mean MF deposition of each NGI stage by actuator) / (mean MF deposition of that NGI stage for all actuators) x 100%. USP: APSD testing using USP induction port and compendial method as described in USP <601>;[8] USP+IP / OPC+IP / VCU+IP: APSD testing using of IP with USP induction port or M-T model.

- ***OD produced the strongest effects on FPDs.***
  - ***Demonstrated by increased MF deposition on lower NGI stages for actuators C and D which have smaller OD compared to actuators A and B (Figure 4)***
  - ***Consistent across all three formulations and APSD testing conditions (compendial and more realistic).***
- ***Small effect of a shorter JL (Figure 4).***
  - ***A slight increase of MF deposition on lower stages of the NGI was observed from actuator D compared to C, and actuator B compared to A.***

Table 4. Least Square (LS) Means (µg) by actuator OD dimension (0.35 vs. 0.48 mm), formulation (F1, F2, F3) and APSD testing condition (USP, USP+IP, OPC+IP, VCU+IP) for each FPD. % Change by OD was calculated. Statistically significant p-values < 0.05 are marked red (ANOVA).

Parameter	F	USP			USP+IP			OPC+IP			VCU+IP		
		0.35 mm	0.48 mm	% Change	0.35 mm	0.48 mm	% Change	0.35 mm	0.48 mm	% Change	0.35 mm	0.48 mm	% Change
FPD<8µm (µg)	F1	108.2	95.0	+14	101.6	87.5	+16	38.9	27.2	+43	67.3	51.6	+30
	F2	100.9	80.9	+25	96.3	74.1	+30	40.9	28.4	+44	65.3	48.9	+34
	F3	104.8	88.3	+19	104.5	80.0	+31	35.1	23.0	+53	61.4	46.3	+33
FPD<5µm (µg)	F1	79.3	68.9	+15	66.4	57.3	+16	28.2	20.3	+39	47.4	37.5	+26
	F2	84.1	67.4	+25	75.9	58.1	+30	34.1	24.1	+42	53.7	40.7	+32
	F3	77.1	65.4	+18	69.5	53.2	+31	26.2	17.4	+51	44.9	34.1	+31
FPD<2µm (µg)	F1	9.0	7.7	+18	8.7	7.6	+15	4.7	3.5	+35	7.0	5.9	+18
	F2	17.1	13.2	+29	16.8	12.8	+32	8.8	6.4	+37	13.0	10.0	+30
	F3	9.0	7.6	+19	9.5	7.3	+30	4.5	2.9	+52	7.2	5.3	+34

$$(\%\ \text{Change}) = \left[\frac{(LSmean_{OD0.35mm} - LSmean_{0.48mm})}{LSmean_{0.48mm}} * 100\%\right]$$

- ***The reduction in OD from 0.48 to 0.35 mm caused significant increases in FPDs (Table 4).***
  - ***FPD<8µm: 14-53%.***
  - ***FPD<5µm: 15-51%.***
  - ***FPD<2µm: 14-52%.***

Conclusions

- 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 parameters.
- The MF MDI F2 produced significantly finer 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 – compendial (USP) and more realistic [incorporation of an IP with USP induction port (USP+IP), OPC M-T model (OPC+IP) and VCU M-T model (VCU+IP)] – were consistent for the different formulations (F2 being most influential compared to F1 and F3) and actuators (OD being most influential actuator parameter).
- The systematic investigation of this work may enhance QbD approaches that may streamline development of branded and generic MDI products and provide insights on how formulation factors and device parameters can be changed to achieve the desired in vitro performance.

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- In memory of Dr. Dennis Sandell, deceased October 29, 2020.