Factors Influencing Plume Characteristics of Flovent® HFA Following Passage through Bio-Relevant Mouth-Throat Models

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Abstract

BACKGROUND AND PURPOSE: Changes in a metered dose inhaler's (MDI) performance characteristics, such aerosol droplet size distribution (DSD) during the passage through the mouth-throat region, can be critical for regional lung deposition and performance. This study evaluated the effect of various factors on DSD of a model suspension MDI, Flovent® HFA (fluticasone propionate inhalation aerosol metered, 0.11 mg/inh), exiting bio-relevant mouth-throat (MT) models. METHODOLOGY: The influence of five different factors including ten different MT models (MTs: USP [metal, (Me) and plastic, (P)], Alberta Idealized Throat, AIT [Me and P], Oropharyngeal Consortium, OPC [P; small (S), medium (M) and large (L)] and Virginia Commonwealth University, VCU [P; small (S), medium (M) and large (L)]), two types of MT model coatings (CT: Brij solution and silicone), two MT insertion angles (IAs: normal and tilted), three inhalation profiles (IP: weak, medium and strong) and two MDI firing points (FP: 0.2 and 0.5 s after the start of IP) were studied on the volume weighted 10th (Dv10), 50th (Dv50) and 90th (Dv90) percentile distribution (µm) of the aerosol's DSD and average transmission (AT, %). RESULTS: Overall, Dv50 reduced after passage through the different MT models, which may be attributed to the propellant evaporation during this passage. Substantial differences were observed between different sizes of MT models (i.e., S, M and L models), but differences were less pronounced between different MT models of the same size (i.e., USP, AIT, VCU M, OPC M). Differences in Dv50 after the MT were also observed with different MT materials (e.g., AIT Me vs. AIT P). The effects of MT and CT were the most predominant for all the measurements. Silicone coating showed higher Dv50, while a higher degree of variability was observed with Brij coating (except for AIT, medium). Overall, IA and FP did not have significant effects on the droplet size and AT (except for Dv90). CONCLUSIONS: The selection of the MT model and its size have the most impact on the change in DSD followed by the CT. However, IA and FP did not show any notable effect on the change in DSD during passage through MT models.

Introduction

Changes in the performance characteristics, such as the droplet size distribution (DSD) of the aerosol emitted from metered dose inhalers (MDIs) during the passage through the mouth-throat region, play an important role in governing lung deposition and subsequent in vivo performance. This information is not generated by the current in vitro tests standardly used for characterization of aerodynamic particle size distribution (APSD) of MDIs, where aerosol particle properties are generally measured at the MDI mouthpiece.

As the lung deposition of MDI products is governed by the particle properties exiting the mouth-throat region, this study sought to assess the effect of various factors on DSD of a model suspension MDI, Flovent® HFA (fluticasone propionate inhalation aerosol metered, 0.11 mg/inh), exiting bio-relevant mouth-throat (MT) models.

Materials and Methods

A total of five different factors were studied using reduced factorial experimental design.

- **MT models (Total 10)**:
  - *USP [metal, (Me) and plastic, (P)]*
  - *Alberta Idealized Throat, AIT [Me and P]*
  - *Oropharyngeal Consortium, OPC [P; small (S), medium (M) and large (L)]*
  - *Virginia Commonwealth University, VCU (P; S,M,L)*
- **MT model coatings (CT, 2 types):**
  - *Brij solution*
  - *Silicone*
- **Insertion angles for the MT models (IAs, 2):**
  - *Normal*
  - *Tilted*
- **Inhalation profiles[1] (IPs, 3):**
  - *Weak*
  - *Medium*
  - *Strong*
- **MD firing points (FPs):**
  - *0.2 s after the start of IP*
  - *0.5 s after the start of IP*
- **Volume weighted 10th (Dv10), 50th (Dv50) and 90th (Dv90) percentile diameter (µm) and Average transmission (AT, %) of the aerosol emitted from Flovent® HFA were measured using laser diffraction at the following locations:**
  - *At the exit of the inhaler actuator (before; about 8 cm away from the laser beam).*
  - *At the exit of the coated anatomical throat (after).*

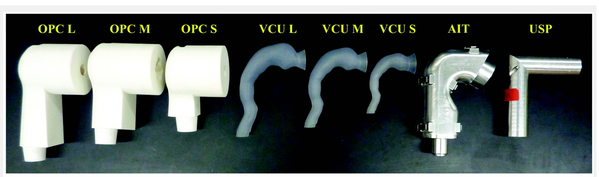

Figure 1. MT models, OPC Large (OPCL), OPC Medium (OPCM), OPC Small (OPCS), VCU Large (VCUL), VCU Medium (VCUM), VCU Small (VCUS), AIT (Medium), and USP Induction Port[1]

Results and Discussion

- Overall, Dv50 reduced after passage through the different MT models, which may be attributed to the evaporation of the propellant during this passage.
- Similar results were also observed for Dv10, Dv90 and AT.
- Substantial differences were observed between different sizes of MT models (i.e., S, M and L models), but differences were less pronounced between different MT models of same size (i.e., USP, AIT, VCU M, OPC M).
- Some differences in Dv50 after the MT were also observed when different materials i.e., plastic or metal were used (USP Me vs. USP P and AIT Me vs. AIT P).
- The MT model, IP and CT showed significant effect on Dv50, while only MT model and CT showed significant effect on AT.
- Least square means estimate showed that the effects of MT and CT were the most predominant for all the measurements.
- Overall, IA and FP did not have significant effects on the droplet size and AT (except for Dv90).
- Silicone coating showed higher Dv50 as compared to Brij coating
- A higher degree of variability was observed when Brij was used for coating (except AIT, Metal).

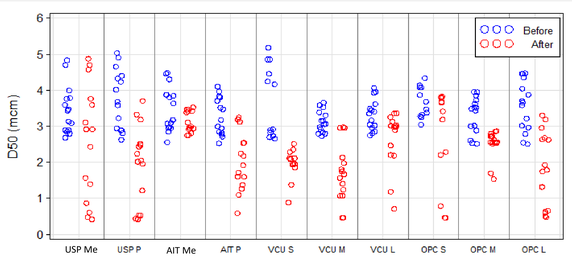

Figure 2. Dv50 at the exit of the inhaler actuator (before MT models) and at the exit of the coated anatomical throat (after MT models)

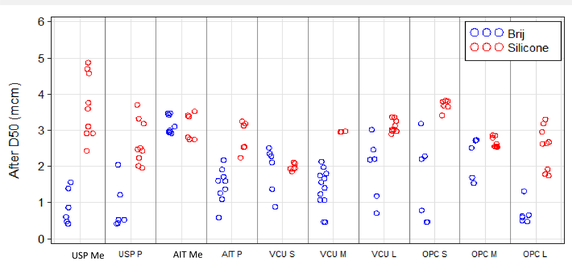

Figure 3. Effects of Brij Vs Silicone coating of MT models on Dv50 at the exit of the coated anatomical throat (after MT models)

Table 1. Summary of least square means after MT model by each factor. Max-Min (%) differences are shown in red.

Factor	Level	Dv10	Dv50	Dv90	AT
MT	USP-Metal	0.27	1.73	6.22	84.91
	USP-Plastic	0.24	1.65	6.10	84.61
	AIT-Metal	0.79	3.18	7.12	95.67
	AIT-Plastic	0.38	2.49	6.49	93.01
	VCU S	0.31	1.93	7.07	87.15
	VCU M	0.41	2.33	6.56	90.48
	VCU L	0.41	2.52	6.29	92.74
	OPC S	0.48	2.57	10.64	91.24
	OPC M	0.93	2.57	6.55	96.60
	OPC L	0.45	1.80	5.04	90.99
	Max-Min (%)	279.03	93.01	111.14	14.17
IP	Weak	0.50	2.61	8.21	91.52
	Medium	0.46	2.19	6.18	90.31
	Strong	0.44	2.02	6.04	90.38
	Max-Min (%)	13.64	29.01	36.07	1.34
FP	0.2 sec	0.50	2.40	7.32	91.16
	0.5 sec	0.44	2.15	6.30	90.32
	Max-Min (%)	13.66	11.75	16.09	0.94
IA	Normal	0.47	2.38	7.18	90.73
	Tilted	0.47	2.18	6.44	90.74
	Max-Min (%)	0.01	9.37	11.49	0.01
CT	Brij	0.36	1.69	6.01	87.86
	Silicone	0.58	2.86	7.60	93.62
	Max-Min (%)	62.67	68.83	26.43	6.55

Table 2. Summary of ANOVA p-values for measurements after MT model by each factor. Significant differences (p<0.05) are shown in red.

Parameter	MT	IP	FP	IA	CT
Dv10	<0.0001	0.5344	0.1377	0.9988	<0.0001
Dv50	<0.0001	0.0040	0.0595	0.0908	<0.0001
Dv90	<0.0001	<0.0001	0.0013	0.0085	<0.0001
AT	<0.0001	0.5834	0.4089	0.9935	<0.0001

Conclusion

- The results obtained from this study suggest that out of all the factors studied, the selection of the anatomical MT models and the type of coating have substantial impact on the change in DSD during passage through anatomical throats for Flovent® HFA.
- The systematic investigations carried out in this study have the potential to enhance the development of branded and generic suspension MDIs by considering the effects of these factors on in vitro performance and thereby provide improved understanding of in vivo effects.

Reference

1. Wei X, Hindle M, Kaviratna A, Huynh BK, Delvadia RR, Sandell D and Byron PR. In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth–Throat Models and In Vitro—In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. Dec 2018.358-371.http://doi.org/10.1089/jamp.2018.1454

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- In memory of Dr. Dennis Sandell, deceased October 29, 2020.
- This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.