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Optimising Actuator Geometries of Low GWP Propellant HFA-152a Solution Formulations

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SUMMARY

Low Global Warming Potential (GWP) propellants are being explored for pressurised metered dose inhalers (pMDIs) to reduce the carbon footprint. The selection of propellant in a metered dose inhaler is a substantial change to the product that will require not only a good deal of consideration with regards to the formulation, but also the device componentry for example actuators.

Actuator geometries are critical parameters which influence the shape and size of the aerosol plume and can significantly affect the aerodynamic drug distribution, thereby affecting the overall efficacy of the product for the patient.

Through spray pattern testing, the plume characteristics are used as a comparative tool against other actuator configurations, including a reference device (RLD) and can help predict in-vitro device performance.

The performance of three different solution formulations, with HFA-152a as the propellant and ethanol as a co-solvent, with different actuator geometries were evaluated by assessing the spray behaviour at two distances[1]. The results were compared against commercially available products with HFA-134a formulations. Several actuator geometry configurations showed comparable performance to the RLD at one distance ($p \geq 0.05$, n=15); however, no configuration tested, showed $p \geq 0.05$ at both distances.

RESULTS

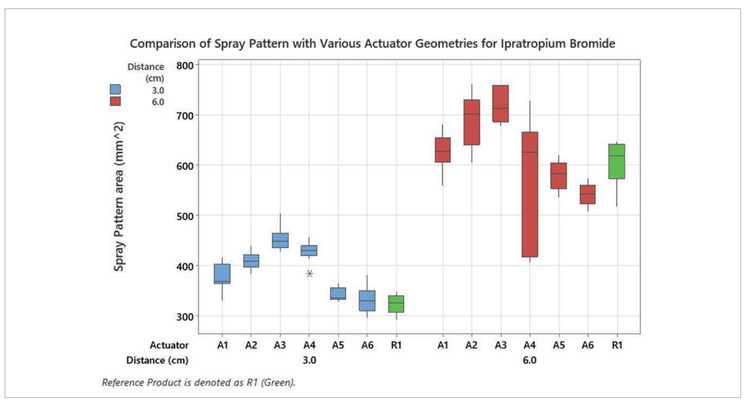


Figure 1: Comparison of Spray Pattern with Various Actuator Geometries for Ipratropium Bromide

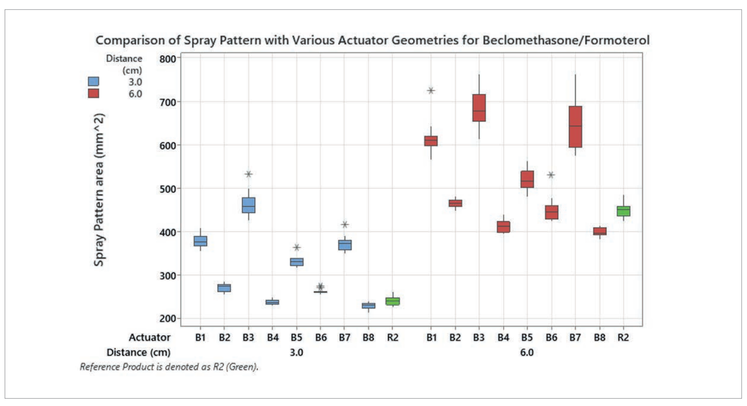


Figure 2: Comparison of Spray Pattern with Various Actuator Geometries for Beclomethasone/Formoterol

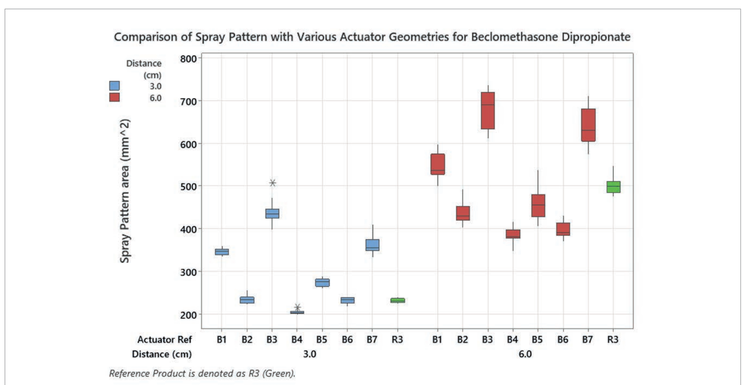


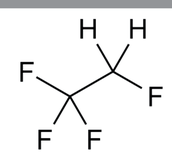
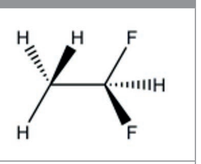
Figure 3: Comparison of Spray Pattern with Various Actuator Geometries for Beclomethasone Dipropionate

INTRODUCTION

With new regulations on the horizon from an environmental and sustainability standpoint, the industry is looking at switching inhaler propellants to greener alternatives. HFA-152a as a propellant has more than a tenfold reduction in GWP compared with the current HFA-134a propellant.

Along with the propellants and the medication, container closures and formulation characteristics[2,3] play an important role within product development. A critical part of achieving in-vitro bioequivalence is understanding the spray plume characteristics of the solution formulations, as the amount of ethanol, vapour pressure and evaporation rate of the new propellants play a significant role towards target performance.

Table 1: Summary Table of Key Differences Between HFA-134a and HFA-152a

Parameters	HFA-134a	HFA-152a
Structure		
Vapour Pressure	6.652 bar	4.95 bar
Liquid Density (25°C)	1.207 g/cm^3	0.899 g/cm^3
Vapour Density (25°C)	0.333 g/cm^3	0.185 g/cm^3
GWP Value	1430	124

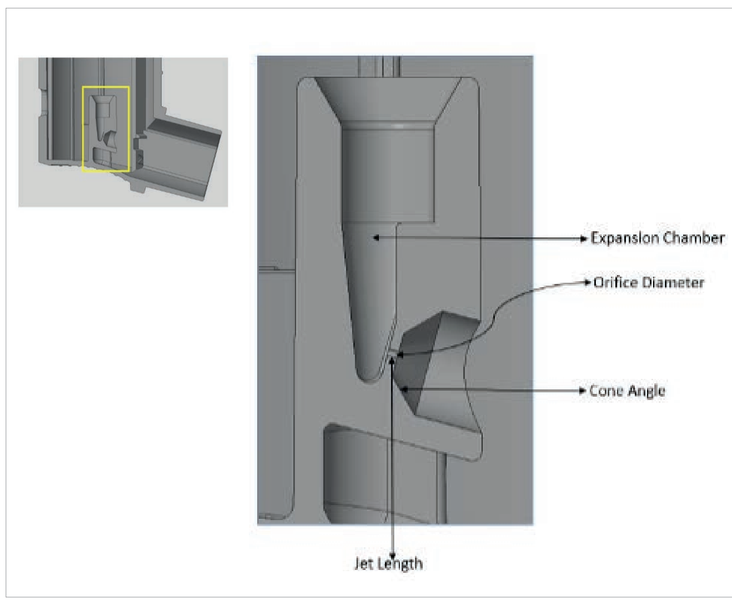


Figure 4: Schematic of Actuator Stem Block

OBSERVATIONS

There are several factors of actuator geometry viz orifice diameter, jet length and expansion chamber (sump volume) that can influence the shape and size of the aerosol plume. Changing one or a combination of parameters can profoundly affect the spray area, leading to differences in invitro product performance.

Student's T-tests were performed to generate p-values for comparisons of each actuator against the reference product for each test condition. Several actuator geometry configurations showed comparable performance ($p \geq 0.05$, n=15) at either 3.0 or 6.0 cm distance, however, no configuration tested showed $p \geq 0.05$ at both distances.

Of the actuator geometries tested the spray areas observed at a distance of 6.0 cm were a closer match to the reference product on average as compared to a distance of 3.0 cm. None of the actuators showed comparable performance for spray area at both distances. This suggests that the plume dynamics are different for HFA 152a and HFA134a propellant.

The formulations with HFA-152a will also play a key role in developing a product comparable to the traditional HFA-134a counterparts in addition to actuator selection and other device componentry considerations.

KEY MESSAGE

In the effort to switch to new low GWP propellants for pMDIs, actuator selection and formulation strategies will play a key part in achieving in-vitro bioequivalence when compared with currently marketed HFA-134a formulations.

METHOD AND MATERIALS

The formulations with HFA-152a (technical grade) were filled into 19 ml plasma-treated H&T Presspart canisters. H&T Presspart's patented Fluorocarbon Polymerisation (FCP) plasma treatment offers an excellent alternative solution to overcome the challenges of drug adhesion and interaction (degradation) with the aluminium alloy canister. The FCP plasma provides an excellent long term sustainable solution complementing the low GWP propellant. For the above reasons plasma treated canisters were the choice for HFA-152a formulations.

All samples were prepared with HFA-152a as the propellant. The Ipratropium Bromide formulation, (20 µg/actuation with approximately 15 %w/w ethanol as cosolvent and citric acid as excipient) was crimped using Aptar 50 µL valves. The Beclomethasone/Formoterol Fumarate (BDP/FFD,100/6 µg /actuation with about 15% w/w ethanol as cosolvent and 1M HCl as excipient) and Beclomethasone (100 µg per actuation, with about 15% w/w ethanol as cosolvent) formulations were crimped using Bespak 50 µl valves. The sample devices were manufactured at H&T Presspart's Inhalation Product Technology Centre (IPTC) facility using a manual benchtop crimper filler supplied by DH Industries UK.

The HFA152a test formulations were compared to commercially marketed reference products consisting of HFA-134a as their propellant: Atrovent 20 µg (Boehringer Ingelheim), Fostair 100/6 µg (Chiesi Ltd) and Clenil Modulite 100 µg (Chiesi Ltd).

A selection of actuators manufactured by H&T Presspart was chosen with range of orifice diameters between 0.2 and 0.3 mm and jet length between 0.34 and 0.70mm based on the experience of pMDIs solution based formulations. Five samples of each actuator type were tested, and each sample was tested in triplicate.

The test methods were developed internally at IPTC. All samples were quarantined valve down at room temperature for at least 14 days prior to analysis. Spray pattern testing was performed using Proveris SprayVIEW® (Proveris Scientific Corporation, USA)[4] at 3.0 cm and 6.0 cm distance from the actuator mouthpiece. Optimum actuation parameters were determined using a Vereo® (Proveris Scientific Corporation, USA) SFMDx Automated Actuator during the characterisation & priming of each sample prior to analysis. The Viota® Imaging software and spray pattern analysis algorithms were used to quantify several parameters of the pMDI spray pattern.

Table 2: Actuator Geometries for Testing of the HFA-152a Formulations

Product Description	Actuator Reference	Orifice Diameter (mm)	Jet Length (mm)
Ipratropium	A1	0.26	0.34
	A2	0.25	0.35
	A3	0.30	0.35
	A4	0.26	0.35
	A5	0.26	0.35
	A6	0.25	0.35
BDP and BDP+FFD	B1	0.25	0.50
	B2	0.23	0.50
	B3	0.25	0.35
	B4	0.25	0.70
	B5	0.25	0.35
	B6	0.25	0.50
	B7	0.25	0.35
BDP+FFD	B8	0.28	0.65

The length of the expansion chamber was varied between 10.00 and 20.00 mm and the cone angle between 70 and 120 deg. for the actuator variants. See Figure 4.

CONCLUSION

pMDI solution formulations are dynamic in their spray behaviour due to the presence of ethanol and other excipients. Differences in propellant characteristics, such as vapour pressure, density etc. make achieving equivalence with currently marketed products a complex endeavour.

Imaging techniques such as spray pattern and plume geometry provide a rapid screening tool for actuator selection for further in-vitro and in-vivo bioequivalence studies and prove to be a valuable part of the product development process.

Additional analytical testing such as Aerodynamic Particle Size Distribution, is needed to assess if the selected actuator types show good correlation with the reference product. Understanding the pMDI actuator's various dimensions is crucial to optimise the low GWP solution formulations to achieve comparable product performance.

References

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[3] Newman S P: Principles of Metered-Dose Inhaler Design, Respir Care 2005;50(9):1177–1188
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Acknowledgements

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