Effects of Formulation and Actuator Design on Spray Velocity of Mometasone Furoate Metered Dose Inhalers

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INTRODUCTION

Drug deposition in the oropharynx and within the lungs is expected to depend on the velocity of the particles or droplets in the metered dose inhaler (MDI) spray plume [1]. However, the spray velocity of MDIs has been explored less than other spray metrics (e.g., spray pattern, plume geometry, and aerodynamic particle size distribution) and there is limited understanding of the sensitivity of spray velocity parameters (e.g., average velocity and peak velocity) to changes in formulation and/or device components [1, 2]. Recent product-specific guidances for generic solution-based MDIs have supported characterization of velocity profiles and evaporation rates for the assessment of bioequivalence [3]. To better understand the utility of spray velocity testing in the assessment of suspension-based MDI performance, this study systematically investigated the effects of changes in excipients and drug particle size distribution, and actuator orifice diameter (OD), jet length (JL) and sump depth (SD) on mometasone furoate (MF) suspension-based MDIs. The relationships between the parameters for spray velocity, spray pattern (i.e., ovality and area) and plume geometry (i.e., angle and width) as well as Next Generation Impactor (NGI) stage deposition data were also explored.

METHODS

Spray velocity was measured for 12 MF MDI formulations and actuator combinations shown in Table 1 [4] by particle image velocimetry (PIV, Envision Pharma R&D System, Oxford Lasers Ltd., Oxon, UK). The system consisted of a computer-coordinated high-speed (CMOS) camera operating at 1000 pairs of images per second and lens focused on a pre-selected field of view (FOV) illuminated by a laser light-sheet less than 1 mm thick (FireFLY, Oxford Lasers) linked to an automated MDI actuation platform which actuated all devices under constant conditions (OL pMDI Actuation Station, Oxford Lasers). Average velocity, which we defined as the average speed obtained from all particles and droplets within a 10 mm by 10 mm FOV at 1, 3, 6, and 9 cm from the exit of the pMDI actuator mouthpiece, was measured using flow field velocity analysis software (four replicate measurements on each actuator formulation combination) [5]. Peak velocity between 0–50 ms into the aerosol release event and area under the mean velocity profile between 50–100 ms were calculated from the average velocity over time curves at the four distances. Spray duration was determined from light intensity data. The canisters were primed between tests with the different actuators and between each spray, according to the labeling instructions for DULERA [6]. The results for average spray velocity (m/s), peak velocity (m/s) and area under the mean velocity profile between 50–100 ms with different formulation-actuator combinations were analyzed by analysis of variance (ANOVA) using all MF MDI manufactured batches as a fixed effect and distance between actuator and laser sheet, and actuator dimensions as covariates. Attempts were made to correlate the spray velocity with spray ovality, spray area, plume angle and plume width as well as the NGI stage deposition data, obtained from the same 12 formulation-device combinations [4, 5].

Table 1.
MF MDI formulation factors and actuator variants tested.

MF Formulation Factors*			
Formulation	API D50 (µm)**	Ethanol (% w/w)	Oleic acid (% w/w)
F1	1.69	0.53	0.004
F2	1.10	2.15	0.015
F3	1.69	1.35	0.010
Actuator Variants			
Actuator	Orifice Diameter (OD, mm)	Jet Length (JL, mm)	Sump Depth (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

*Experimentally measured results, not targets.
**D50 = the median diameter (the particle diameter at 50% in the cumulative distribution).

RESULTS AND DISCUSSION

The average velocities measured at 1, 3, 6, and 9 cm from the exit of the MDI mouthpiece for formulations F1, F2, and F3 with different actuators A, B, C, and D are shown in Figure 1. Overall, average velocity changed with the distance from the mouthpiece within a formulation-actuator combination and with different formulations and actuator combinations. Differences in spray duration were also noted for different formulation-actuator combinations. The p-values for average spray velocity, peak velocity between 0–50 ms, area under the mean velocity profile (50–100 ms) and spray duration with different MF MDI formulations and actuator covariates (OD, JL and SD) are summarized in Table 2. Average velocity was found to significantly decrease ($p < 0.05$) with the distance from the mouthpiece and a decrease in JL, while different MF MDI formulations as well as OD and SD had no significant effect ($p > 0.05$) on the average spray velocity. The peak velocity between time 0–50 ms was only shown to be significantly affected ($p < 0.05$) by the distance from the mouthpiece. In contrast, MF MDI formulations, distance from the mouthpiece, OD and JL all had a significant effect ($p < 0.05$) on the area under the mean velocity profile calculated between the time period 50–100 ms, which suggested that this velocity parameter could be more sensitive to the changes in formulation factors and actuator geometries. Spray duration was significantly different ($p < 0.05$) for different MF formulations and increased with increase in JL.

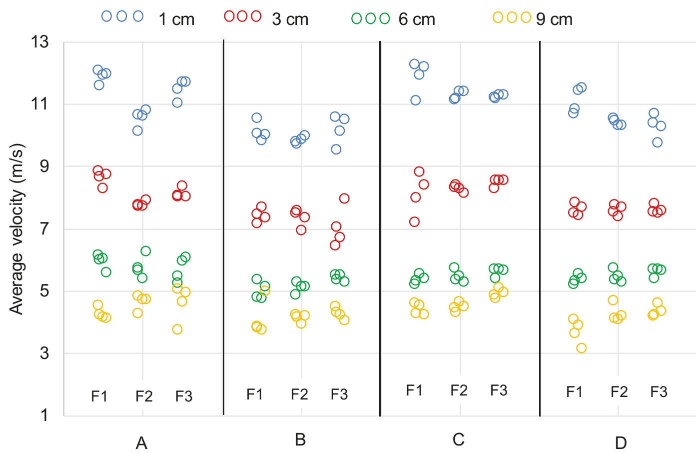

Figure 1. Average velocity (m/s; four replicates) for the three MF MDI formulations (F1, F2, F3) and four actuators (A, B, C and D) (12 combinations) at distances 1, 3, 6, and 9 cm from mouthpiece.

Table 2.

Summary of ANOVA p-values for average spray velocity, peak spray velocity, area under the mean velocity profile and spray duration. Significant differences ($p < 0.05$) are shown in red.

Study parameters	Average spray velocity (m/s)	Peak spray velocity (0–50 ms)	Area under the mean velocity profile (50–100 ms)	Spray duration (ms)
MF Formulation	0.4179	0.0984	0.0198	<0.0001
Distance	<0.0001	0.0000	0.0000	–
Orifice Diameter	0.0536	0.0522	0.0000	0.8059
Jet Length	<0.0001	0.0587	0.0119	0.0027
Sump Depth	0.5449	0.8970	0.2692	0.1826

Average spray velocity showed the highest correlation ($|r| > 0.6$) to spray pattern area and plume geometry angle, particularly for distances closer to the mouthpiece (Table 2). Spray velocity increased with decrease in spray area, plume angle and width, which suggests that spray velocity and spray shape measurements (spray pattern and plume geometry) may serve as analogous tests for characterizing the spray. No significant correlations were seen between spray velocity and NGI stage deposition data. Spray velocity (FOV area of 80 × 80 mm; global velocity), has been previously shown to correlate with the fine particle fraction for beclomethasone dipropionate solution MDI [5]. Accordingly, further evaluation of the relationship between APSD parameters (e.g., fine particle fraction, mass median aerodynamic diameter and impactor stage mass) and spray velocity parameters for the MF suspension MDI is warranted. Apart from the spray velocity parameters studied in this work, global spray velocity [5] and plume front velocity [7] may also be explored to evaluate their sensitivity in characterizing potential differences in MDI spray velocity.

Table 3.

Summary of correlation of average spray velocity to spray pattern (ovality and area) and plume geometry (angle and width) measurements. Pearson's Correlation Coefficient (|*r*|) values greater than 0.6 are shown in red.

Spray parameters	Average spray velocity at a specific distance from the mouthpiece			
	1 cm	3 cm	6 cm	9 cm
Ovality	0.02	-0.10	-0.29	-0.29
Area	-0.76	-0.68	-0.71	-0.48
Angle	-0.89	-0.91	-0.71	-0.56
Width	-0.50	-0.68	-0.31	-0.42

CONCLUSIONS

MF suspension-based MDI formulations with different drug particle size distributions and concentration of excipients (ethanol and oleic acid) exhibited differences in certain spray velocity parameters (i.e., area under the mean velocity profile (50–100 ms), spray duration), while other velocity parameters (i.e., average spray velocity, peak spray velocity) were found to be unaffected. MDI actuator parameters (JL and OD) had significant effects on average spray velocity and spray duration of MF MDI formulations studied in this work. Spray shape measurements (spray pattern and plume geometry parameters) were well correlated with average spray velocity. These results suggest that the relationship between MDI performance measures for spray velocity with deposition and spray shape is complex and warrants further study.

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