The development of a novel metered dose inhaler cyclic olefin copolymer elastomer sealing system

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Introduction

The objective of this work was to develop a new and improved sealing system for MDI (metered dose inhaler) products. The sealing of a metered dose valve to a canister in an MDI is a key part of the overall integrity of the MDI system and has historically been most frequently done using nitrile (black or white) or EPDM (ethylene propylene diene monomer) seals. The main MDI sealing system ensuring the container closure between the metered dose valve and the canister could influence many attributes of the resulting MDI including moisture content, leak rate, impurities and degradation products, dose content uniformity, particle size distribution (or fine particle mass) and extractable & leachables.

The potential for moisture to contribute to instability and particle aggregation in non-aqueous pharmaceutical aerosols formulations is well known [1], and minimizing moisture ingress and content are of interest in order to develop and manufacture stable aerosol formulations. The cleanliness of the materials used in the MDI container closure system, and minimizing extractables and leachables are also seen by regulatory authorities as key elements with regard to both safety [2] and eventual stability of the MDI products [3]. In addition any sealing system for MDIs has to have low long term leak rates over a wide range of environmental conditions.

This work describes the development of an innovative sealing material, cyclic olefin copolymer elastomer (COCe), which can offer several advantages in terms of the overall performance of the MDI system, specifically with regard to moisture resistance and cleanliness and thus eventually to the overall stability and performance of such MDI products incorporating this kind of valve to canister sealing technology. Key performance characteristics were studied such as leak rates, moisture ingress, extractables and compatibility with different HFA (hydrofluoroalkane)/ethanol ratios as well as other manufacturing related parameters such as crimping and recycling have also been investigated.

Cyclic olefin copolymers [4] are a new class of polymeric materials with property profiles which can be varied over a wide range during polymerization. These new materials exhibit a unique combination of properties which can be customized by varying the chemical structure of the copolymer. Interesting performance benefits for MDI applications could be considered as - low water absorption, excellent water vapour barrier properties, rigidity, strength and compression set, excellent biocompatibility, good resistance to acids and alkalis and their ability to be moulded into specific component parts. COCs have already found successful industrial applications in the parenteral drug arena and their unique combination of properties, detailed above, make them ideal solutions for applications such as prefilled syringes [5].

Experimental methods

Leak rates were assessed by manufacturing MDIs containing various COCe type sealing gaskets and filled with HFA with and without ethanol. Samples were stored at 20°C and 40°C/75%RH inverted position, over time and their leak rates measured at ambient temperature and compared to EPDM control sealing gaskets by weight loss.

Moisture ingress levels were assessed by manufacturing MDIs containing various COCe type sealing gaskets and filled with HFA, with and without ethanol. Samples were stored at 20°C and 40°C/75%RH, over time and their moisture contents were determined using a validated Karl Fisher method and were compared to EPDM sealing gaskets.

Extractable levels were assessed for Nitrile, EPDM and COCe materials following extraction with appropriate solvents for each material type and quantified using validated HPLC (high performance liquid chromatography, UV detection, reverse phase C18 column, eluting solvents water/ethyl acetate/acetonitrile) and GCFID (gas chromatography flame ionisation detection, dimethylpolysiloxane capillary column, helium carrier gas) analytical methods.

Results

The results of leak rate testing for the various MDIs tested are given in Figure 1.

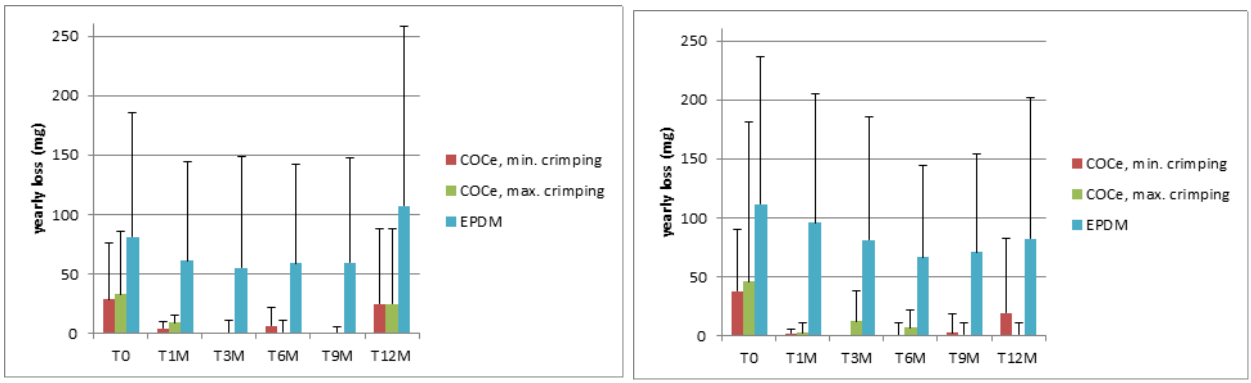

Figure 1 - Leak rate testing of various configurations of MDIs (n=25) with different sealing gaskets containing HFA with 15% w/w (left) and without (right) ethanol at 20°C crimped at different parameters. Bars represent max & min values observed.

The results of moisture ingress testing for various MDIs tested are given in Figure 2.

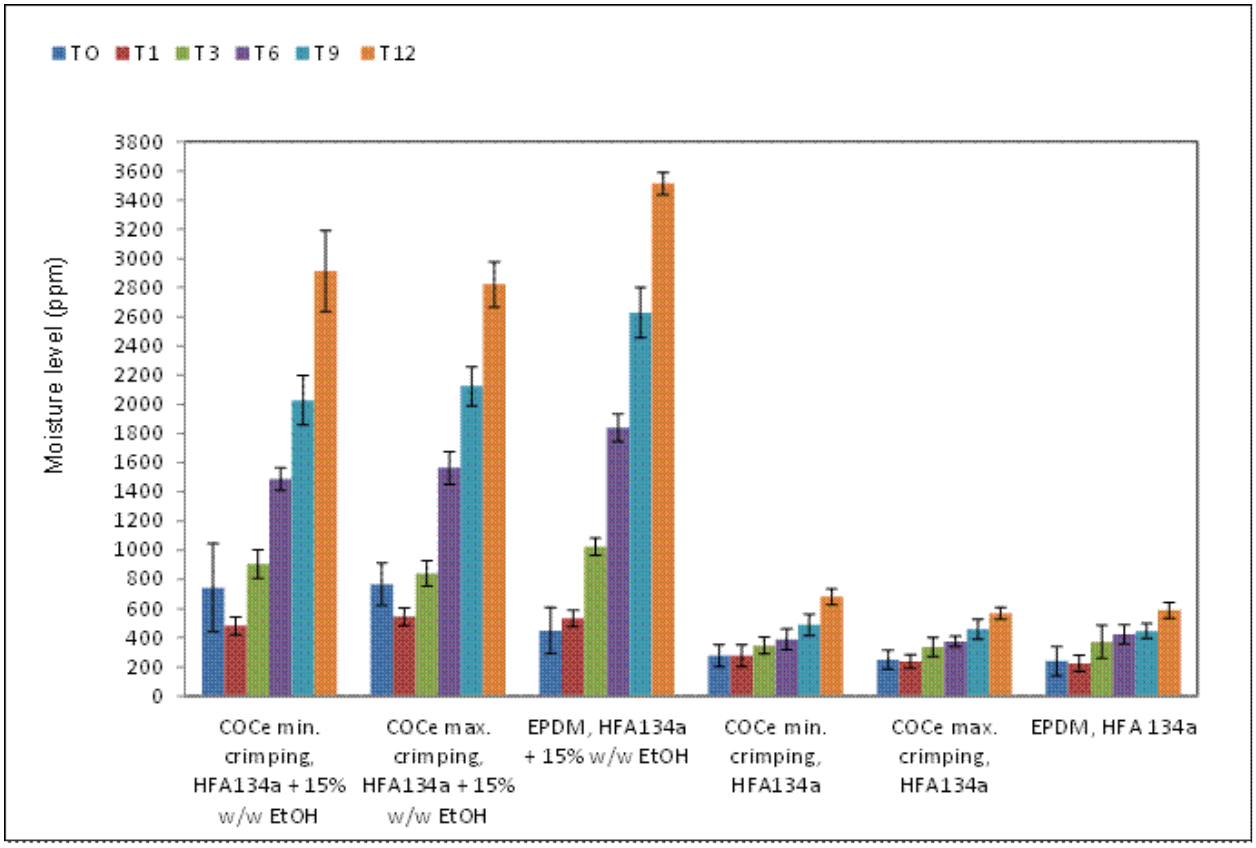

Figure 2 - Moisture level results of various configurations of MDIs (n=15) with different sealing gaskets containing HFA with & without ethanol and crimped at different parameters, tested using Karl Fisher. Error bars represent +/- one standard deviation.

The results of extractables testing for the various materials assessed are given in Figure 3.

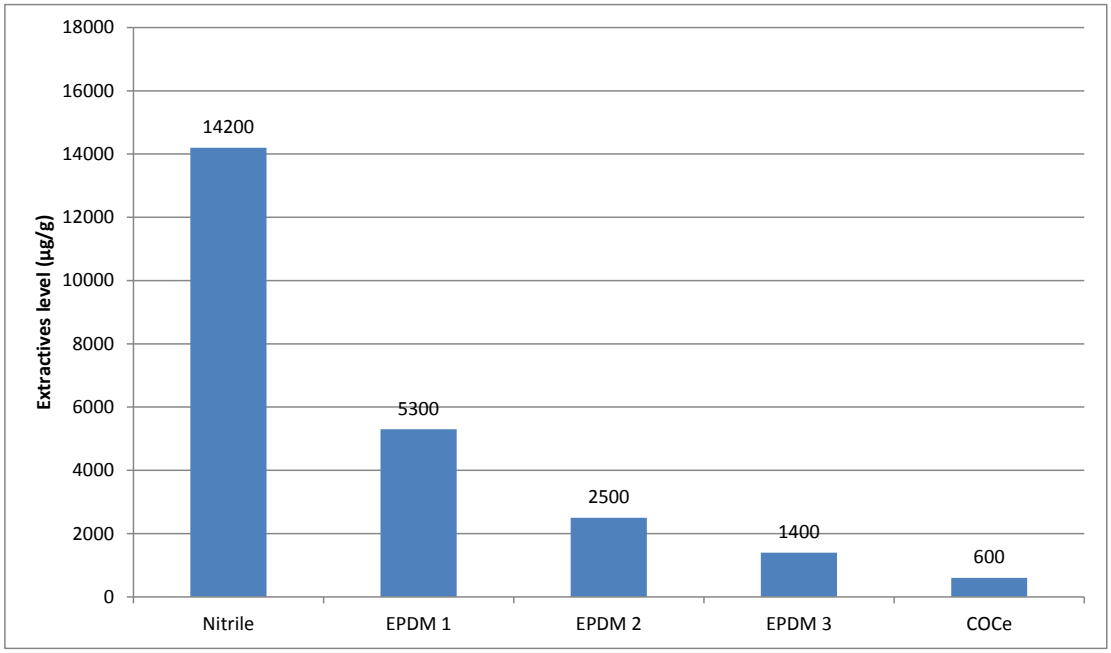

Figure 3 - Extractable levels measured in various gasket sealing materials assessed by HPLC and GCFID

Discussion

The results for leak rates, see Figure 1, measured at 20°C show that the COCe material is superior to the EPDM grades at 20°C (also true for 40°C/75%RH, not shown here) either with or without ethanol present in the HFA formulation.

The results of the moisture testing, see Figure 2, reveal that COCe overall has good moisture protection for the contents of the MDI during storage. Moisture content results with Ethanol present in the HFA are higher as compared with pure HFA and this is not surprising due to ethanols greater affinity and capacity for water. COCe is known to have a low water vapour transmission rate [6] and for aerosol products that may be sensitive to moisture content, COCe could be an interesting choice for the sealing material of the MDI system.

Extractables levels measured from the COCe sealing material, see Figure 3, were found to be significantly less than traditional Nitrile material and lower than both EPDM and 'extracted' EPDM material. The sealing gaskets in an MDI account for the majority of the elastomeric content of the MDI, and if extractables can be minimized from this source, it will significantly reduce the overall extractables burden of the MDI container. The main extractables components from COCe were noted to be antioxidants, alkanes and decahydronapthalene.

Ongoing studies have revealed that COCe performs well in terms of manufacturing with crimping trials revealing acceptable tolerances around parameters such as crimping compression, height and diameters, see Figures 1 & 2. Temperature cycling studies indicate that the material resists well during temperature fluctuations. As sealing gaskets are primarily static with their primary functions being efficient sealing and providing a barrier during the shelf life of the product, (as opposed to stem gaskets in MDIs which have a mechanical function during movement & dosing), COCe would seem like a suitable material for such purposes.

COCe also has the potential to be an 'environmentally friendly' packaging material as it can be recycled several times and still retain its mechanical and physicochemical properties. Overall the objective of finding a new and improved material for sealing MDI systems seems to be well addressed by COCe and ongoing work should bring further proof of its value as an alternative choice of sealing material for MDIs.

Conclusion

This work demonstrates the potential value of COCe as an innovative sealing material, it can offer several advantages in terms of the overall performance of the MDI system, specifically with regard to leak rates, moisture resistance and cleanliness and thus eventually to the overall stability and performance of such MDI products incorporating this kind of valve to canister sealing technology. In terms of manufacturing, COCe appears less sensitive to crimping parameters as compared to other MDI sealing elastomers.

References

[1] Williams G, Tcherevatchenkoff A, *Moisture Transport into CFC-Free MDIs*, Respiratory Drug Delivery VI. Volume 1, 1998: 471-474.

[2] PQRI (Product Quality Research Institute), *"Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products*" (8 September 2006)

[3] U.S. Food and Drug Administration. *Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry, Manufacturing, and Controls Documentation, draft guidance*. Maryland, USA: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research; 1998.

[4] Cyclic olefin copolymers, www.topas.com/

[5] S Makwana, B Basu, Y Makasana, and A Dharamsi, *Prefilled syringes: An innovation in parenteral packaging*, Int J Pharm Investig. 2011 Oct-Dec; 1(4): 200–206.

[6] ASTM, F1249, moisture rate transmission testing at 38°C/90%RH