An improved end-of-life performance for suspension pMDIs with Presspart plasma treated canisters

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Summary

Drug deposition on the inner walls of the pMDI canister is a reported phenomenon, occurring by adhesion [1] or adsorption [2]. The loss of drug to the walls of the canister will result in variability in the delivered dose from the pMDI through life. Interactions between canister and formulation can also catalyse chemical degradation of the drug [2]. Presspart's patented fluorocarbon polymerised (FCP) plasma treatment offers a solution to overcome the challenges of drug deposition and interaction with the aluminium alloy canister.

A study was conducted to evaluate the performance of FCP plasma-treated and untreated aluminium alloy canisters, when used in conjunction with a budesonide HFA suspension formulation. Performance was evaluated by assessment of delivered dose through life, tail-off characteristics and drug deposition on canister walls.

Test		Plain Canister	Plasma-treated Canister
Mean Delivered Dose[1]	Beginning of Life (BOL)	85.5	84.9
	Middle of Life (MOL)	97.8	105.2
	End of Life (EOL)	72.3	102.1
Mean actuation number of final acceptable dose[2]		215	235
Mean residual drug in exhausted canister		4.059	1.334

[1]Expressed as % of label claim
[2]Acceptable dose defined as 65% to 135% of label claim

Table 1: Summary of findings

The delivered dose at end of life (EOL) and tail-off characteristics indicated a strong influence of the FCP plasma treatment on drug deposition properties with the selected formulation, with the change in delivered dose at EOL being significantly less pronounced, and tail-off in emitted dose occurring further beyond the labelled number of doses, in the plasma-treated canisters. These findings were corroborated by the drug deposition assessment. Through further studies, the treatment can also be evaluated for its effect on drug degradation over the shelf-life of various suspension and solution based formulations.

Introduction

Aluminium alloy canisters have been widely used in commercial MDI products over the past 60 years mainly due to their excellent moisture and light barrier characteristics and inert relationship with the drug and propellants. Other materials, including stainless steel have been used depending upon the particular formulation characteristic. Some solution formulations are susceptible to catalytic degradation in the presence of aluminium, while drug adhesion and adsorption on the internal metal surfaces of the canister has also been reported, particularly in suspension formulations [1], [2]. The loss of drug to the walls of the canister will result in variability in the delivered dose from the pMDI during the shelf life.

The most widespread approach to overcome these challenges is the incorporation of internal coating materials to minimize formulation–canister interactions. In particular, low-energy surface coatings are widely used in order to reduce unwanted drug deposition on the surface of the canister. Examples developed include fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), and related materials and blends. Other treatments include anodisation, which renders the canister surface unreactive, but can increase adhesion.

One of the recent innovations in treatment of MDI canisters is by the plasma treatment process patented by Presspart. An *in vitro* study was conducted to understand the performance of Presspart plasma treated canisters in comparison with plain aluminium alloy canisters for suspension pMDIs. The study focussed on the delivered dose performance through life; additionally, depleted canisters were subjected to a confirmatory determination of residual drug.

Fluorocarbon Polymerisation (FCP) treatment at Presspart

Presspart's patented FCP plasma treatment offers an alternative solution to overcome the challenges of drug adhesion and interaction with the aluminium alloy canister. The FCP plasma treatment produces a low surface energy (hydrophobic) fluorocarbon polymerised ('FCP') nanolayer covalently bonded to the internal surface of the canisters. The process uses readily-available high-purity industrial gases and monomers in contrast to the solvents used in spray coating processes, and it does not produce any harmful waste products. The process is validated, and treatment parameters are continually monitored by the system.

Methods and materials

The selected formulation was a dry suspension formulation comprising the active pharmaceutical ingredient (API) budesonide and HFA 134a, which was identified as an example of an extensively studied, wholly suspension based formulation [3]. The label claim is 100 µg delivered by each actuation of the valve. The label claim for the number of doses available to the user is 200 per inhaler.

The formulation was filled into 19 mL canisters by a third party, into Presspart plain aluminium alloy canisters and Presspart FCP plasma-treated canisters. All study materials (API, Aptar valve, Presspart actuator) were kept consistent between both sets of canisters in the study.

The test methods were developed internally at Presspart's Inhalation Product Technology Centre (IPTC), Blackburn, UK. Automated shake and fire systems were used for delivered dose and for firing down of canisters prior to determination of tail-off effects (Vertus® and DecaVertus® by Novi Systems). Dose weights were recorded throughout testing, to exclude the depletion of propellant as an explanation for changes in performance.

Delivered Dose

Delivered Dose through life was determined using the set-up described in US Pharmacopoeia test method <601> Apparatus A. Doses were collected in a through-life regime, with 3 doses collected at the beginning of life, 4 doses in the middle of life and 3 doses at the end, to produce a total of 10 samples per inhaler. 5 plain canisters and 5 plasma-treated canisters were tested in this way. Each sample was prepared by fixed-volume recovery using 25 mL of sample solvent (30:70 acetonitrile:phosphate buffer pH3.2) and manual agitation; quantification of the resulting sample solutions was performed by reversed-phase HPLC. Shot weights were recorded for all testing.

For determination of the tail-off characteristics, 3 cans of each type were depleted by actuating 180 doses to waste, before performing delivered dose testing at intervals of 4 actuations up to dose 200, then intervals of 5 actuations beyond dose 200. Testing at these intervals continued until 3 consecutive shot weights were obtained below 10 mg (a signifier of the depletion of propellant).

Drug Deposition on Canister

Randomly selected canisters were fired to waste using automated shake-and-fire equipment until emitted weights were observed below 10 mg. The canisters were then vented and opened, and any drug residues recovered using sample solvent and ultrasonic agitation. The efficacy of the method was confirmed using a second recovery, performed in the same way, which detected less than 0.5% of the amount detected in the first recovery.

Results

Figure 11 contains a graphical depiction of the delivered dose of budesonide formulation from 5 plasma-treated canisters and 5 plain aluminium canisters, at the beginning, middle and end of life. A student's T-test was performed on the two sets of samples at each stage, at the 95% confidence level, assuming equal variances. Results are displayed on Figure 1 1. The tests do not show a statistically significant difference ($p = 0.794$) at the beginning of life, and both sets of samples are within the 65%-135% limits. At the middle of life a statistical difference was detected ($p = 0.036$), with the mean delivered dose being higher from the plasma-treated canisters than from the plain canisters. The most significant difference was detected at the end of life ($p = 0.000$); at this stage the plain canisters generated several results below 65% of the labelled dose, while the plasma-treated canisters all remained within the acceptable range.

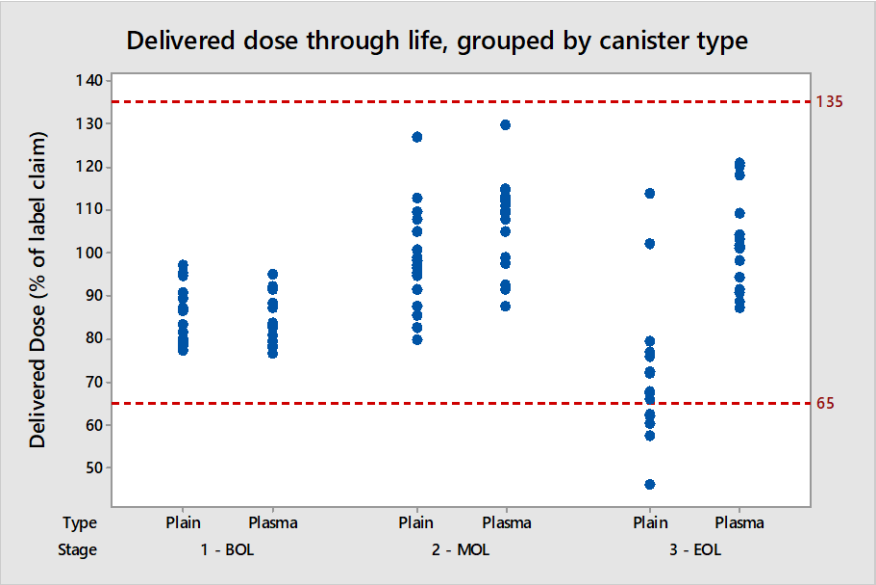

Figure 1 – Comparison of Delivered Dose performance through life

The tail-off characteristics are displayed in Figure 2. These results show a clear difference between the two varieties of canister, with a sharper, later tail-off in performance apparent in the plasma-treated set.

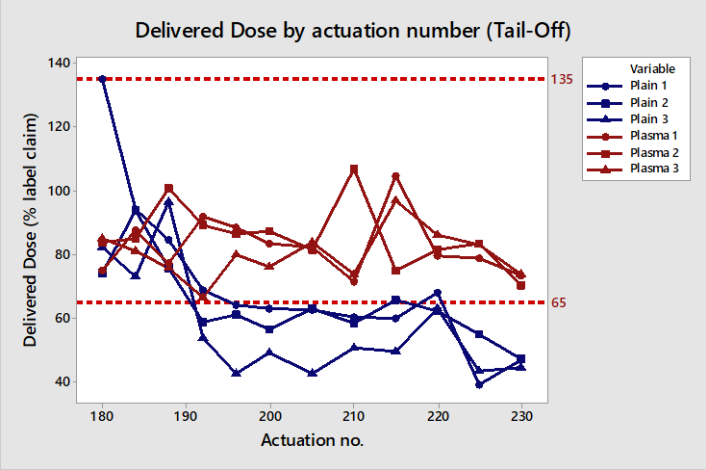

Figure 2 – Tail-off characteristics for Plasma-treated and Plain canisters, using Delivered Dose

This effect was not observed in the shot weights recorded in the test, as illustrated in Figure .

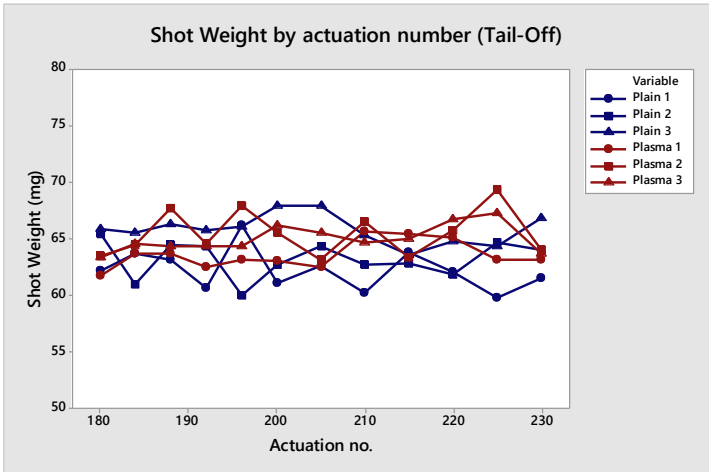

Figure 3 – Shot weights for tail-off testing

The drug deposition assessment (Figure 4) also demonstrates a difference between the two types of canister, with an additional 2.7 mg of residual budesonide being detected in the mean of plain canisters compared with the mean of plasma canisters.

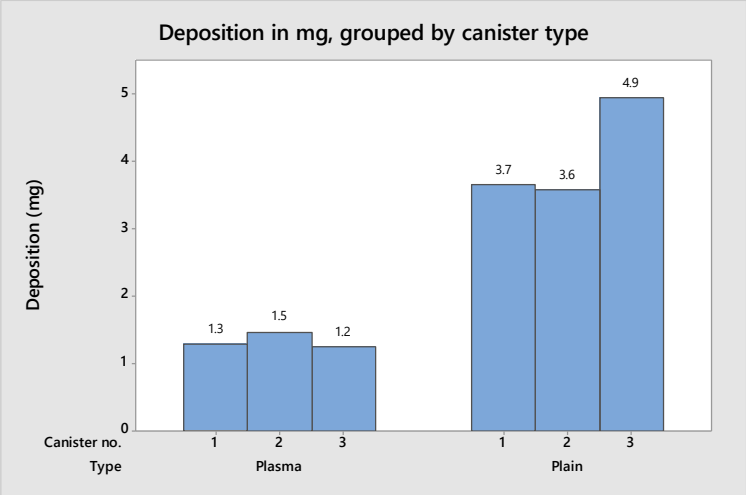

Figure 4 – Drug deposition on canister walls

Discussion and Conclusion

The results demonstrate that FCP plasma-treated canisters can provide improvements in end-of-life delivered dose performance compared with plain aluminium alloy canisters, when used in combination with a budesonide HFA suspension formulation.

By comparison with the corresponding shot weight data, it can be concluded that the tail-off trends seen in the delivered dose results are an effect of the drug concentration in the doses, rather than a depletion of propellant. This study therefore provides evidence that the plasma treatment can be effective in reducing the amount of drug lost to the internal walls of the canister by adhesion or adsorption.

Further studies are necessary to show that this effect occurs in other suspension products.

Acknowledgement

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References

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