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Investigation of In Vitro Techniques for Evaluating Ipratropium Bromide Formulations

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INTRODUCTION

With the Kigali Amendment to the Montreal Protocol, the pharmaceutical industry is at a critical stage regarding reformulation efforts for pMDI with low global warming potential (GWP) propellants. In this study, a brief investigation was done to examine various in vitro techniques for a commercially available Atrovent inhaler (Ipratropium Bromide solution formulation with HFA134a propellant) and Ipratropium Bromide solution formulation inhaler with HFA152a propellant. Several actuator geometries for the HFA152a inhaler were examined. Regional deposition data using a human-realistic breathing simulation profile, aerodynamic particle size distribution (APSD), Spray Pattern (SP) and Plume Geometry (PG) data were studied.

MATERIALS AND METHODS

Ipratropium Bromide formulation (20 µg/actuation with approximately 15 %w/w ethanol as cosolvent, citric acid as excipient, and HFA152a as propellant) was filled in H&T Presspart's plasma canisters and crimped with Aptar's (France) 50 µL valves at H&T Presspart's Inhalation Product Technology Centre (IPTC) facility (Blackburn, UK). Actuators manufactured by H&T Presspart (Tarragona, Spain) were chosen for the study (Table 1).

Table 1 – Actuator Geometries and tests performed

Tests Performed	Sample	Actuator Ref.	Orifice Diameter (OD) (mm)	Jet Length (JL) (mm)
Regional Deposition, APSD, and SP/PG	Atrovent	Atrovent	-	-
	Ipratropium Bromide HFA152a	A1	0.25	0.35
		A2	0.26	0.75
		A3	0.29	0.75

The Ipratropium Bromide HFA152a formulation was tested against Atrovent 17 mcg/actuation (Boehringer Ingelheim, USA). Since both inhalers are solution formulations, no shaking of the inhaler was performed. Prior to testing, inhalers were primed as per the patient information leaflet (PIL). Regional deposition of the inhalers was performed using the In Vitro Inhaled Drug Analysis Platform (INVIDA™), (Proveris Laboratories, USA), which mimics human-realistic testing of aerodynamic deposition. Results are segregated into the mouthpiece adapter, mouth-throat, tracheobronchial, and lung (represented by a filter) segments. INVIDA Figure 1, paired with Proveris Human Breathing Simulator, provides a realistic human flow rate vs. time profile. For both Atrovent and Ipratropium bromide HFA152a formulations studied, three inhalers were tested (6 actuations per inhaler). Inhalers were manually actuated into the INVIDA mouthpiece adaptor with one inhalation cycle and a peak inspiratory flow rate of 74.71 LPM, with an inhaled volume of 1.5 L [1]. The regional deposition stages were extracted, and Ipratropium Bromide was quantified by HPLC. APSD testing (n=3) was performed using Next Generation Impactor (NGI) with Vertus Plus automated system (Copley). 10 actuations were collected for each canister at a flow rate of 30L/min. Spray Pattern and Plume Geometry testing was performed using Proveris SprayVIEW® with a Vereo® SFMDx actuator and Viota® Imaging software (Proveris Scientific Corporation, USA) with device holders custom fit to actuators. SP testing was performed at 3.0 cm and 6.0 cm distances from the actuator mouthpiece, and PG was performed at 6.0 cm from the actuator mouthpiece.

RESULTS AND DISCUSSION

Proveris INVIDA Platform: The depositions in the four regions were added to give the total drug delivered. Students t-tests with 95% confidence were performed to compare Atrovent with Ipratropium Bromide HFA152a with the 3 actuators. No statistical difference was shown for any of the actuators for total drug recovered (p>0.05). However, slight differences were seen between the mouth/throat and lung filter in the individual deposition regions (Figure 2).

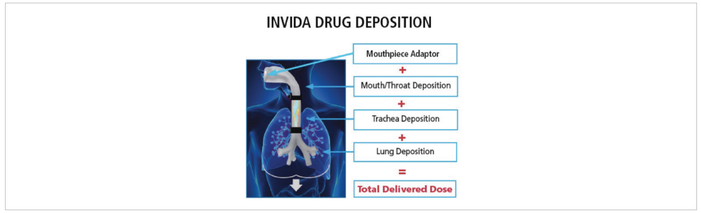

Figure 1 – In Vitro Inhaled Drug Analysis Platform

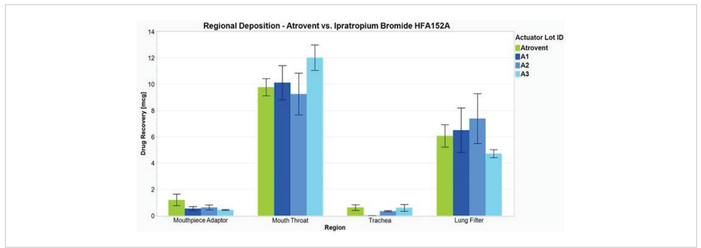

Figure 2 – Regional Deposition - Atrovent and Ipratropium Bromide HFA152a inhalers

Aerodynamic Particle Size Distribution (APSD): Within the Ipratropium Bromide HFA 152a formulation, the effect of actuator geometry can be seen in the difference in drug deposition in the NGI (Figure 3), actuator A3 with a higher OD exhibiting higher IP and lower inter-stage deposition than A1 and A2 actuator [2].Compared with Atrovent, Ipratropium HFA 152a with actuator A3 showed comparable Fine Particle Mass (FPM) (p=0.857), while the other actuators demonstrated a higher FPM than Atrovent.

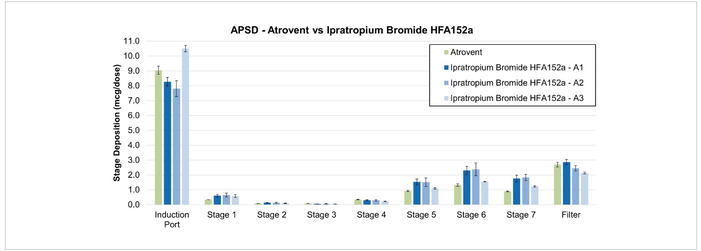

Figure 3 – APSD Atrovent vs Ipratropium HFA152a

Spray Pattern & Plume Geometry: Student's t-tests at 95% confidence intervals for SP indicated that Ipratropium Bromide HFA152a with Actuator A3 was statistically similar to the Atrovent product at 3.0 cm (p=0.20) while Actuator A2 was statistically similar to Atrovent at 6.0 cm (p=0.13) (Figure 4). For the test of PG, Ipratropium Bromide HFA152a with actuator A2 was similar to Atrovent plume width (p=0.46) & spray angle at 6.0cm (p=0.91) (Figure 5).The data demonstrates that it may not be possible to get a direct correlation between the Spray Pattern and plume characteristics between the HFA 152a and HFA134a formulations [3].

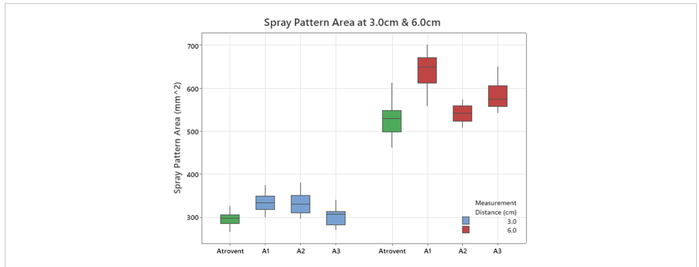

Figure 4 – Spray Pattern Area at 3.0 and 6.0cm

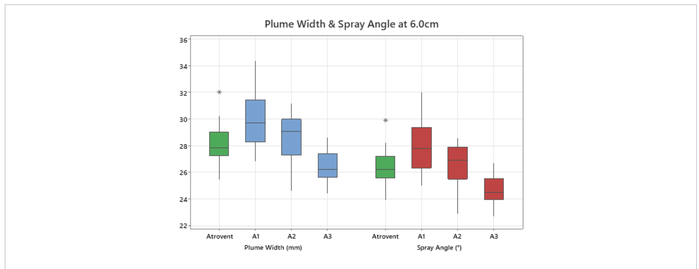

Figure 5 – Plume Geometry and Spray Angle

CONCLUSIONS

In the transition to low GWP propellants, it is critical to understand how the low GWP formulations compare to the current commercially available products. In this study we examined regional deposition of Ipratropium Bromide Inhalers with HFA134a and HFA152a propellant formulation supported with deposition, APSD, SP, and PG data. This work was an initial study; further work is required with larger sample sets and more actuator geometries. A further deep dive into test optimization to mimic In Use scenario is required to correlate the observations.

References

[1] Delvadia R, Wei X, Longest W, Venitz J, Byron P: IN Vitro Tests for Aerosol Deposition. IV Simulating Variations in Human Breathing Profiles for Realistic DPI Testing. In Journal of Aerosol Medicine and Pulmonary Drug Delivery. Volume 29, Number 2, 2016. 196-206.

[2] Designing a Sustainable Ipratropium HFA-152a pMDI: Actuator Geometry Considerations Ameet Sule, Sunita Sule, John Howard, Lauren Liddle, Amala Xavier and Steve McGovern. Respiratory Drug Delivery, May 2024.

[3] FDA-CRCG Workshop on Navigating the Transition to Low Global Warming Potential Propellants, Public Workshop. Session 1: LGWP Propellant Transition for New Drug Product Metered Dose Inhalers (MDIs), December 4-5, 2024. https:/www.complexgenerics.org/education-training/navigating-the-transition-to-low-global-warming-potential-propellants/