H&T PRESSPART

GAS PLASMA PROCESSING: A LONG-TERM SOLUTION FOR RESPIRATORY DEVICES

Ameet Sule, Head of H&T Presspart's Inhalation Product Technology Centre (IPCT), discusses the new challenges arising in metered dose inhaler design since the change from CFC to HFA propellants, in particular focusing on the tendency for drug product to adhere or degrade when in contact with the aluminium interior of the canister. As a solution, Mr Sule proposes new developments in gas plasma processing.

SUMMARY

Hydrofluoroalkane (HFA) propellants are widely used in modern metered dose inhalers (MDIs) due to their lack of hazardous and environmentally damaging effects on the ozone layer, compared with chlorofluorocabons (CFCs). However, an HFA formulated with an API can interact with the canister substrate, causing deposition of the drug on the canister walls or interaction with the pharmaceutical drug solution, causing drug degradation and resulting in reduced shelf life.

H&T Presspart's plasma process, manufactured under license from Portal Medical Ltd (Swaversey, UK), treats the internal surfaces of MDI canisters so that the active drug content does not adhere to the canister wall, and enhances drug stability in formulations where interactions with the aluminium substrate can lead to product degradation.

Plasma technology can also be applied to plastic parts in a dry powder inhaler (DPI), where there are challenges of cohesive powders and the surrounding conditions causing drug to be retained in the device.

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USE OF HFAS IN MDIS

MDIs are commonly used to treat respiratory diseases and nasal disorders. Ensuring that the device delivers a consistent dose and that the formulation is safe (non-toxic) is of paramount importance. The drugs are administered by aerosol and formulated as either a suspension or solution in a liquefied propellant gas. For over 50 years CFCs were the propellants of choice for MDIs, but these were phased out by the end of 2010 in line with the Montreal protocol, due to their contribution to ozone layer depletion.

Replacement propellants have been developed over the past two decades based on HFAs, most notably HFA134a and HFA227ea. These propellants are non-ozone depleting and chemically inert, making them the ideal candidates for medicinal products. However, some properties of

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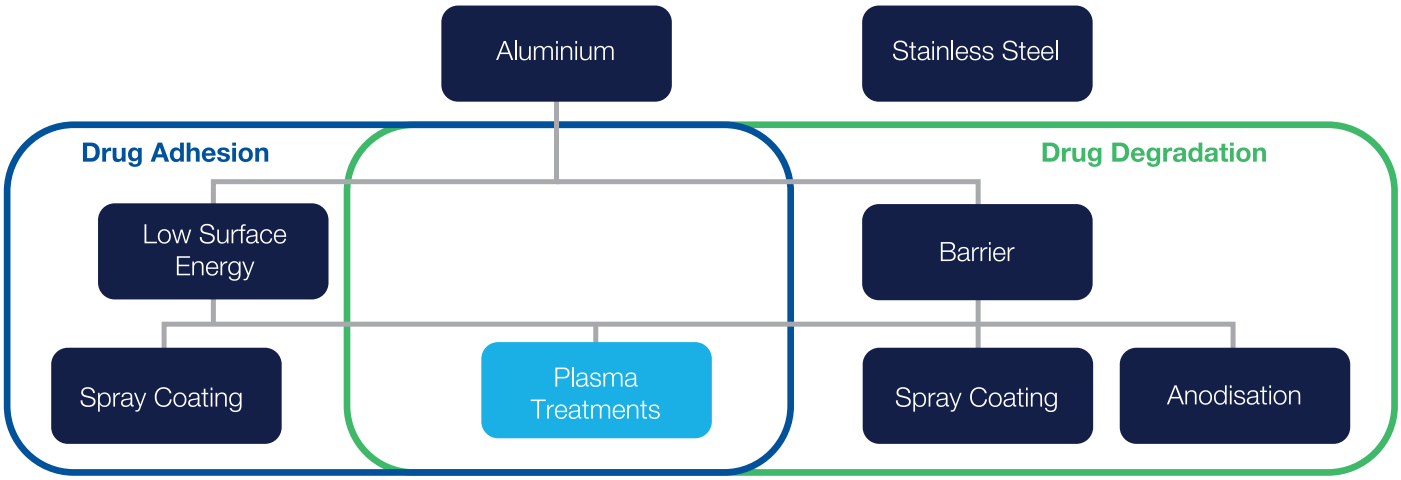

Figure 1: Types of surface treatment.

these compounds are substantially different from those of the CFCs traditionally used in MDIs, resulting in new challenges.

With HFA drug suspension formulations, interactions with the canister substrate can cause deposition of the drug on the canister walls or on exposed surfaces of the valve components. Interactions with solutions more commonly cause degradation, resulting in increased impurity levels. In both cases, the interaction leads to a reduction in the drug content in the formulation, resulting in the patient receiving less than the prescribed dose.

The surface chemistry of the MDI canister therefore has a vital role in the overall performance of the MDI and the drug. To protect the contents from deposition and degradation, a number of surface coatings have been developed that can be applied to MDI canisters and valve components (Figure 1).

COATING MATERIALS & TECHNIQUES

Over some years a number of surface coatings have been developed to protect the drugs from deposition or degradation.

Fluorocarbon polymers (FCPs) are commonly used to coat the interior canister surfaces in order to eliminate adhesion or deposition of, for example, salbutamol on canister walls. These polymers can be made from multiples of one or more of a variety of monomers – particularly preferred coatings tend to be pure perfluoroalkoxyalkylene (PFA) or blends of polytetrafluoroethylene (PTFE) and polyethersulphone (PES), due to their relatively high ratios of fluorine to carbon. In addition, coatings that combine fluorocarbon polymers with non-fluorocarbon polymers, such as polyamides, are used for certain formulations to improve adhesion of the coating to the canister walls. Other coating types include epoxy-phenol resins.

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Standard metal coating techniques can be used to pre-coat the metal substrate and cure it, prior to shaping the metal into the components, for example via deep-drawing or extrusion. This pre-coating method has the advantage of being well suited to high volume production. Other coating techniques include spraying the insides of preformed cans, dipping and electrostatic dry-powder coating, all of which can be followed by curing.

Many of these processes require high temperatures, up to 400 °C when curing, which can create additional costs and complications, and increase the environmental impact. Furthermore, only the most robust canisters (that is, those produced through deep-drawing) should be subjected to such high temperatures, as less robust canisters can become unrolled or suffer other morphological changes under these conditions.

PLASMA PROCESSING TECHNOLOGIES

More recently, plasma processes have been developed to modify the surface of an MDI canister and this approach has proved to have a number of advantages over traditional coating methods. Gas plasma processing (GPP) is an industrial technique that is carried out under vacuum to treat a wide range of substrate materials. The process involves constant or pulsed excitation of gas, either by radio frequency (RF) or microwave field, to produce an energetic plasma. The process can create an ultra-thin layer that protects against deposition and corrosion or modify the surface to prevent degradation.

It is a low-temperature process and is ideal for uniform treatments of components with complex shapes, including small components in large volumes. The coating adheres well to the component substrate, because the plasma process cleans the component surface while in the vacuum, resulting in an ultra-clean substrate-coating interface.

Using GPP to tailor the surface chemistry has the advantage of providing uniform surface treatment without changing the properties of the bulk material. The process can be used to change the outermost layers of the material only, without polymerising a coating, resulting in modifications to the functional chemistry. These modifications can be used stand-alone or with the addition of a subsequent surface coating through a single process cycle, depending on the application and desired properties.

OPTIMISING THE PLASMA PROCESS

Plasma processing of MDI canisters can bring multiple benefits to the MDI

performance, helping to reduce drug deposition and improve the stability of formulations where interactions with the aluminium substrate would lead to product degradation and reduced shelf life. However, the process needs to be highly controlled to ensure complete consistency of treatment and uniformity of coating to the internal walls of the canisters.

Plasma chemistry is critical to the performance of the coated canisters – the right choice of precursor chemistry enables a robust process with excellent performance. A variety of plasma treatments have been tried in the past, including single- and dual-layer technologies with a range of monomers, but these have failed to penetrate the market due to poor scalability and cost viability. However, alternative developments have become available that have made plasma a viable choice.

A cost-effective process has been established, using an optimised plasma chemistry consisting of an intrinsically robust monomer, highly ionised to form a high crosslink density. The ultra-pure gases and monomers do not contain any solvents, so do not produce any waste by-products. The result is a coating technology without the extractables issues potentially encountered with some polymer systems.

It is critical that plasma processing achieves complete and consistent coating across the entire surface of the inside of the canister. Traditional plasma processes, be they RF or microwave, are particularly difficult to control when internal surfaces are to be treated. Poor penetration of plasma ions with low energy results in a non-uniform, thin or porous coating, which will inevitably perform poorly. Increased ion energy to aid depth of can penetration gives rise to ion etching at the can neck and a more "line-of-sight" process.

This partial "line-of-sight" process leads to non-uniformity/thickness variation in such geometries. For nanometre thin coatings on MDI cans this is observed as striations in colour or colour bands down the can. With the best compromise, the coating builds up around the canister lip, throat and base, with depletion at the rim, shoulders and can corners.

More recently, an improved process has been developed that eliminates the issues associated with typical plasma system designs. Using proprietary gas/monomer delivery configurations and electric field control, designed specifically for can coating geometry, uniform coatings can be deposited.

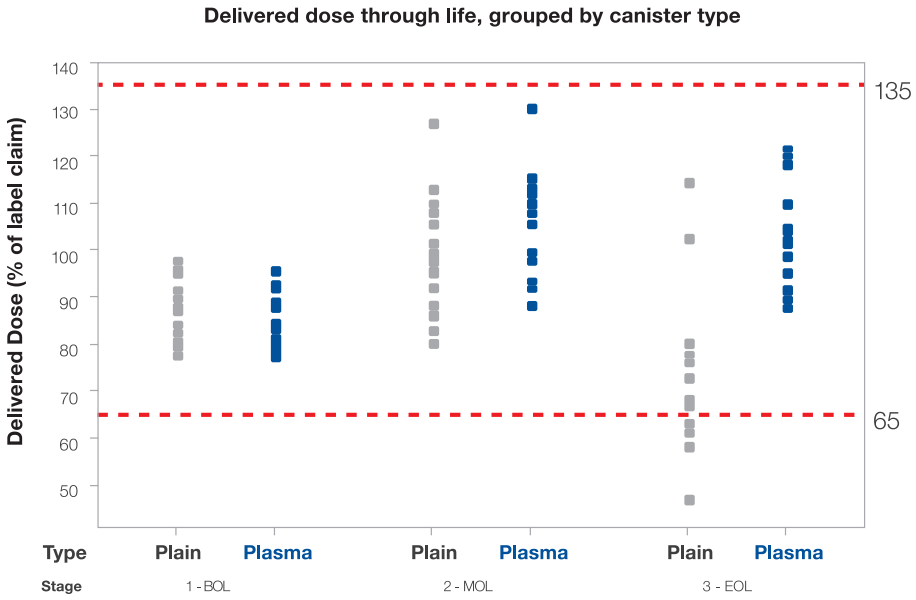

Figure 2: Comparison of delivered dose performance of a budesonide HFA suspension formulation at beginning (BOL), middle (MOL) and end of life (EOL), using plain aluminium and plasma-treated MDI canisters.

Dedicated system design configurations mean constant, high deposition rates with extreme reproducibility in terms of coverage, chemical speciation and product performance. The unique combination of process equipment design and precursor monomer means the technology is now scalable to handle the throughput and commercial demands of the global MDI market.

Example: Budesonide HFA Suspension

GPP has been used to develop several different plasma coating options that have successfully prevented drug deposition on the can walls and drug degradation in solution or suspension. For example, a surface treatment has been especially developed for deep-drawn 5052 aluminium canisters, which is suitable for budesonide suspension in HFA.

As can be seen in Figures 2 and 3, plasma-treated canisters exhibited more reliable performance at the end of life. The difference in profiles observed with delivered dose and shot weight tests confirms that the primary tail-off effect relates to the concentration of drug in the formulation, as opposed to the weight of formulation emitted.

Figure 4 illustrates the conclusion that the improved end-of-life performance was achieved by reducing the amount of drug deposited on the canister walls throughout use. The canister contents were determined after depletion of formulation, with an additional 2.7 mg of residual budesonide being detected in the mean of plain canisters compared with the mean of plasma canisters.

DRY POWDER INHALERS AND PLASMA TECHNOLOGY

Another possible application of plasma technology is in the plastic component surfaces of a DPI. The various flow paths the powder needs to take through a DPI can make it difficult to achieve a consistent delivery performance. Plasma treatments are suitable for a wide range of materials, including plastics such as PTFE, polypropylene, polyethylene and polystyrene. It might therefore be beneficial to treat these parts to achieve a smoother flow and more complete evacuation of the formulation from the capsule, blister, reservoir or cartridge.

Modifying the active sites to render them more hydrophobic or more hydrophilic, dependent on the particular drug substance of interest, could enable a formulator to achieve more consistent delivery of the drug from the DPI.

CONCLUSIONS

Respiratory devices are complex in nature. Even though the MDI has been in a generic form for the last 50-plus years, it has been a challenge for R&D chemists to deliver a robust product to the market. MDIs combine a mixture of mechanical components, physical dimensions, the

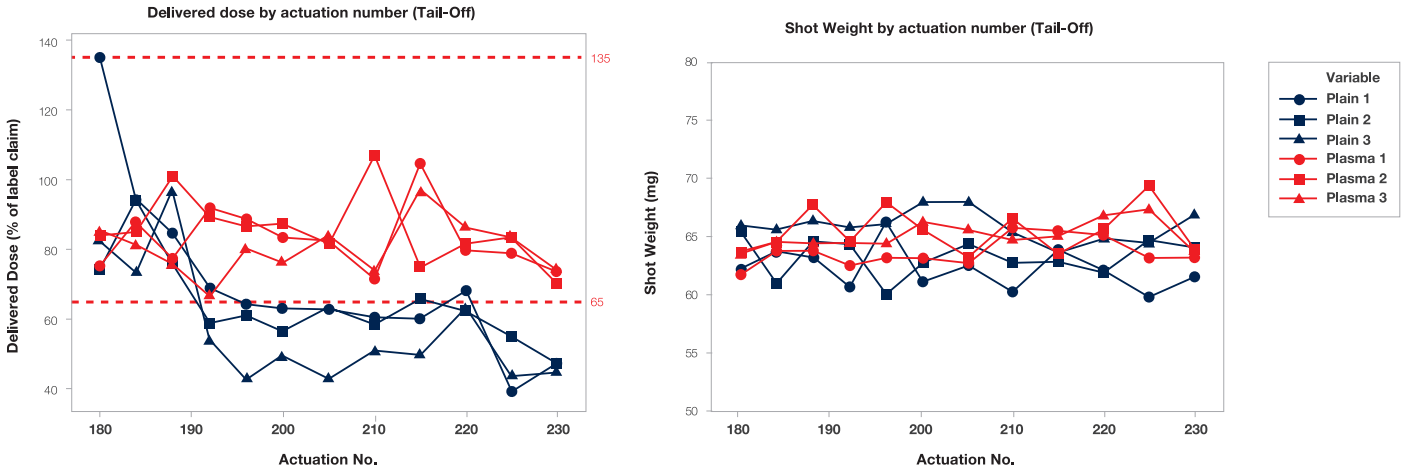

Figure 3: Tail-off characteristics for plasma-treated and plain canisters, using delivered dose testing (left) and shot weight (right), for a budesonide HFA suspension formulation.

chemical composition of the formulation and physical properties (e.g. temperature, pressure, moisture ingress), all of which affect the product characteristics.

GPP offers considerable advantages in the coating and treating of MDI canisters, improving the stability of the formulation and extending product shelf life. In addition, the ability to plasma process high volumes of the canisters fulfils the demand for high volumes from the MDI market.

Laboratory tests have already demonstrated 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. Other respiratory medicine applications which have been, or are being, developed include the prevention of drug degradation in solution MDIs, and the treatment of DPI components to aid the evacuation of formulation.

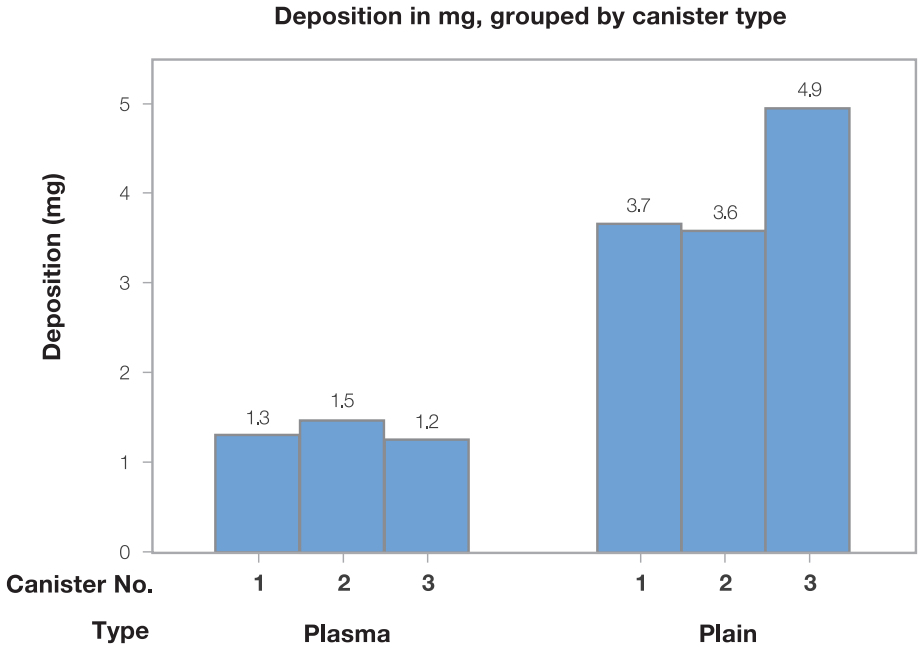

Figure 4: Drug deposition on canister walls after depletion of formulation.

ABOUT THE COMPANY

H&T Presspart offers pharmaceutical customers high-precision, injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems. The company has more than 45 years' experience and a worldwide reputation for competence, quality and innovation in the pharmaceutical and other industrial sectors. The H&T Presspart Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with sales offices in China, India, South America and the US.

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Ameet Sule, Director of H&T Presspart's Inhalation Product Technology Centre, is a pharmaceutical professional having worked in the industry for more than 20 years, specialising in the development of inhalation products and devices.

REFERENCES

1. *Newman SP, "Principles of Metered-Dose Inhaler Design". Respir Care, Sep 2005, Vol 50(9), pp 1177–1190.*
2. *Smyth HD, "The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers" Adv Drug Deliv Rev, Jul 2003, Vol 55(7), pp 807–828.*
3. *Sukasame N, Boonme P, Srichana T, "Development of budesonide suspensions for use in an HFA pressurized metered dose inhaler". ScienceAsia, 2011, Vol 37, pp 31–37.*