A COMPARISON OF SPRAY CHARACTERISTICS OF P-134A AND LOW GWP P-152A PMDIs WITH AND WITHOUT ETHANOL

Lynn Jordan[1], Sheryl Johnson[2], Ramesh Chand[1], Grant Thurston[1], Deborah Jones[1], Vanessa Webster[2], Sally Stanford[2]

[1]Proveris Scientific Corporation, Hudson, Massachusetts, USA [2]Koura, Thornton Science Park, Cheshire, UK

INTRODUCTION

As a result of increasing focus on the potential environmental impact associated with pressurized metered dose inhalers (pMDIs) propellants, it is important to understand the options available as well as their possible impact on delivery performance.[1] 1,1-difluoroethane (P152a) is being explored as one such option as an alternative low Global Warming Potential (GWP), non-Per- and Polyfluoroalkyl Substance (PFAS) pMDI propellant. One challenge for the pMDI sector, when developing new formulations based on any new low GWP propellant, is ensuring it can provide adequate or equivalent performance to existing inhalers. Making a change from one pMDI propellant to another is not without challenges and this investigation sets out to study initially the potential impact of a switch from P134a to P152a on spray characteristics using propellant-only cans.

METHODS

Canisters were manufactured with P152a (development grade) and P134a (Zephex® grade) propellants with ethanol (8%) and ethanol-free at bench scale at Koura, UK. The propellant formulations were prepared in plain, uncoated aluminum cans (H&T Presspart, UK) and sealed with 63 µL valves (Aptar, France) with the use of a manual benchtop crimper filler. All canisters were quarantined valve down at room temperature for at least 14 days prior to analysis. Canisters were shipped to Proveris for spray characterization. Table 1 shows the manufactured propellant formulations.

Variant	Propellant	Ethanol Content (w/w%)	Propellant Formulation Designation	Calculated Target Shot Weight (mg)
1	134a	0	134a	77.18
2	152a	0	152a	57.46
3	134a	8	134aE	74.98
4	152a	8	152aE	56.84

Table 1. Manufactured propellant formulations

All formulations were studied for metered shot weight, spray pattern, and plume geometry using a H&T Presspart actuator (3.16 mm stem diameter, 0.65 mm jet length, and spray orifice 0.23 mm) and following the methodologies outlined below.

Optimum actuation parameters were determined using a Vereo® (Proveris Scientific® Corporation, USA) SFMDx Automated Actuator with target shot weight as an indicator (Table 1). The optimized actuation profile was used for all devices with the Vereo SFMDx Automated Actuator to eliminate user variability. Each inhaler was shaken by the automated actuator prior to each actuation, specifically to exclude any ethanol and propellant layers from forming and primed 5 times prior to any testing. This study was performed as an initial screening without Active Pharmaceutical Ingredients and as such with small sample size.

Metered Shot Weight: Metered shot weight for each formulation was collected using a SFMDx Vereo Automated Actuator with a device holder designed specifically for the H&T Presspart actuator. The shot weights were recorded from 10 inhalers (n=10 shots) by weighing each inhaler before and after actuation.

Spray Pattern and Plume Geometry: Spray pattern and plume geometry were measured using a SprayVIEW® Measurement System (Proveris Scientific Corporation, USA) shown in Figure 1, and a SFMDx Vereo Automated Actuator with the above specifically designed device holder. Spray pattern and plume geometry measurements were performed in triplicate with each of the 10 inhalers. Spray pattern methods were developed at 30 mm and 60 mm from the inhaler mouthpiece edge as shown in shown in Figure 3. The plume geometry method was developed at 60 mm from the inhaler mouthpiece edge as shown in Figure 4. Development of the spray pattern methods was performed to obtain a spray pattern centered in the field of view (FOV), with an area % between 5 – 10%[2]. Separate methods were developed for spray pattern at 30 and 60 mm for P134a and P152a formulations. When compared to P134a formulations, P152a formulations required the camera to be positioned 2 cm further from the inhaler for both spray patterns, 30 mm and 60 mm. Plume geometry methods have a wider tolerance, and one plume geometry method worked for all four propellant formulations at 60 mm.

Data Analysis: JMP Software (SAS Institute, Cary, NC USA).

Figure 1. SprayVIEW Measurement System SFpMDI Model

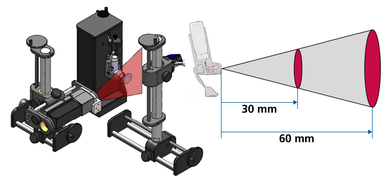

Figure 3. Spray Pattern (Horizontal Sprays)

Figure 2. SFMDx Vereo Automated Actuator and H&T Presspart actuator in a Proveris device holder

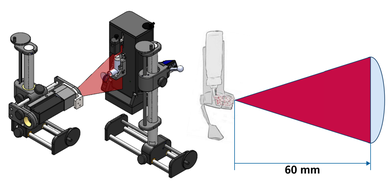

Figure 4. Plume Geometry (Horizontal Sprays)

RESULTS AND DISCUSSION

Metered Shot Weight: Metered shot weight data is shown in Table 2.

Propellant Formulations		Metered Shot Weight			
		134a	152a	134aE	152aE
Target Shot Weight (mg)		77.18	57.46	74.98	56.84
Shot Weight (mg)	Mean	79.9	56.1	72.4	56.0
	Std Dev	0.8	1.0	1.3	0.7
	CV	1.0	1.8	1.9	1.2
Variation from Target SW (%)		3.5	2.4	3.4	1.5

Table 2. Metered shot weight results for all four (4) Propellant Formulations

The measured average shot weight for all formulations was found to be within 4% of target shot weight, well within the Food and Drug Administration (FDA) Guidance of not more than ±10% of the mean of actuations relative to the target[3].

Spray Pattern: Spray pattern data analysis was performed automatically through the Proveris Viota® software. Figure 5 presents the area and ovality for spray pattern at 30 mm and 60 mm distances for all propellant formulations.

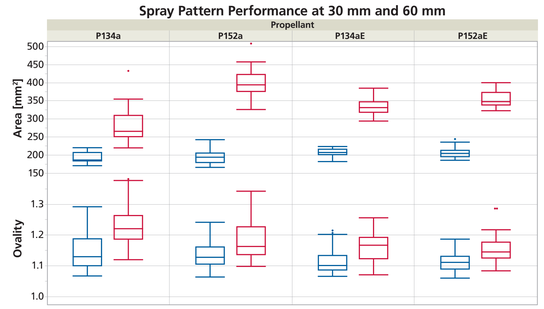

Figure 5: Spray pattern performance at 30 mm (blue) and 60 mm (red) for all four (4) propellant formulations

All four propellant formulations show similar area at 30 mm distance, with ethanol having almost no effect. At spray pattern 30 mm the mean area percent difference[4] between the formulations was 0.9% without ethanol and 0.1% with ethanol. More variation in area was seen at 60 mm, both with and without ethanol. At spray pattern 60 mm, the mean area difference between the formulations was 33.8% without ethanol and 6.8% with ethanol. It should be noted that the average spray pattern area at 60 mm for P152a was 40.7% higher than the current propellant, P134a, indicating a potential difference in spray behaviors between the propellants. At spray pattern 30 mm, the mean ovality difference between the formulations is less than 1% both with and without ethanol. At SP 60 mm, the mean ovality difference between the formulations was 4.6% without ethanol, and showed a tighter ovality with ethanol, at 0.34% mean ovality difference.

Plume Geometry: Plume geometry data analysis was performed through the Viota software, as described in the instrument manual.[2] Figure 6 shows an example plume for each formulation along with the associated average image intensity graph.

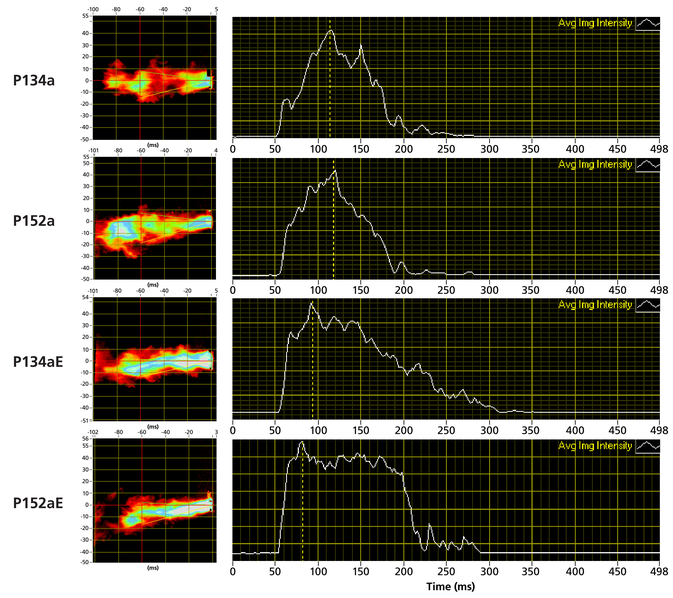

Figure 6: Plume geometry images for the four (4) formulations and associated average image intensity graphs

RESULTS AND DISCUSSION *(CONTINUED)*

Figure 6 plume geometry and average image intensity plot show that the addition of ethanol in the P134aE formulation resulted in a continuous, more intense plume than that of P134a alone. The P152a formulations showed a more intense plume both with and without ethanol, indicating a difference in spray characteristics between P134a and P152a. PG data is represented graphically in Figure 7, showing plume width and angle for all propellant formulations.

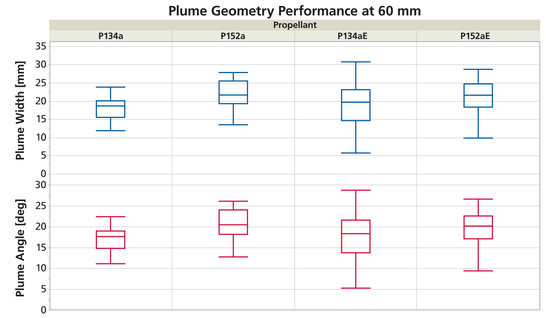

Figure 7: Plume geometry performance at 60 mm for all four (4) propellant formulations

The P134aE formulation showed higher variability in both plume width and plume angle. There is a statistically significant difference between the plume widths for P134a and P152a (p=0.0009, Student's t-test). For plume angle there is also a statistically significant difference between the plume angles for P134a and P152a (p=0.0009, Student's t-test). There is no statistical significance between the P134aE and 152aE plume width and plume angles. It is important to note that for this study only one type of valve and actuator were used for all propellant formulations for comparison. Optimization of the valve and actuator may reduce some of the variations noted in SP and PG between the different propellant formulations.

CONCLUSION

- Average metered shot weight across all formulations was well within the FDA Guidance for pMDI products.
- This work indicated that separate spray pattern methods would need to be developed for P152a upon transition from P134a to achieve a desirable spray pattern Field of View.
- Spray pattern area for all four propellants performed similarly at 30 mm. Variations were seen at 60 mm, ethanol had a larger effect on the spray pattern, and P152a showed a significantly higher spray pattern area.
- Spray pattern ovality for all four propellant formulations with and without ethanol remained consistent..
- In plume geometry at 60 mm the addition of ethanol causes P134a to show an increase in variation in median plume angles and width, and the plume is more continuous and intense.
- The effect of ethanol was diminished in plume geometry for P152a formulations.
- A full evaluation should be performed to choose the optimum valve and actuator for the specific propellant formulation.

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ACKNOWLEDGEMENTS

The authors would like to thank Proveris Laboratories Technical Data Scientist Alyssa Rubino for her assistance with the data analysis for this work.

Proveris Scientific thanks Koura for kindly providing inhaler propellant formulations for testing.

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