H&T PRESSPART

Comparison of In-Vitro Performance Characteristics of Salbutamol pMDI with Low GWP Propellant (HFA-152a) vs The Current Propellant (HFA-134a)

Ameet Sule[1], Sunita Sule[1], Tracey Mullington[1], Arslan Khan[1], Lauren Liddle[1], Robert Bootle[1]
[1]H&T Presspart Inhalation Product Technology Centre, Whitebirk Industrial Estate, Blackburn BB1 5RF, UK

Summary

Pressurised metered dose inhalers (pMDIs) though complex systems, remain highly preferred drug delivery devices for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Low GWP propellants are now being explored to reduce the carbon footprint of the pMDI. HFA-152a and HFO-1234ze are two current low GWP alternatives. Even after almost four decades, Salbutamol is still the most sought-after short-acting beta$_2$-adrenergic agonist as a reliever for Asthma. Along with the propellants, the container closures and formulation characteristics play an essential role in product development.

To understand the behaviour of Salbutamol API with HFA-152a and HFA-134a in a plasma-treated canister, a series of in-vitro tests were conducted at an initial time point and 12 months at ambient conditions. The test results indicated that HFA-152a is a promising potential alternative to HFA-134a as a low GWP propellant. The data generated shows a close match for fine particle dose between the two propellants with a p-value of 0.903. Modifications to actuator geometries are to be considered to allow for the differences in the physical properties of the propellants. The delivered dose performance throughout canister life showed acceptable performance for each propellant at initial and 12-month time points with no individual results exceeding ± 25% of the target dose. Due to the differences in density between the propellants, the difference in spray area is significant, with a p-value of 0.000, with HFA-152a generating a larger spray area and wider plume.

Introduction

The pharmaceutical industry is evaluating low GWP propellants as sustainable alternatives to traditional propellants.[1].HFA-152a is one of the new low global warming potential (GWP) propellants for pressurised metered dose inhalers (pMDIs). HFA-152a has a greater than 90% reduction in global warming impact compared to HFA-134a. By using HFA-152a as a propellant of choice, a huge step change in the environmental footprint of the MDI can be achieved

Presspart's patented[5] fluorocarbon polymerised (FCP) plasma-treated canisters offer an excellent alternative solution to overcome the challenges of drug adhesion and interaction with the aluminium alloy canister[4]. The FCP plasma treatment produces a low surface energy (hydrophobic) nanolayer covalently bonded to the internal surface of the canisters[5]. The process uses readily available high-purity industrial gases and monomers in contrast to the solvents used in spray coating processes so harmful waste products are drastically reduced. Hence, plasma-treated canisters are an excellent long-term sustainable solution complementing the use of low GWP propellants.

Key Message

Salbutamol formulation in plasma-treated canisters with the new low GWP HFA-152a propellant showed acceptable performance at initial and 12 months for APSD and delivered dose. Further studies are needed to arrive at a suitable shelf life and robust product development before clinical studies can be initiated.

Method and Materials:

The selected formulation is a dry suspension comprising the active pharmaceutical ingredient (API) Salbutamol Sulphate in HFA-152a and HFA-134a, respectively. The formulation was filled by a third party into 19 mL plasma-treated H&T Presspart canisters fitted with 63 µL DF316 Aptar valves and H&T Presspart actuators (0.5 mm and 0.4 mm orifice diameter (OD)).

The HPLC test method was developed internally and validated at Presspart's Inhalation Product Technology Centre (IPTC). For delivered dose, dose tail-off and aerodynamic particle size distribution (APSD) testing, the automated shake and fire Vertus system (Copley Scientific) was used. The automated shake and fire Deca Vertus system (Copley Scientific) was used to fire down the samples to waste.

Delivered Dose and Tail-Off

Delivered dose through life was determined as described in the European Pharmacopoeia. Testing was performed in triplicate on plasma-treated canisters containing HFA-152a and plasma-treated canisters containing HFA-134a with 0.5mm OD actuators. Ten doses per inhaler were collected using a through-life testing regime where three doses were collected at beginning of life, four doses at the middle of life, and three doses at the end of life.

Each sample was prepared by fixed volume recovery using 25 mL of purified water and manually agitated for drug recovery. For determination of tail-off, additional doses were collected post 200 shots up to spray number 240 on the same canisters used for HFA-152a delivered dose uniformity.

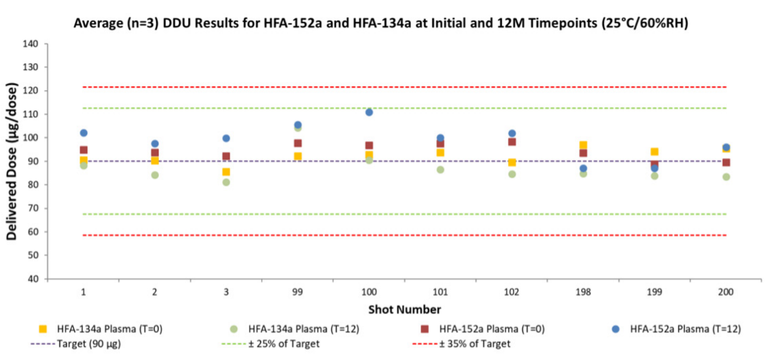


Figure 1 – Delivered Dose Uniformity Comparison of HFA-152a and HFA-134a and T=0M and T=12M

Figure 2 depicts that the delivered dose values for tail-off up to spray 220 were within ± 25% of the target dose (90 µg).

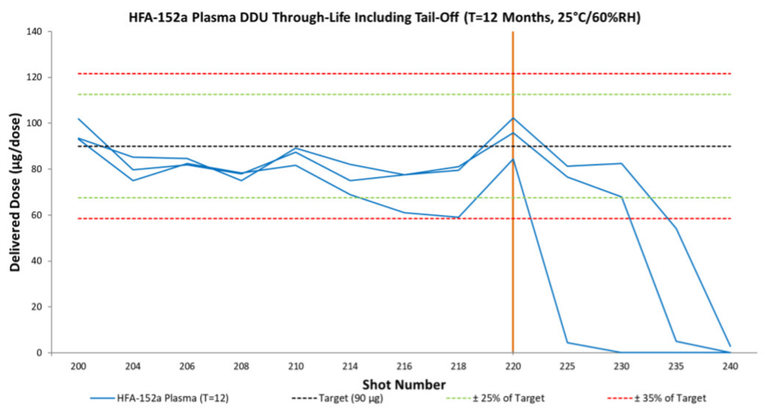


Figure 2 – Tail off characteristics using delivered dose for HFA-152a plasma canisters

Results

Figure 1 contains a graphical depiction of the delivered dose uniformity of HFA-152a and HFA-134a at initial and 12-month time points. Both propellants demonstrated acceptable performance throughout the life of the product up to 12 months, and all the results were within ± 25% of the target dose (90 µg).

It can be seen from Figure 3 the APSD profile remains consistent at T=12M at ambient conditions (Zone II) for the plasma-treated canisters. Figure 4 and Table 1 show that with a 0.4 mm OD actuator, the APSD closely resembles the APSD generated by the HFA-134a samples in a 0.5 mm OD actuator. The p-value of HFA-152a with 0.4mm OD actuator versus HFA-134a with 0.5mm OD actuator for the FPD is 0.903, which is a closer match, most likely due to the difference in aerosolisation properties of HFA-152a.

In Figure 5. the spray area for the spray pattern test at both 30 mm and 60 mm was found to be higher with HFA-152a compared to HFA-134a. Although similar APSD performance can be achieved between propellants, the difference in spray area is significant (a p-value of 0.000 between 0.4 mm OD actuator with HFA 152a and 0.5 mm OD actuator with HFA-134a for both distances).

Aerodynamic Particle Size Distribution (APSD)

APSD testing was performed as described in the European Pharmacopoeia. This testing involved performing ACI (Andersen Cascade Impactor) analysis in triplicate on plasma-treated canisters containing HFA-152a at initial and 12 month time points.

For the test of APSD, HFA-134a canisters were tested with 0.5mm OD actuators and HFA-152a canisters were tested with 0.4mm and 0.5mm OD actuators. Testing was performed using five doses per ACI, where each stage was recovered using 25 mL of purified water. These samples were then mechanically agitated using an orbital shaker (Shalom).

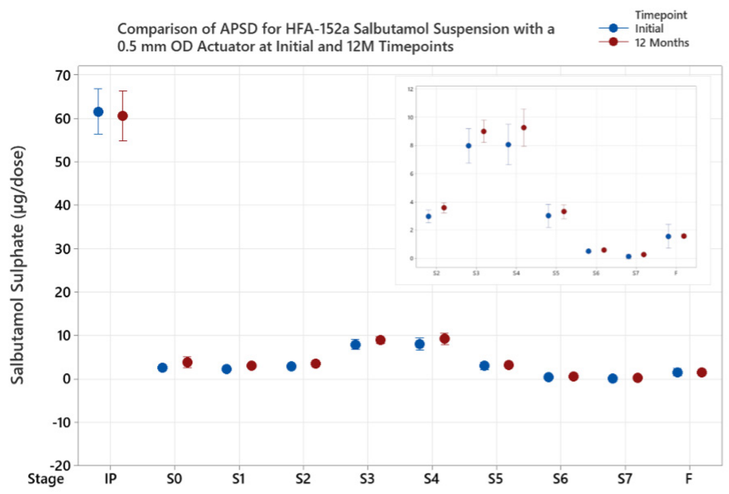


Figure 3 – Comparison of APSD for HFA-152a on Stability

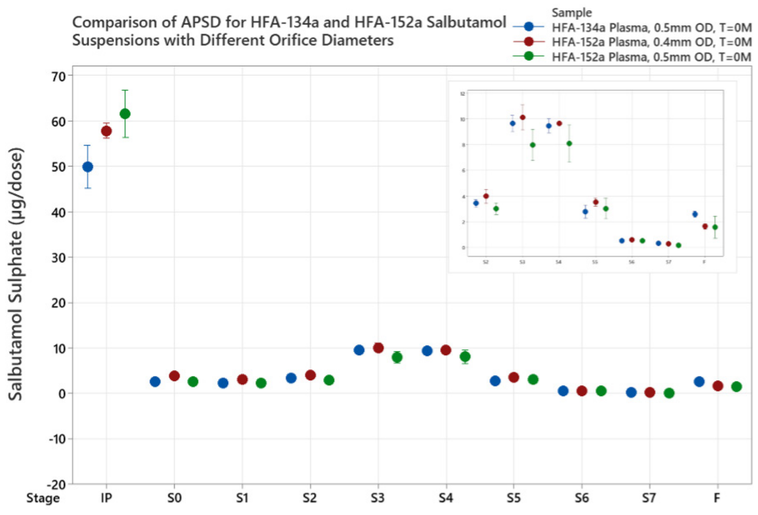


Figure 4 – Comparison of APSD between Propellants and Orifice Diameters

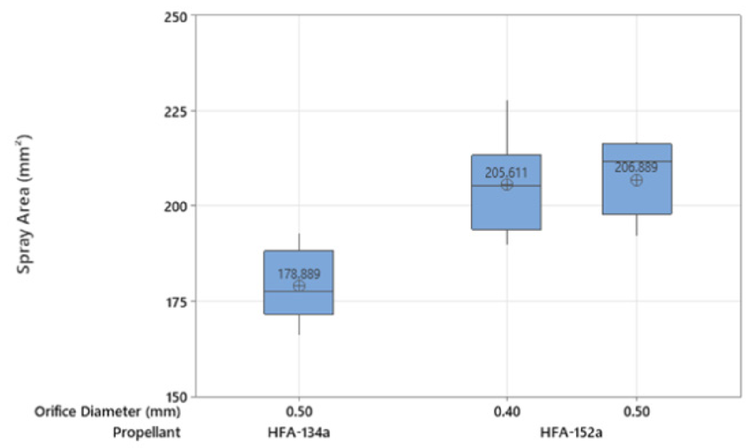
		Delivered Dose (µg/dose)	Fine Particle Dose (µg/dose)	Fine Particle Fraction (%)
HFA-134a Plasma, 0.5 mm OD	Mean	83.47	26.39	31.63
	RSD (%)	**2.48%**	**1.33%**	**2.79%**
HFA-152a Plasma, 0.5 mm OD	Mean	90.90	22.27	24.50
	RSD (%)	**2.53%**	**4.90%**	**4.32%**
HFA-152a Plasma, 0.4 mm OD	Mean	94.50	27.00	28.57
	RSD (%)	**1.10%**	**1.24%**	**0.96%**

Table 1 – APSD Data for HFA-152a and HFA-134a Plasma Canisters with Different Actuator Geometries

Spray Pattern

Spray pattern measurements were performed using the SprayView system (Proveris). The spray pattern was performed at two nominal distances: 30 mm and 60 mm, which was determined relative to the mouthpiece edge of the actuator. Nine readings were performed for each actuator geometry, 0.5 mm OD for HFA-134a and 0.4 mm OD for HFA-152a.

Comparison of Spray Area Between HFA-134a and HFA-152a at 30mm Distance



Comparison of Spray Area Between HFA-134a and HFA-152a at 60mm Distance

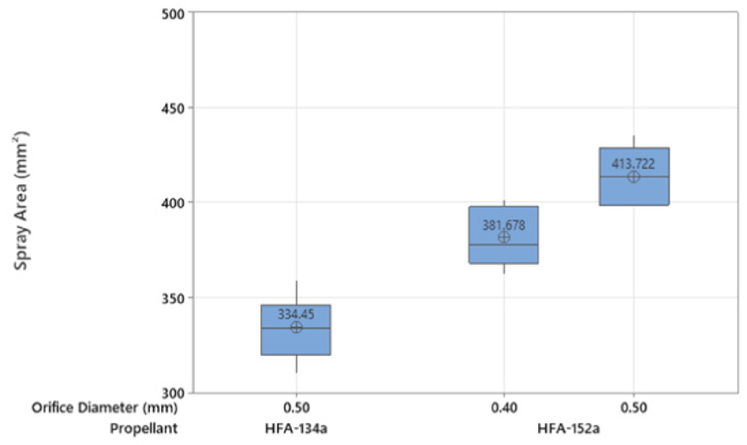


Figure 5 – Spray pattern at 30mm and 60mm for HFA-152a and HFA-134a

Discussion and Conclusion

The results show that the delivered dose through-life with the low GWP HFA-152a are within specification as per the European pharmacopoeia at T=0M and T=12M with plasma-treated canisters. The delivered dose tail-off results indicate a possibility of reducing additional overfill doses within the pMDI canister, thereby reducing the amount of propellant used. The APSD data indicated that the optimisation of actuator geometries would be necessary to achieve comparable performances to the existing HFA-134a product.2 . The spray pattern indicated some differences for the spray area at both distances. This will need to be evaluated further to have a better correlation with HFA-134a formulations. 3.

Overall, the results demonstrate that Salbutamol HFA-152a pMDI formulation with plasma-treated canisters delivers stable in-vitro performance for up to 12 months at ambient conditions. Further laboratory investigation beyond 12 months is needed to ascertain a suitable shelf life and achieve robust product development at various stability conditions before clinical studies can be initiated.

Acknowledgement

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