

Budesonide Solution MDIs: Plasma Treated Canister Performance and other Canister Types

David A. Lewis¹, Rob. D. Johnson¹, Daniel I. Lewis¹, Jacqueline Green²

¹Oz-UK Limited, Chippenham, Wiltshire, UK

²Presspart Mfg Ltd, Blackburn, UK

Summary

Drug delivery performance and chemical stability has been evaluated for an ethanol-based budesonide solution HFA 134a MDI formulation packaged within five alternative canister types. The chemical stability of the budesonide was observed to be directly dependent upon canister choice.

Following 3-months valve-up storage at 40°C/75%RH, surface treated canisters (plasma, anodised and FEP) were observed to have a budesonide residual of $97.3 \pm 0.5\%$, $97.5 \pm 1.3\%$ and $97.6 \pm 0.6\%$ respectively. However, under the same conditions the drug residual for the same formulation packaged in non-surface treated stainless steel and aluminium canisters was much lower; $65.5 \pm 0.3\%$ and $88.6 \pm 0.6\%$ respectively.

With regards to drug delivery performance, when packaged in Plasma treated canisters, no significant difference ($p > 0.05$) was observed in budesonide drug delivery metrics (delivered dose, fine particle dose and MMAD) before and after 3-months valve-up storage at 40°C/75%RH.

The data presented in this study highlights the importance of selecting a suitable canister type during formulation and product development. With regards to the budesonide formulation evaluated in this study, surface treated canisters (plasma, anodised and FEP) outperformed plain stainless steel and plain aluminium canisters.

Key Message

A solution Metered Dose Inhaler (MDI) budesonide formulation has been evaluated in five alternative canister types. The chemical stability of the budesonide is observed to be directly dependent upon canister choice.

Introduction

Budesonide is a glucocorticoid used in the management and treatment of the inflammatory diseases, including asthma and chronic obstructive pulmonary disease (COPD) [1]. In a recent study, early administration of inhaled budesonide was reported to reduce the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19 [2, 3].

The importance of selecting a suitable canister during formulation development has previously been highlighted [4, 5, 6]. Chemical degradation of budesonide within ethanol base HFA 134a solution formulations has previously been reported when packaged in non-surface treated canisters [7]. In this abstract, a budesonide solution formulation is packaged in five alternative metered dose inhaler canister types: Fluorocarbon Polymerised (FCP) plasma treated, anodised, Fluorinated Ethylene Propylene (FEP) coated, Stainless Steel, and aluminium. In-vitro drug delivery and chemical stability data are presented from three timepoints; initial; 1-month at 40°C/75%RH; and 3-months at 40°C/75%RH. The data presented demonstrates that the chemical stability of the budesonide formulation is dependent upon canister choice.

Experimental Methods

Metered Dose Inhalers (MDIs) containing Budesonide 50µg/50µl in HFA 134a propellant and 13%w/w ethanol were manufactured by weight 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 DF30+ 50µl metering valves. Drug delivery characterisation was performed using Presspart Actuators (0.30mm exit orifice diameter).

For each MDI canister type, the chemical stability of Budesonide was evaluated (in triplicate) after; 1-month storage (upright and inverted) at 40°C 75%RH; and 3-months storage (upright and inverted) at 40°C 75%RH. 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=3) immediately following manufacture (t=0); which was $100.8 \pm 0.9\%$ of budesonide mass (11.7-12.1mg) added to each MDI during manufacture.

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>. Results presented are an average of three measurements each taken from three separate MDIs (Plasma treated canisters); measurements were obtained following manufacture (t=0) and after 3-months storage (valve up) at 40°C 75%RH.

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

Results and Discussion

Chemical Stability: Residual Can Content

The chemical stability of Budesonide packaged within five alternative canisters is presented in Table 1 and Figure 1 following 1-month (40°C/75%RH) and 3-months (40°C/75%RH) storage (valve-up and valve-down). Low budesonide can content residual was observed for non-surface treated canisters due to drug degradation [7].

Valve-Up Storage

At 1-month the residual masses observed for valve-up MDIs packaged with surface treated canisters (plasma, anodised and FEP) were $100.2 \pm 0.2\%$, $99.4 \pm 0.4\%$ and $100.2 \pm 0.5\%$ respectively (i.e., no significant difference $p>0.05$). After 3-months storage at 40°C/75%RH the respective values decreased slightly to $97.3 \pm 0.5\%$, $97.5 \pm 1.3\%$ and $97.6 \pm 0.6\%$ (see Table 1).

For the non-surface treated canister types investigated; Budesonide residual fell (degraded [7]) significantly ($p<0.05$) to $65.5 \pm 0.3\%$ and $88.6 \pm 0.6\%$ after 3-months storage within stainless steel and plain aluminium canisters respectively.

Valve-down Storage

In all cases, Budesonide residual was observed to be lower for MDIs stored valve down. At the 3-month time point 1 - 2% lower values were observed for surface treated canisters. For untreated stainless steel and aluminium canisters, values were respectively 4 - 10% lower when stored valve down. Detailed discussion regarding the valve selected for this study is out of the scope for this abstract.

The data presented here highlights the importance of selecting a suitable canister type during formulation and product development. With regards to the budesonide formulation evaluated in this study, surface treated canisters outperformed plain stainless steel and plain aluminium canisters.

Table 1 – Percentage Budesonide residual can content (relative to initial time point, t = 0) following storage at 40°C and 75%RH for 1 month and 3-months (mean $\pm$ standard deviation, n = 3).

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	100.2 ± 0.2	99.4 ± 0.3	97.3 ± 0.5	95.3 ± 0.3
Anodised Canister	99.4 ± 0.4	98.7 ± 0.1	97.5 ± 1.3	95.4 ± 0.5
FEP Coated Canister	100.2 ± 0.5	99.6 ± 0.2	97.6 ± 0.6	96.6 ± 0.5
Stainless Steel Canister	84.0 ± 1.4	82.0 ± 0.4	65.5 ± 0.3	61.5 ± 1.6
Plain Aluminium Canister	99.6 ± 0.8	95.7 ± 0.7	88.6 ± 0.6	78.6 ± 1.2

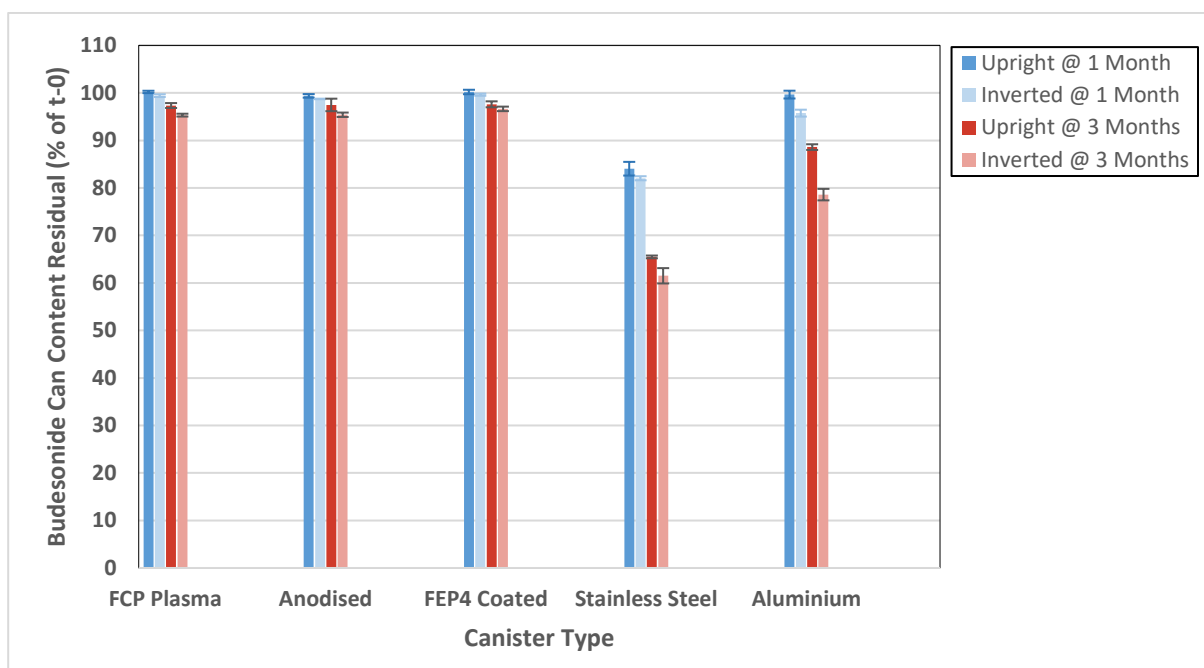


Figure 1 - Percentage Budesonide residual can content (relative to initial time point, $t = 0$) following storage at 40°C and 75%RH for 1 month and 3-months (mean $\pm$ standard deviation, $n = 3$).

Drug Delivery Performance

The Budesonide delivery performance was evaluated for the formulation packaged in plasma treated canisters immediately after manufacture and again following 3-months storage (valve-up) at 40°C/75%RH. Figure 2 presents the cumulative budesonide mass undersize as a function of upper aerodynamic diameter. No significant difference ($p > 0.05$) was observed in the Budesonide drug delivery metrics; delivered dose; fine particle dose ($< 5 \mu\text{m}$); and Mass Median Aerodynamic Diameter (MMAD) when comparing $t=0$ and $t=3$ -months data (see Table 2).

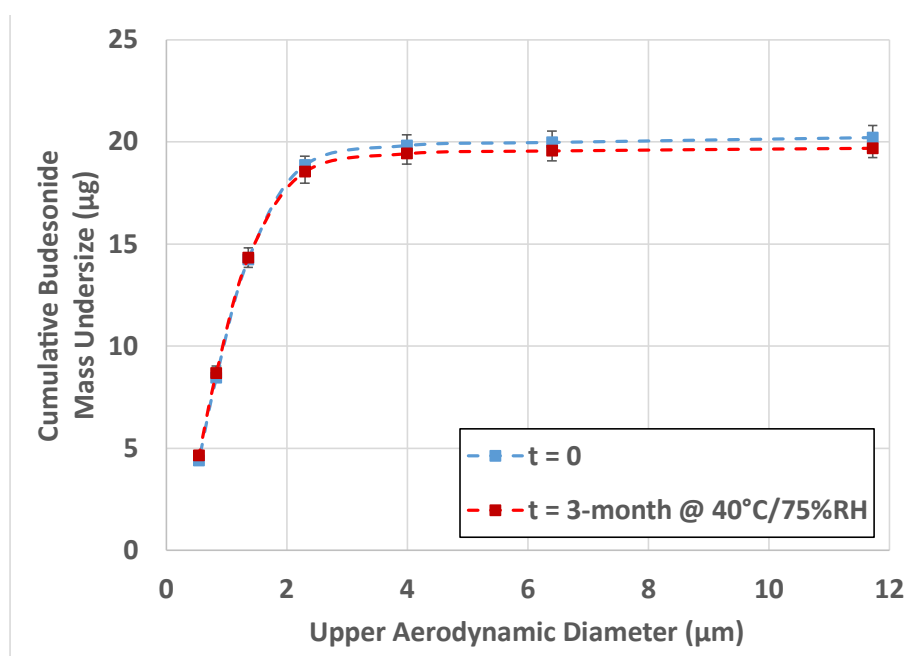


Figure 2 – Cumulative Budesonide Mass Undersize as a function of Upper Aerodynamic Diameter obtained at the Initial time point for Plasma Treated Canister. Data obtained immediately after manufacture ($t = 0$) and again following 3-months storage (valve-up) at 40°C/75%RH (mean $\pm$ standard deviation, $n = 3$).

Table 2 – Drug delivery metrics obtained at the initial time point and 3-month (40°C/75%RH) time point for Plasma Presspart canister (mean ± standard deviation, n = 3).

	Initial	3-months @ 40°C/75%RH
Metered Dose (µg)	49.0 ± 1.3	52.1 ± 0.6
Delivered Dose (µg)	43.6 ± 2.2	46.1 ± 0.6
FPD < 5µm (µg)	19.9 ± 0.5	19.5 ± 0.5
FPF < 5µm (%)	45.7 ± 1.4	42.3 ± 1.6
MMAD (µm)	1.0 ± 0.1	0.9 ± 0.1

Conclusion

Chemical stability has been evaluated for an ethanol bases budesonide solution HFA 134a MDI formulation packaged within five alternative canister types. The chemical stability of the budesonide was observed to be directly dependent upon canister choice.

Following 3-months valve-up storage at 40°C/75%RH, surface treated canisters (plasma, anodised and FEP) were observed to have a budesonide residual of 97.3 ± 0.5%, 97.5 ± 1.3% and 97.6 ± 0.6% respectively. Under the same conditions the drug residual for the same formulation packaged in non-surface treated stainless steel and aluminium canisters were 65.5 ± 0.3% and 88.6 ± 0.6% respectively (i.e., significantly lower, p<0.05).

With regards to drug delivery performance, when packaged in Plasma treated canisters, no significant difference (p>0.05) was observed in budesonide drug delivery metrics (delivered dose, fine particle dose and MMAD) before and after 3-months valve-up storage at 40°C/75%RH.

The data presented in this study highlights the importance of selecting a suitable canister type during formulation and product development. With regards to the budesonide formulation evaluated in this study, surface treated canisters outperformed plain stainless steel and plain aluminium canisters.

References

- [1] Weiner P, Weiner M, Azgad Y, Zamir D: *Inhaled Budesonide Therapy for Patients with Stable COPD*, Chest 1995, 108(6), 1568-1571.
- [2] Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, Krassowska K, Fox R, Binnian I, Glover V, Bright S, Butler C, Cane JL, Halner A, Matthews PC, Donnelly LE, Simpson JL, Baker JR, Fadai NT, Peterson S, Bengtsson T, Barnes PJ, Russell REK, Bafadhel M: Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial, The Lancet, 2021; 9 (7) 763-772.
- [3] Aghjayan R: *Inhaled Budesonide May Improve Outcomes in Early COVID-19 Treatment*, Lung Infection 2021 May, <https://www.pulmonologyadvisor.com/home/topics/lung-infection/inhaled-budesonide-may-improve-outcomes-in-early-covid-19-treatment/> accessed July 2021.
- [4] Lewis DA, Johnson DA, Lewis DI,: *Fluticasone Propionate Suspension MDIs: Plasma Treated Canister Performance and other Canister Types*, Drug Delivery to the Lungs, 2021 (32).
- [5] Baron C, Grosjean B, Heyworth D, Robins E, Sule A, Turner R, Williams G: *Evaluation of Powder Adhesion and Stability of pMDIs with Different Canister Types Including Plasma Treated Canisters*, Respiratory Drug Delivery 2014. Volume 2, 2014: 349-354.
- [6] Stevenson P: *Controlling Surface Performance Characteristics of Medical Devices: A Critical Review of the Latest Industrial Techniques*, Respiratory Drug Delivery 2016. Volume 1, 2016: 147-156.
- [7] Lewis D, Ganderton D, Meakin B, Ventura P, Brambilla G, Garzia R: *Pressurised metered dose inhalers (MDI)*, U.S. Patent 7,223,381 B2, May 29,2007