A Tale of Three Propellants: Understanding the In-Vitro Characteristics of a Solution pMDI

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INTRODUCTION

The pMDI formulation and the actuator geometry play a critical role in the shape and size of the aerosol plume and can significantly affect the critical quality attributes (CQAs) [1].

In a solution formulation, the vapour pressure and density of the propellants and the ethanol content can affect the evaporation rate, thereby affecting the overall efficacy of the product for the patient. In this study, Ipratropium bromide solution formulations with HFA134a, HFA152a, and HFO1234ze, respectively, as the propellant were evaluated.

KEY MESSAGE

The study highlights the necessity of formulation characterisation and role of actuator geometry in the development of low GWP propellant formulations to achieve in vitro equivalence. The adoption of new methodologies, such as Plume Front Velocity (PFV) and Spray Duration (SD), will further support the understanding of the plume characteristics.

METHOD AND MATERIALS

The formulation consisted of Ipratropium bromide 20 µg/actuation with approximately 15% w/w ethanol as cosolvent and approximately 0.004% of citric acid as excipient filled into 17 mL plasma-treated canisters (H&T Presspart), crimped with a 50 µL valve before filling with the appropriate propellant. An actuator (H&T Presspart) with an orifice diameter of 0.25 mm and a jet length of 0.35 mm studied earlier was used to test all the formulations [2].

APSD testing was performed at the beginning of the life (n=3) at a flow rate of 30L/min using Next Generation Impactor. DDU testing was performed at the beginning of life (BOL), middle of life (MOL), and end of life (EOL). SP and PG testing were performed using Proveris SprayVIEW® with a Vereo® SFMDx actuator and Viota® Imaging software (Proveris Scientific Corporation, USA) [3]. SP testing was performed at 3.0 cm and 6.0 cm distances from the actuator mouthpiece [4]. APSD, DDU and SP experiments were performed at H&T Presspart's IPTC facility, UK. The PG at 6.0 cm, PFV, and SD experiments (n=6 and five sprays per pMDI) were performed at Proveris Scientific, USA. Statistical analysis (Students t-test $p \leq 0.05$) was performed using Minitab software. The graphs and stats statistical analysis (Students t-test $p \leq 0.05$) was performed using Minitab software at H&T Presspart and at Proveris was done using JMP® Statistical Software.

RESULTS AND DISCUSSION

Aerodynamic Particle Size Distribution: Figure 1 shows the APSD of the three formulations. Statistical differences were not observed for FPD between HFA152a and HFA134a (p=0.200). However, HFA152a exhibited a higher induction port (IP) deposition, which can be attributed to the lower vapour pressure and lower density of the propellant. HFO1234ze was not statistically equivalent to HFA134a (p=0.014).

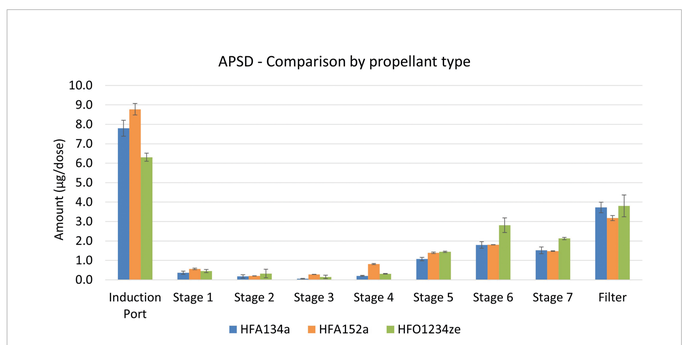

Figure 1 – APSD (µg/dose) of Ipratropium formulations with HFA134a, HFA152a and HFO1234ze

Delivered Dose Uniformity: The delivered dose uniformity, Figure 2, calculated as a percentage of the target value of 18 µg/ dose, was found to be consistent through-life for the pMDI and within acceptable limits with all the three propellants, as expected from solution formulations.

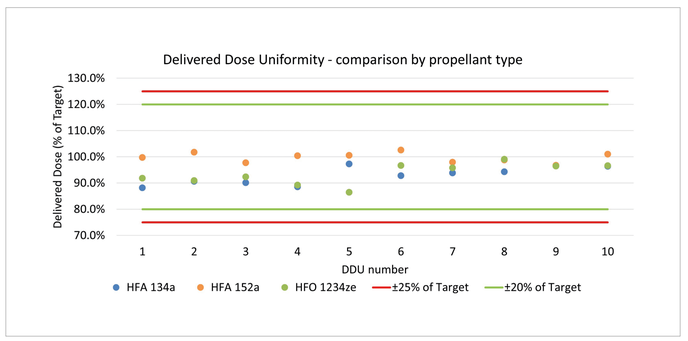

Figure 2 – Delivered Dose Uniformity data of Ipratropium Bromide pMDI

Spray Pattern: SP areas of HFA134a Vs HFA152a and HFO1234ze formulations at each measurement distance are shown in Table 2. There were significant differences in SP values at each distance except for HFA134a Vs HFO1234ze at 6.0 cm (p = 0.750). The spray area was higher for the HFA152a formulation as compared to the other two formulations. This could be due to the effect of lower density and lower pressure of the propellant. The difference in propellant properties is further supported by the ovality ratios which were significantly different, except between HFA134a and HFO1234ze at 3.0 cm (p=0.597).

Table 2 – Spray Pattern Area at 3.0 cm and 6.0 cm for Ipratropium formulation with all propellants

Spray Pattern Area		Propellant		
		HFA134a	HFA152a	HFO1234ze
Spray Area at 3.0cm (mm^2)	Mean	299	355	315
	St Dev	21.9	23.3	12.8
	Ovality ratio	1.14	1.20	1.13
Spray Area at 6.0cm (mm^2)	Mean	547	594	543
	St Dev	39.2	43.9	37.6
	Ovality ratio	1.16	1.21	1.10

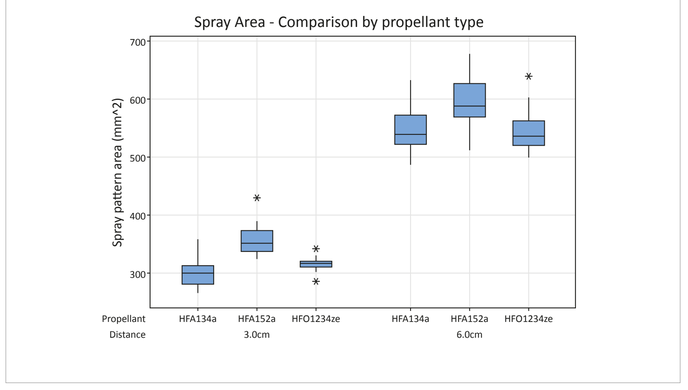

Figure 3 – Spray Pattern area for Ipratropium formulation by propellant type

Plume Geometry: Wider Plume Angle and Plume Width (Table 3) further support the observation of larger Spray Area for the HFA152a formulation. The Plume Angle and Plume Width values for HFO1234ze were a closer match to the HFA134a formulation.

Table 3 – Plume Geometry results at 6.0 cm for Ipratropium formulation by propellant type

Plume Geometry		Propellant		
		HFA134a	HFA152a	HFO1234ze
Plume Angle [deg]	Mean	26.8	29.1	27.6
	SD	3.7	4.3	5.5
Plume Width [mm]	Mean	28.8	31.5	29.8
	SD	4.2	4.8	6.2

Plume Front Velocity and Spray Duration: The variability between the propellants is low for the PFV (Table 4), showing no statistical differences between any of the propellants at either the 30 mm or 60 mm distance (Student's t-test, $p \leq 0.05$) (Figure 4). From the Spray Duration perspective (Table 5), there were slight differences in the means of the three propellants and are not considered statistically equivalent by the student's t-test; however, it is considered that the low variations (range of 39 ms) would not be a discernable difference from the patient perspective.

Table 4 – Plume Front Velocity (PFV) at 30 and 60 mm by propellant type

Plume Front Velocity			Propellant		
	PFV Distance [mm]		HFA134a	HFA152a	HFO1234ze
PF Velocity [mm/ms]	30	Mean	6.2	6.5	6.1
		St Dev	1.4	1.4	1.6
	60	Mean	4.7	4.7	4.4
		St Dev	1.0	0.9	1.2

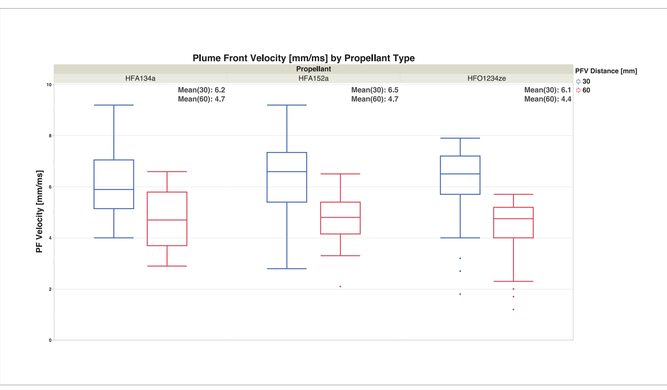

Figure 4 – Analysis of PFV at 30 and 60 mm by propellant type

Table 5 – Analysis of Spray Duration data by propellant type

Spray Duration		Propellant		
		HFA134a	HFA152a	HFO1234ze
Spray Duration [ms]	Mean	276	297	315
	SD	14.2	55.2	21.7

CONCLUSION

In this study, Ipratropium bromide HFA152a and HFO1234ze formulations were studied as potential LGWP propellant alternatives to the HFA134a propellant. Statistical equivalence as well as differences were observed in the experiments performed. This indicates that further understanding of the effect of propellant properties on formulation characteristics is required for product development. In addition, the actuator has a significant impact on in vitro performance parameters (i.e., APSD and Spray Plume characteristics). Therefore, actuator geometries such as orifice diameter, jet length, sump shape, and volume need to be optimised to achieve in vitro equivalence. New methodologies like PFV and SD provide insights into the correlation between the formulations and propellant properties. The study demonstrates that substitution of the existing propellant with LGWP propellant is a challenge yet to be overcome.

References

[1] Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations, Guidance for Industry, US FDA, CDER, April 2018

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[3] Proveris SprayVIEW® Measurement System User Manual (Rev. J). Proveris Scientific Corporation, Hudson, MA, 2022: 54–64.

[4] Draft guidance on Ipratropium bromide Aerosol Metered Inhalation, FDA, March 2015