Candidate Device Selection for pMDI In-Vitro only Bioequivalence focussing on Spray Pattern and Plume Geometry Analysis

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Introduction

In-Vitro only bioequivalence (IVBE) submissions for orally inhaled and nasal drug products (OINDP) have become an increased focus for the generic pharmaceutical industry in recent years. Spray pattern (SP) and plume geometry (PG) testing can be included as in-vitro studies to help facilitate a weight of evidence based approach to submission for a pMDI product. SP and PG are well-established techniques for OINDP characterisation and are good indicators of spray performance - and therefore the likely deposition of delivered drug product. Likely bioavailability and pharmacokinetic (PK) profiles can then start to be modelled from here for many molecules.

A pMDI contains three key physical components; a canister containing the drug formulation and propellant, a metering valve which ensures the correct volume is delivered and an actuator that supports atomisation [1]. Understanding the relationship between a device and formulation with relation to spray performance is crucial to achieving reproducible performance during development and ensuring bioequivalence of a generic product. If the spray performance is investigated too late in the development process this increases the risk of issues with product bioequivalence and can result in costly product redesign and delays for approval.

Two different commercially available pressurized metered dose inhalers (pMDIs) were selected to investigate performance - these devices were a generic pMDI device and its' reference listed drug (RLD). Three additional commercially available actuators were also investigated using the canister from the generic pMDI device to examine the impact of actuator selection on product performance. SP and PG were analysed for a full range of actuator/canister combinations along with force to actuate, spray duration and spray intensity.

Method

In this study, the Proveris SprayVIEW® was utilised to characterise SP and PG produced by the pMDIs.

SP is defined as the cross-sectional area perpendicular to the axis of the spray and is measured at two set distances from the mouthpiece of the device. Key measurements parameters include Dmax, Dmin, Ovality and Area. The US FDA guidelines state SP analysis should be performed using time averaged images over the duration of a single spray [2].

PG is defined as the side view of the plume parallel to the axis of the plume and is measured at a set distance from the mouthpiece of the device. Key measurements parameters include the plume angle and width. The US FDA guidelines state PG analysis should be performed for a single time point when the spray is fully developed, and not be time averaged images over the duration of a single spray [2].

In this study two commercially available pMDIs which were a reference listed drug (RLD) and associated generic product (containing the same APIs, dosage, and propellant), were analysed in triplicate on three devices of a single batch. SP was performed at two distances; PG was performed at one distance and actuation measurements were performed. Canister B was also placed into actuator A, C, D and E and each combination was analysed in triplicate for one device per actuator/canister combination.

Results and Discussion

Actuator A was analysed with both Canister A and Canister B and gave comparable results which a T-Test showed were statistically similar - this suggests the change in canister has limited effect. The remaining actuators examined did demonstrate impact on performance and this was more visibly seen for the SP area.

When Canister B was used Actuator D produced the largest SP area whereas Actuator C produced the smallest area. Compared to Actuator B a T-Test showed these actuators were statistically different, at the furthest distance from the laser the same trend in SP area is observed (Figure 1 and Table 1).

The PG analysis was processed for a single time point when the spray was fully developed and still attached to the actuator tip (Table 1). The fully developed spray at a single timepoint measures the width and angle when the spray is at optimal performance. Variability within the PG data generated for the Actuator/canister combinations tested in triplicate was observed. By taking a single timepoint at the highest intensity when the spray is fully developed the PG appears to not be as sensitive to the changes in actuator as for SP, however the data are somewhat variable (Figure 2).

The PG was also processed using time averaged images over the duration of a single spray. The PG data generated for this processing method (Figure 2) show less variability in the data and reveal a clearer relationship between actuator and performance. The PG width data also show a similar trend to the change in SP area previously seen. The averaged processing gave an indication of the performance across the sprays lifetime.

Spray variation over time can be visualised by recording the light intensity in the field of view during the data collection period, allowing a more complete characterisation of spray performance throughout the event. Two different pMDIs can produce circular SPs but visual comparison of the spray intensity can give information on the duration and uniformity of the spray - this is essentially a measure of SP variation over time. When the same actuator is used but with different canisters the spray intensity graphs are similar, however when the same canister was used in different actuators the spray intensity are visually different suggesting the actuator is driving spray intensity variation rather than the can, valve, or formulation (Figure 3).

Canister A and B in Actuator A showed comparable spray durations at both SP distances, and Canister B in the other actuators showed a range of spray durations suggesting that the actuator used drives the variation in spray duration as opposed to the canister.

pMDI 2 measured a larger force to actuate than pMDI 1 (Table 2). When Canister B was tested in Actuator A it gave a more similar force to actuate data as pMDI 1, which suggests the force to actuate value is driven by the actuator and valve used.

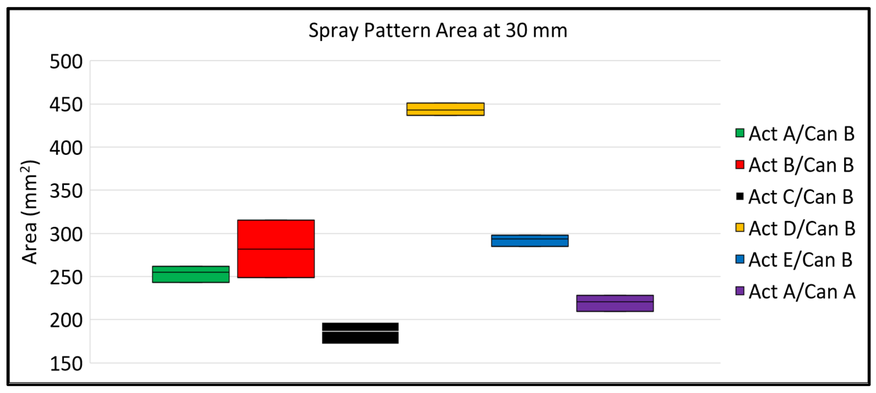
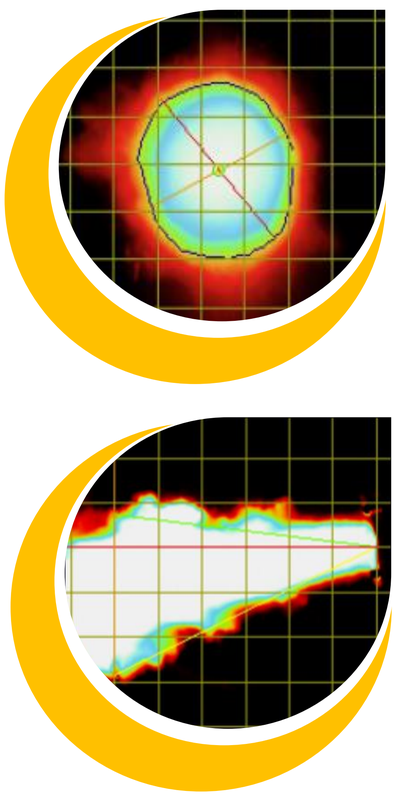
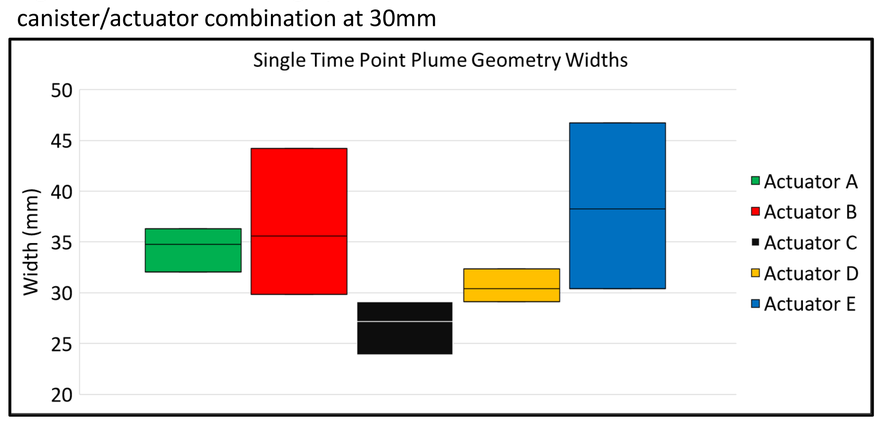
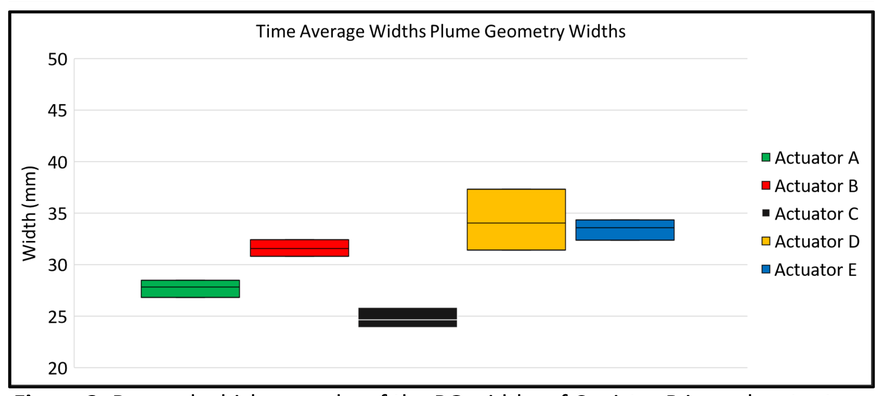


Figure 1: Box and whisker graphs of the SP mean area for each canister/actuator combination at 30mm







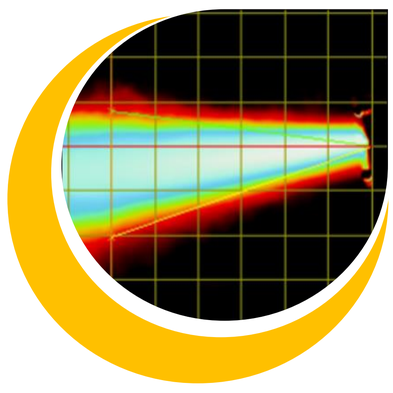


Figure 2: Box and whisker graphs of the PG widths of Canister B in each actuator when processed at a single time point and a time average.

Distance	Canister	Actuator	Spray Pattern					Plume Geometry		Mean Actuation Force (kg)
			Mean Dmin (mm)	Mean Dmax (mm)	Mean Ovality	Mean Area (mm^2)	Mean Spray Duration (ms)	Mean Angle (°)	Mean Width (mm)	
30	A	A	16.81	18.08	1.077	240.9	126	-	-	3.80
	B	A	17.24	18.85	1.093	254.8	131	-	-	3.98
		B	18.82	20.85	1.110	309.4	172	-	-	5.09
		C	14.81	15.94	1.077	186.9	224	-	-	3.78
		D	22.14	25.39	1.147	442.8	213	-	-	3.84
		E	18.13	20.47	1.129	293.6	227	-	-	4.13
60	A	A	22.18	24.98	1.126	426.1	114	27.5	29.76	-
	B	A	23.12	25.55	1.105	458.8	124	31.6	34.78	-
		B	24.92	28.16	1.13	550.7	147	33.1	36.16	-
		C	19.47	21.27	1.092	324.1	219	25.2	27.15	-
		D	25.20	31.35	1.248	634.5	215	28.3	30.42	-
		E	23.15	27.38	1.183	496.4	219	35.3	38.25	-

Table 1: Key measurement parameter data for SP and PG of each actuator/canister combination

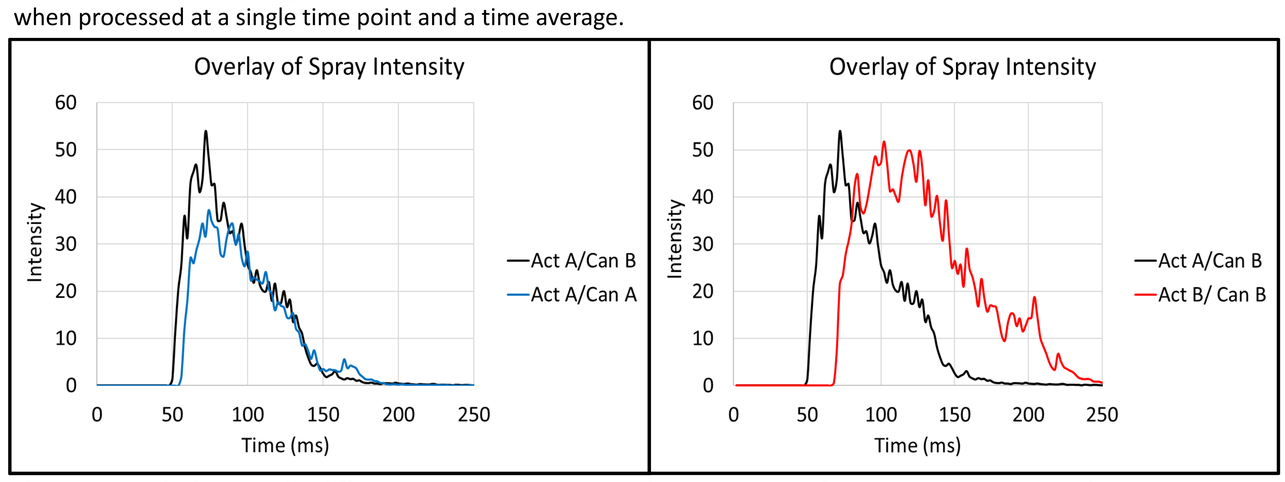


Figure 3: Graph showing the difference in spray intensity and actuation time for actuator/canister combinations

Conclusion

This study shows how SP and PG analysis can be used as a fast and effective screening tool for actuator candidate selection for a generic pMDI, as preliminary analysis to characterize an OINDP product, and also as an indicator of final device performance and in demonstrating in vitro equivalence.

This study shows that changing the actuator will alter the spray characteristics of the device such as the SP area. Screening SP and PG data for changes in the pMDI properties can be useful to help optimize a product. Reference products may have been developed to limit the number of possible options available for a component of the product and screening a wide range of components can help generic developers find the best possible match to a reference product [3].

The US FDA guidelines state explicitly how to process for SP and PG which are over the duration of the spray and a single time point respectively. PG processing by selecting a single snapshot of the fully developed plume measures the spray at its optimal performance and will assist confirming in-vitro equivalence during development. The time averaged PG processing showed changes in plume characteristics between various actuators and could be a useful tool during screening in early-stage development of pMDIs.

References
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[2] Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, FDA.gov [Online] April 2013.
[3] Liao L, Chauhan H, Newcomb A, L'Ecuyer T, Liu-Cordero SN, Leveille C, Spray pattern: A rapid and sensitive early development tool for respiratory drug products, Inhalation Magazine, October 2017