Plasma Technology: An Innovative and Sustainable pMDI Surface Treatment

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KEYWORDS: plasma, canister, pressurised metered dose inhaler (pMDI), sustainable, fluorocarbon polymer (FCP), presspart

INTRODUCTION

Pressurised Metered Dose Inhalers (pMDIs) typically use aluminium canisters; however, there are two main failure modes that formulations can exhibit: drug adhesion, encountered with suspension formulations [1] and drug degradation, observed in solution formulations.

Alternative canister types have been created to address this, in particular the plasma canister, by providing both a barrier and low surface energy. With numerous canister types available, selecting a suitable canister is important during formulation development [2, 3]. In this study, two formulations, a budesonide solution and a fluticasone propionate suspension, are packaged in five pMDI canister types.

Plasma treatment is a nanolayer that is covalently bonded to the internal surface of the canister; so it is a change in the molecular structure, rather than a coating, of the canister interior through a combination of pharmaceutical gases that cannot be removed from the canister surface. Anodised and fluorinated ethylene propylene (FEP) treatments both use solvents to coat the canisters. Stainless canisters are typically used for more aggressive formulations, but neither stainless nor anodised address adhesion problems since they are only useful for solution formulations.

METHODS

pMDIs were manufactured using five alternative 19 mL Presspart canisters: plasma, anodised, FEP, stainless steel, and plain aluminium. MDIs were crimped with Aptar DF316 61 µL valves (fluticasone propionate) and Aptar DF30+ 50 µL valves (budesonide).

Budesonide 50 µg/50 µL MDIs in hydro-fluoroalkane (HFA) 134a propellant and 13% w/w ethanol were manufactured by weight. Fluticasone propionate MDIs were manufactured by weight to contain 125 µg/61 µL in HFA 134a.

The chemical stability of budesonide was evaluated for each MDI canister type after 1 month and 3 months storage (both upright and inverted), all at 40°C/75% Relative Humidity (RH). Results are presented as a percentage of the initial drug residual canister content immediately following manufacture (t=0).

Drug delivery characterisation was performed for the fluticasone propionate MDIs using Presspart Actuators (0.30 mm orifice diameter) by Next Generation Impactor (NGI) fitted with US Pharmacopeia (USP) induction port, performed according to the USP. Results are an average of four measurements taken from two MDIs from each of three can types (plasma, FEP and plain). Measurements were obtained following manufacture (t=0) and after 3 months storage (valve up) at 40°C/75%RH.

Drug delivery was also characterised for the commercial Flixotide (fluticasone propionate) 125 µg pMDI. All MDIs were shaken in accordance with the Flixotide patient instruction leaflet.

Drug content was quantified using a validated HPLC stability indicating assay.

RESULTS AND DISCUSSION

Budesonide Study

The chemical stability of a budesonide 50 µg solution formulation contained within five canister types was tested and compared. Figure 1 shows the results following 1-month (40°C/75%RH) and 3-months (40°C/75%RH) storage (valve-up and valve-down).

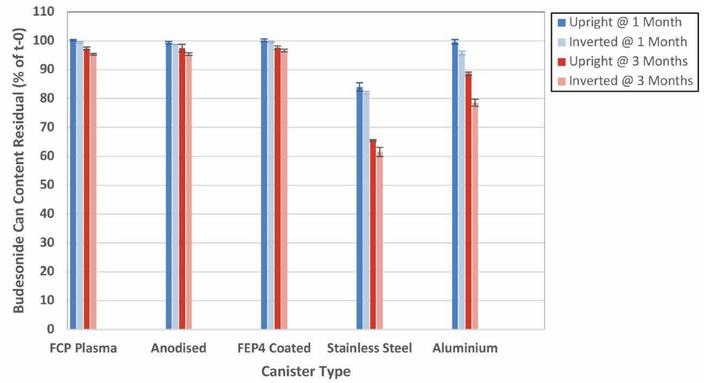

FIGURE 1 - Percentage budesonide residual can content (relative to initial time point, t = 0) following storage at 40°C/75%RH for 1 and 3 months.

For budesonide, surface treated cans outperformed stainless steel and aluminium cans, showing an inert relationship with the formulation and therefore less degradation with the treated can types. In all cases, budesonide residual was lower for MDIs stored valve down.

Fluticasone Propionate Study

Delivery characterisation was performed for plasma, FEP and plain canisters with regards to a 125 µg fluticasone propionate suspension formulation. Fine particle dose (FPD) and fine particle fraction (FPF) was lower for all MDIs following 3 months storage at 40°C/75%RH. MMAD is seen to increase (see Table 1 and Figure 2).

	Plasma Treated Canister		FEP Coated Canister		Plain Aluminium Canister	
	Initial Time Point	3-months @ 40°C/75%RH	Initial Time Point	3-months @ 40°C/75%RH	Initial Time Point	3-months @ 40°C/75%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 < 5µm (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 < 5µm (%)	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

TABLE 1 – Drug delivery metrics obtained at the initial time point and 3-month (40°C/75%RH) time point for three canister types.

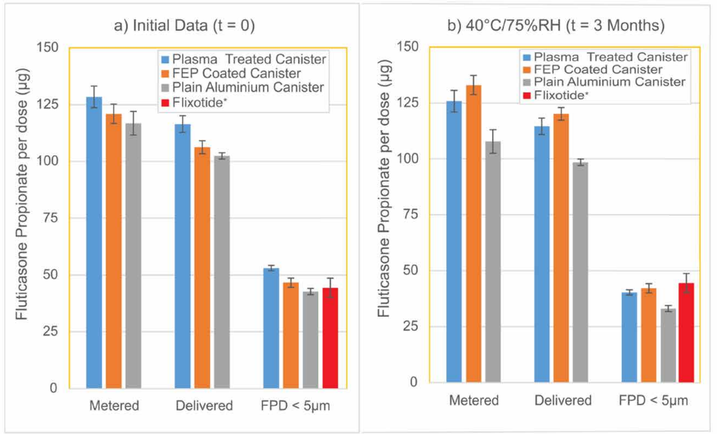

FIGURE 2 - Metered, Delivered and FPD ≤ 5µm for three canister types at initial time point and following 3 months storage at 40°C/75%RH. Flixotide* (n=8), not stored at 40°C/75%RH, is shown for comparison.

When compared to Flixotide (FPD = 44.1 ± 4.7µg, n = 8, see Figure 2), no significant difference (P>0.05) was observed in the FPD (≤5 µm) for plasma canisters (FPD = 40.4 ± 0.8µm) and FEP canisters (FPD = 42.2 ± 1.6µm) following 3-month storage (40°C/75%RH, valve-up). However, a significant difference (P<0.05) was observed for the plain can following storage (FPD = 33.5 ± 1.1µg, see Figure 2), showing drug loss, likely due to plain can wall deposition, since all MDIs were shaken in the same way according to the Flixotide patient instruction leaflet.

CONCLUSIONS

In-vitro drug delivery performance for fluticasone and chemical stability data for budesonide were analysed. The data demonstrates that the patented plasma canister is an effective choice for improving chemical stability and drug delivery performance.

The chemical stability of budesonide was observed to be directly dependent upon canister choice. Fluticasone propionate adhesion was shown to be less with treated cans compared to plain cans due to the higher metered dose results obtained. The role of the canister is an integral part of the drug delivery system itself, rather than just a means of safe containment.

Plasma treated canisters can provide improvements by limiting adhesion and degradation of budesonide solution and fluticasone suspension formulations when compared to plain, stainless steel and anodised cans. Plasma canisters were found comparable to FEP cans for these formulations. However, the use of an FEP canister adds environmental issues associated with using solvent-based coatings and the higher costs related to using a thick-walled canister required for withstanding the heat required during this process. Higher costs are also observed with stainless canisters, which have material surcharges, as well as anodising, which is a third party process, thus increasing variable costs and reducing the economies of scale.

In this study, using a plasma canister provides the most sustainable treated can option and tackles two failure modes commonly seen with pMDIs, whilst being the most cost effective treated canister. Plasma canisters are future-proof since there are no solvents, as with FEP or other coatings, which raise environmental concerns.

H&T PRESSPART

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REFERENCES [1] Vervaet C, Byron PR, Drug–surfactant–propellant interactions in HFA-formulations, Int J Pharm, 1999, 186(1), 13-30.
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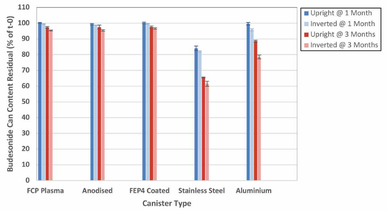

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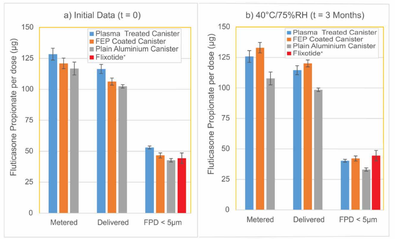

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