

Fluticasone Propionate Suspension MDIs: Plasma Treated Canister Performance and other Canister Types

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Summary

Selection of a suitable canister during Pressurised Metered Dose Inhaler (MDI) product development is of primary importance. Canister material and surface treatment has a direct influence upon drug chemical stability and formulation physical stability. Adhesion of drug(s) to a canister's surface during a product's shelf-life or canister's use-life will affect drug delivery performance metrics including content uniformity of the delivered and therapeutic dose.

This study evaluates the drug delivery performance and chemical stability of a Fluticasone Propionate suspension within HFA 134a in various canister types: Fluorocarbon Polymerised (FCP) Plasma treated, Anodised, Fluorinated Ethylene Propylene (FEP) coated, Stainless Steel, and Aluminium. The drug delivery performance was observed before and after 3-months storage of the MDIs at 40°C and 75%RH. At the 3-month time point, no significant difference was observed between the performance of plasma treated canisters and FEP coated canisters ($p>0.05$); both of which out-performed non-surface treated canisters. When compared to Flixotide (FPD = $44.1 \pm 4.7\mu\text{g}$) data collected during this study, no significant difference ($p>0.05$) was observed after 3-months valve-up storage at 40°C and 75%RH in the FPD $\leq 5\mu\text{m}$ for plasma treated canisters (FPD = $40.4 \pm 0.8\mu\text{g}$) and FEP coated canisters (42.2 ± 1.6). However, significant difference ($p<0.05$) was observed for the uncoated plain aluminium canister following storage (FPD = $33.5 \pm 1.1\mu\text{g}$).

Key Message

A Fluticasone Propionate suspension within HFA 134a was evaluated in various canister types for drug delivery performance and residual drug total can content. No significant difference was observed in the performance of plasma treated canisters and FEP coated canisters ($p>0.05$); both of which out-performed non-coated canisters.

Introduction

Adhesion of suspended micronized drug particulates to the pMDI canister walls may result in deviation from the label claim [1, 2]. The importance of controlling surface-API integration via robust engineering processes of medical devices has previously been highlighted; emphasizing that plasma-based technologies can outperform more conventional coatings methodologies [3].

In this study, micronized Fluticasone Propionate was suspended in HFA134a and packaged within five alternative canister types: Fluorocarbon Polymerised (FCP) plasma treated, anodised, Fluorinated Ethylene Propylene (FEP) coated, Stainless Steel, and aluminium. Drug delivery performance and chemical stability of Fluticasone Propionate is evaluated before and after 3-months storage at 40°C and 75%RH.

Experimental Methods

Metered Dose inhalers (MDIs) were manufactured using five alternative 19ml Presspart canisters; plasma (C0128-F03), Anodised (C0128P), fluorinated ethylene propylene, FEP (C0128P), Stainless Steel (C1202), aluminium (C0128P). All MDIs were fitted with Aptar DF316 61 μl metering valves.

Fluticasone Propionate was micronised, in-house, using a small-scale air-jet mill (LaboMil-1, FPS, Italy). For each formulation, between 17.83 - 18.35mg of micronized Fluticasone Propionate and 10.75 - 11.23g of HFA 134a was added by weight to each can prior to dispersion by ultrasonication. Drug delivery characterisation was performed by next generation impactor (NGI) fitted with USP induction port at a sampling flow rate of 30l/min in accordance with the USP <601>. Drug delivery characterisation was performed using Presspart Actuators (0.30mm exit orifice diameter). Results presented are an average of four measurements taken from two separate MDIs from each of three alternative canister

types (Plasma coated canisters, FEP Coated Canisters, and Plain Aluminium canisters). Measurements were obtained following manufacture (t=0) and after 3-months storage (upright) at 40°C 75%RH.

Drug delivery was also characterised (n = 4) for Flixotide 125 (Batch GU3U); as supplied by a local pharmacist.

All MDIs were actuated in accordance with the Flixotide Patient instruction leaflet and shot weights were recorded for all doses by weight difference.

Chemical stability of Fluticasone Propionate was evaluated (in duplicate) after; 1-month storage (upright and inverted) at 40°C 75%RH (t=1-month); and 3-months storage (upright and inverted) at 40°C 75%RH (t=3-month). Drug mass was recovered from each MDI by evaporation of propellant and solvent; quantitative rinsing into volumetric flasks; and analysis of test-sample content by HPLC. Results are presented as a percentage of the initial drug residual can-content (n=12) immediately following manufacture (t=0); which was $99.3 \pm 1.7\%$ of the target value for all canister types.

Drug content in all test samples was quantified using a validated HPLC stability indicating assay.

Results and Discussion

Drug Delivery Performance

Shot weights were consistent for all doses fired during the study ($77.9 \pm 0.9\text{mg}$). At the initial time point, no significant difference ($p > 0.05$) was found in the drug delivery metrics presented in Table 1 for canister types investigated (Plasma coated, FEP Coated, Plain Aluminium). Particle size distributions were observed to be consistent ($p > 0.05$) for all canister types (see Figure 1b); grouped MMAD = $3.4 \pm 0.2\mu\text{m}$.

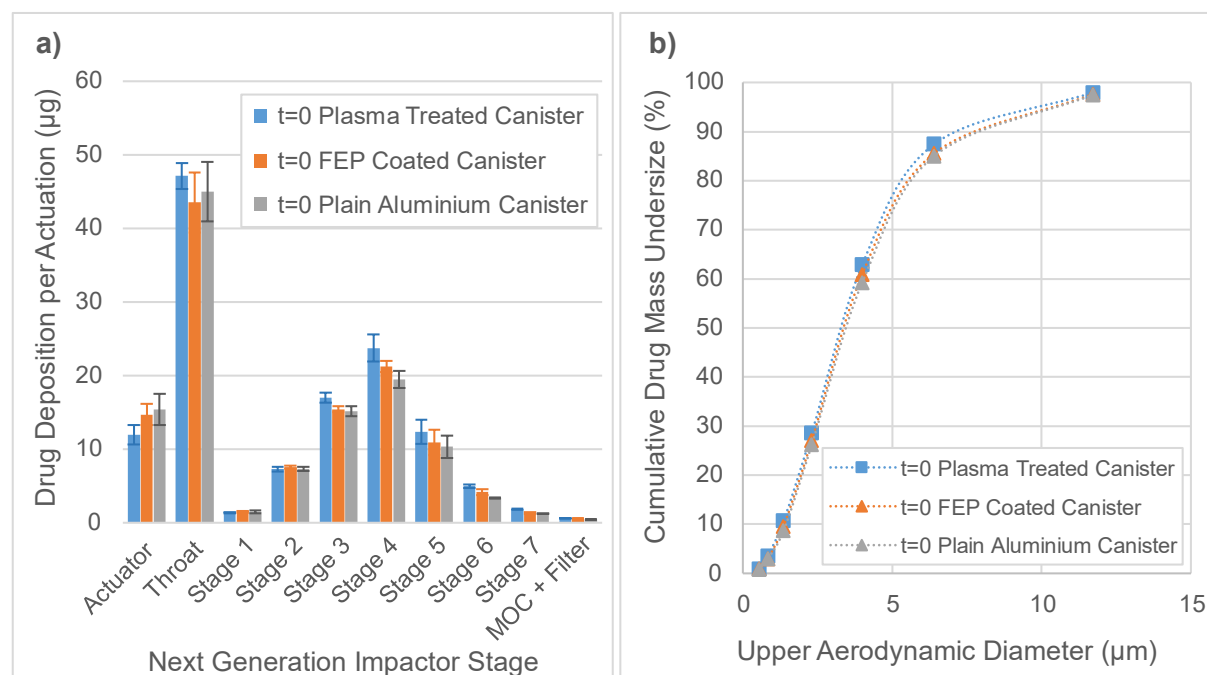


Figure 1 - Data obtained at the Initial time point for three Presspart canister types (mean $\pm$ standard deviation, n = 4). a) Fluticasone Propionate deposition on Next Generation Impactor (NGI) Stages, b) Cumulative percentage drug mass undersize.

At the initial time point, the observed metered doses were within $103 \pm 4\%$ (Plasma Treated), $97 \pm 3\%$ (FEP Coated) and $93 \pm 4\%$ (Plain Aluminium) of target ($125\mu\text{g}$). The plain aluminium canister having an average metered dose 7% below the $125\mu\text{g}$ target dose (see Figure 2); indicating drug loss of $1.3 \pm 0.7\text{mg}$; potentially resulting from wall deposition within the uncoated plain aluminium canister [1, 2, 3].

Following 3-months storage at 40°C/75%RH (valve-up) the surface treated canisters were observed to maintain a metered dose close to the $125\mu\text{g}$ target; $101 \pm 2\%$ (Plasma), $106 \pm 4\%$ (FEP). However, the

observed metered dose from the MDIs packaged with uncoated Aluminium canisters dropped to $86 \pm 9\%$; a further indication of drug loss ($2.5 \pm 1.6\text{mg}$) to the wall of the plain uncoated Aluminium canister.

Fine particle dose and fine particle fraction was observed to be lower for all MDIs following 3-months storage at $40^\circ\text{C}/75\%\text{RH}$. MMAD is also seen to increase (see Table 1). This change in the physical nature of the suspension has been reported to be the result of moisture ingress during the 3-month $40^\circ\text{C}/75\%\text{RH}$ storage period and can be limited by selection of sealing gasket materials and controlled manufacturing conditions [4, 5, 6].

Table 1 – Drug delivery metrics obtained at the initial time point and 3-month ($40^\circ\text{C}/75\%\text{RH}$ - valve up) time point for three Presspart canister types (mean $\pm$ standard deviation, $n = 4$).

	Plasma Treated Canister		FEP Coated Canister		Plain Aluminium Canister	
	Initial	3-months @ $40^\circ\text{C}/75\%\text{RH}$	Initial	3-months @ $40^\circ\text{C}/75\%\text{RH}$	Initial	3-months @ $40^\circ\text{C}/75\%\text{RH}$
Metered Dose (μg)	128.4 ± 4.8	125.8 ± 2.9	120.9 ± 4.2	133.0 ± 4.4	116.9 ± 5.2	107.8 ± 11.9
Delivered Dose (μg)	116.4 ± 5.4	114.6 ± 2.5	106.2 ± 4.8	120.2 ± 2.7	102.5 ± 4.4	98.5 ± 10.3
FPD < $5\mu\text{m}$ (μg)	53.0 ± 3.6	40.4 ± 0.8	46.6 ± 2.8	42.2 ± 1.6	42.7 ± 1.4	33.1 ± 4.0
FPF < $5\mu\text{m}$ (%)	45.5 ± 1.2	35.2 ± 0.5	43.9 ± 2.0	35.1 ± 1.4	41.7 ± 1.4	33.5 ± 1.1
MMAD (μm)	3.3 ± 0.1	3.6 ± 0.1	3.4 ± 0.1	3.6 ± 0.1	3.4 ± 0.1	3.8 ± 0.1
Shot Weight (mg)	77.1 ± 0.4	78.5 ± 0.6	77.3 ± 0.7	78.2 ± 1.0	78.2 ± 0.8	78.1 ± 0.8

When compared to Flixotide (FPD = $44.1 \pm 4.7\mu\text{g}$), no significant difference ($p > 0.05$) was observed in the fine particle dose ($\leq 5\mu\text{m}$) for plasma treated canisters (FPD = $40.4 \pm 0.8\mu\text{g}$) and FEP coated canisters (FPD = $42.2 \pm 1.6\mu\text{g}$) following 3-month storage ($40^\circ\text{C}/75\%\text{RH}$, valve-up). However, significant difference ($p < 0.05$) was observed for the uncoated plain aluminium canister following storage (FPD = $33.5 \pm 1.1\mu\text{g}$, see Figure 2).

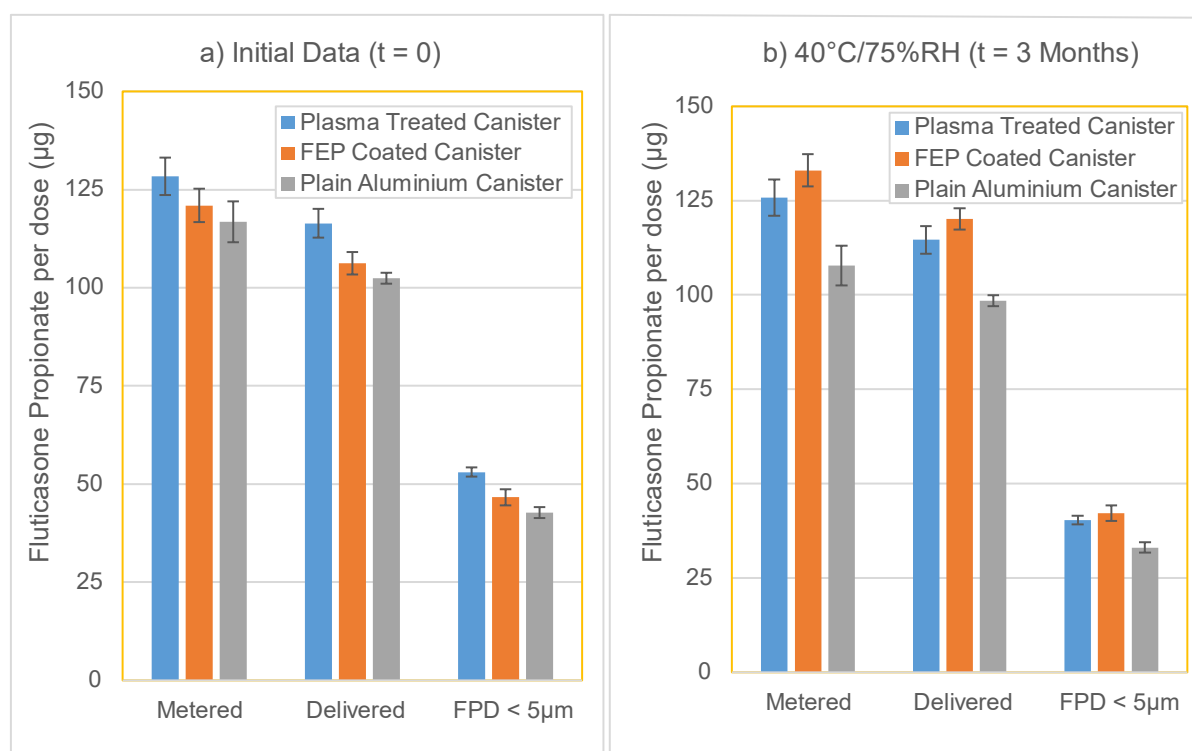


Figure 2 - Metered, Delivered and Fine Particle Dose $\leq 5\mu\text{m}$ (mean $\pm$ standard deviation, $n = 4$) for three Presspart canister types at a) Initial time point and b) following 3-months storage at 40°C and $75\%\text{RH}$.

Chemical Stability: Residual Can Content

The chemical stability of Fluticasone Propionate packaged within five alternative canisters is presented in Table 2 following 1-month (40°C/75%RH) and 3-months (40°C/75%RH) storage (valve-up and valve-down). At 1-month and 3-month time points the residual masses observed for valve-up MDIs were 100 ± 1% (pooled results relative to t=0) indicating canister choice has little effect upon the chemical stability of the Fluticasone Propionate suspension. Data was consistent for canisters stored valve-down except for the Stainless Steel and Plain Aluminium canisters (91.7 and 92.9% residual respectively).

Table 2 – Percentage Fluticasone Propionate residual can content (relative to initial time point, t = 0) following storage at 40°C and 75%RH for 1 month and 3-months.

Storage Condition	T=1 month @ 40°C/75%RH		t=3 months @ 40°C/75%RH	
	Valve up	Valve Down	Valve up	Valve Down
Plasma Treated Canister	100.0	99.6	100.6	98.1
Anodised Canister	100.8	100.1	98.7	97.3
FEP Coated Canister	100.5	100.6	100.2	98.7
Stainless Steel Canister	100.7	97.3	98.2	91.7
Plain Aluminium Canister	101.3	100.5	100.2	92.9

Conclusion

Drug delivery performance and chemical stability has been evaluated for micronized Fluticasone Propionate suspended within HFA 134a and packaged within five alternative canister types.

At the 3-month time point, no significant difference was observed between the performance of Plasma treated canisters and FEP coated canisters ($p>0.05$); both of which out-performed non-coated canisters.

References

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