The continued development of a cyclic olefin copolymer elastomer sealing system for metered dose inhalers

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Summary

This work reports further proof around the potential value of cyclic olefin copolymer elastomer (COCe) as an innovative sealing material for metered dose inhalers. As previously reported cyclic olefin copolymers 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 metered dose inhalers (MDIs) 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.

This work details further proof around the performance of COCe as an innovative sealing material, during this study key performance attributes were investigated such as leak rates and moisture ingress, and new investigations have been made into formulation compatibility and the characterisation of any potential extractables from the COCe material. Other manufacturing related parameters such as crimping and recycling have previously been investigated and reported.

Introduction

The sealing of a metered dose valve to a canister is a key part of the overall integrity of the MDI system and this work reports on the continued development of a novel COCe elastomer sealing system. As previously reported cyclic olefin copolymers [1] 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 [2].

This work reports further proof around the potential value of COCe as an innovative sealing material, during this study key performance attributes were investigated such as leak rates and moisture ingress, and new investigations have been made into formulation compatibility and the characterisation of any potential extractables from the COCe material. Other manufacturing related parameters such as crimping and recycling have previously been investigated and reported (1).

Experimental methods

Moisture ingress levels were assessed by manufacturing MDIs containing COCe type sealing gaskets coupled with various gathering rings and filled with hydro fluoro alkane (HFA) without ethanol. Samples were stored at 40°C/75%RH, inverted position, over 12 months and their moisture contents were determined using a validated Karl Fisher method[3] and were compared to EPDM (ethylene propylene diene monomer) and nitrile sealing gaskets.

Leak rates were assessed by weight loss on MDIs containing COCe type sealing gaskets and filled with HFA without ethanol stored at 40°C/75%RH inverted position, and their annual leak rates calculated and compared to EPDM and nitrile sealing gaskets. Crimping parameters were optimized in order to get the best fit for each of the material evaluated.

Compatibility was evaluated for both suspension and solution types formulations upon accelerated ageing, considering that the main compatibility risks for such formulations are respectively drug adhesion on materials and drug loss.

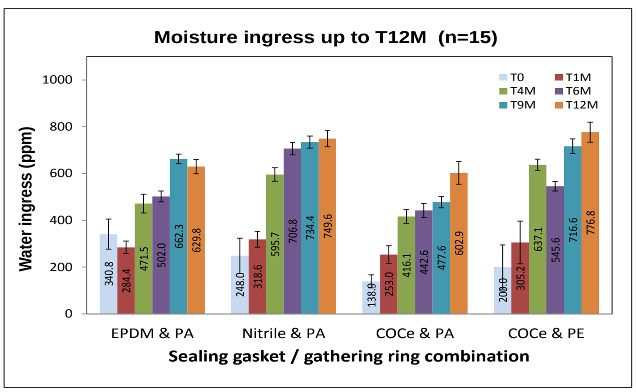
Drug adhesion was investigated using a suspension of micronized salbutamol sulphate with HFA134a, which was manufactured in-house and pressure-filled through Aptar DF30 metering valves, stored for 6 months at 40°C/75%RH, inverted position. Adhesion of powder to canister, neck gasket & gathering ring and the rest of the metering valve were determined using a validated HPLC (high performance liquid chromatography) method and compared to EPDM sealing gaskets.

Two different model solution formulations were also employed, chosen to evaluate the compatibility of COCe with both weak organic and strong mineral acids: a mixture of Ipratropium bromide, ethanol, water, citric acid and HFA134a and a mixture of formoterol fumarate, ethanol, hydrochloric acid, isopropyl myristate and HFA134a. Both were manufactured in house, by first preparing a concentrated solution (ethanol, active pharmaceutical ingredient and excipients) which was introduced into canisters, and then adding the propellant through the crimped valve. Although the second formulation shows rapid and high loss of active ingredients when stored at accelerated conditions, it serves as an investigative method only to assess material compatibility over a shorter time period. An Aptar DF30 metering valve was used and the remaining percentage of the active ingredient was determined after storage for 6 months at 40°C/75%RH, inverted positon, using validated HPLC methods and compared to EPDM sealing gaskets.

Extractable levels were assessed for EPDM and COCe raw materials components following reflux extraction with ethyl acetate 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 moisture ingress and leak rate testing for the various MDIs assessed are given in Figure 1 and 2 respectively.



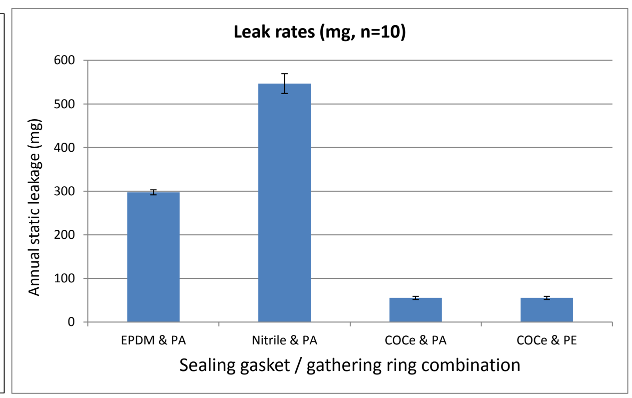
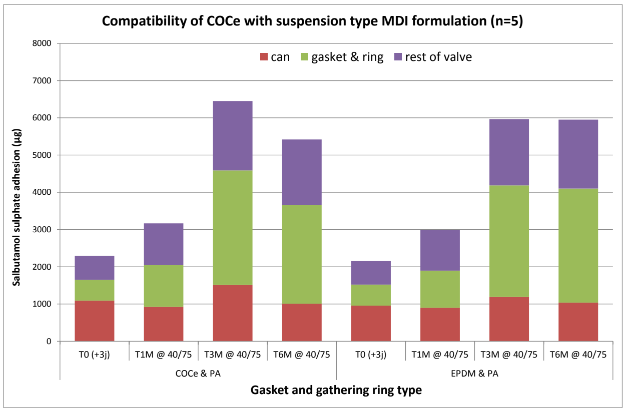


Figure 1 (left) - Moisture level results of various configurations of MDIs (n=5) with different sealing gaskets containing HFA 134a without ethanol tested using Karl Fisher. Error bars represent +/- one standard deviation.

Figure 2 (right) - Leak rate testing of various configurations of MDIs containing HFA with different sealing gaskets. Error bars represent one standard deviation.

The results of COCe compatibility with suspension and solution type formulations are detailed in Figure 3 and 4 respectively.



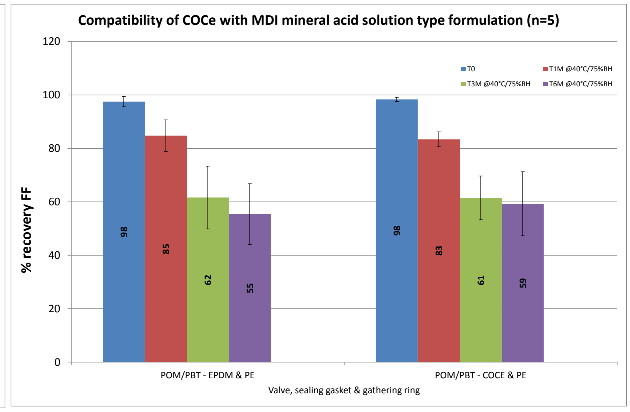


Figure 3 (left) – Adhesion of salbutamol sulphate to various MDI components following storage for up to 6 months at 40°C/75%RH.

Figure 4 (right) – Recovery of Formoterol Fumarate following storage for up to 6 months at 40°C/75%RH.

The results of extractables testing for the various materials assessed are given in Figure 5. Calculations are based on elastomers only (internal and neck gaskets), considering them fitted into a final product (DF30 valve).

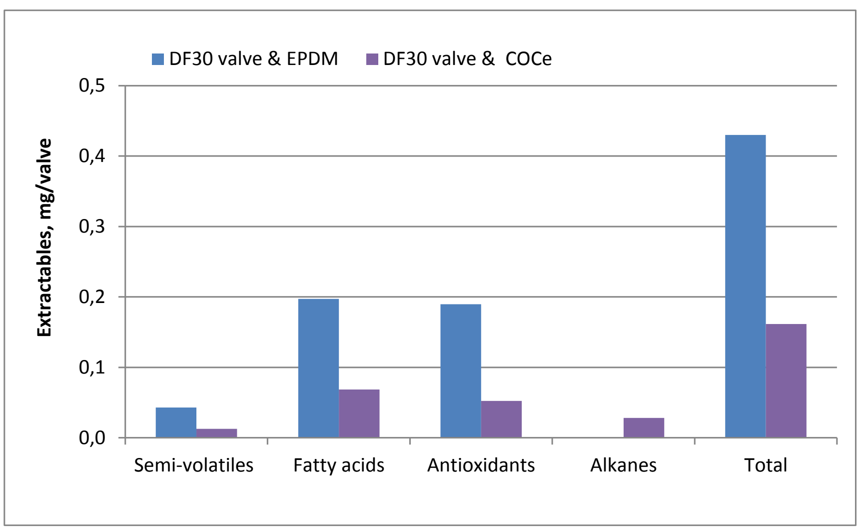


Figure 5 - Extractable levels per MDI valve containing different gasket sealing materials.

Discussion

The results of the moisture testing, see Figure 1, reveal that COCe overall has good moisture protection for the contents of the MDI during storage for up to 12 months under accelerated conditions. When coupled with a polyamide (PA) ring (which is a material well known for its capacity to absorb water), it shows the best results, while when coupled with a polyethylene (PE) ring, results are equivalent to those obtained for nitrile gasket and PA ring. COCe is known to have a low water vapour transmission rate [2] 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.

The results for leak rates, see Figure 2, show that the COCe material is superior to both EPDM and Nitrile when stored at accelerated stability test conditions.

Results of drug adhesion, see Figure 3, show that there is no more drug deposition on a valve fitted with COCe neck gasket, compared to EPDM neck gasket.

When evaluated with a model formulation containing mineral acid, the MDI valves fitted with COCe material show equivalent chemical compatibility to valves fitted with EPDM sealing gaskets, see Figure 4.

Extractables levels measured from MDI valves containing COCe, see Figure 5, were found to be significantly less compared to those found in valves with EPDM sealing materials. 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 semi-volatiles, fatty acids, antioxidants and alkanes.

Conclusion

This work provides further evidence for 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 formulation compatibility thus eventually to the overall performance of such MDI products incorporating this kind of valve to canister sealing technology. COCe leak rates and extractables levels were noted as measurably better in comparison to traditionally used materials such as Nitrile and EPDM.

References

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