Evaluation Permeation and Leachable Characteristics in Metered Dose Inhalers

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Key Message

COCE (cyclic olefin copolymer with unique properties) valves demonstrate significantly lower leakage rates compared to nitrile valves due to their lower dipole moments and less polar structure, making them ideal for applications requiring minimized permeation and leachables.

Introduction

This study aimed to explore the relationship between the dipole moments of elastomers and their permeation characteristics, focusing on the performance of cyclic olefin copolymer (COC) and nitrile valves in metered dose inhalers (MDIs) [1]. The ability of a material to prevent permeation and minimize leachables is critical in many industrial applications, particularly in the field of inhaled drug delivery where the integrity and efficiency of the delivery system are paramount. Permeation through valve materials can lead to significant loss of propellants and active ingredients, compromising the efficacy of the drug delivery system [2].

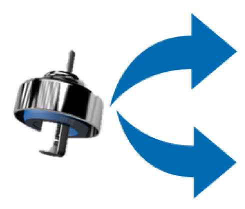
Understanding leachable characteristics is equally important as they directly affect the safety and efficacy of the drug product. Leachables can migrate from the elastomeric components into the drug formulation, potentially causing adverse reactions or affecting the stability and performance of the drug [3]. Therefore, evaluating the interactions between elastomers and propellants, and their impact on both permeation and leachables, is essential for optimizing the design and selection of materials used in MDIs [4].

COCE is known for its low-loss characteristics at high frequencies and a low mechanical loss factor, indicating a moderate to low dipole moment [2]. These properties suggest limited interactions with polar molecules, potentially reducing permeation. In contrast, nitrile polymers typically exhibit higher dipole moments due to the presence of polar nitrile groups (−C≡N), which can enhance interactions with polar permeants and increase permeation rates.

The dipole moment measures the polarity of a substance, determined by the distance between charged ions. When the polarity of the solvent and the seal are similar, diffusion rates increase, while dissimilar

Materials and Methods

MATERIALS



COCE neck gasket

Nitrile neck gasket

H&T Presspart; C0842P

+ HFA 134a, HFA 227 ea, HFA 152a, HFO 1234ze

N=20 / configuration

LEAKAGE TEST METHOD

Systems are:
- Weighed: W1
- Stored in temperature-controlled room (25°C) for 14 days (T)
- Weighed after storage: W2

Leakage evaluation (mg per year)

$$\frac{(W1 - W2)}{T} \, x \, 365$$

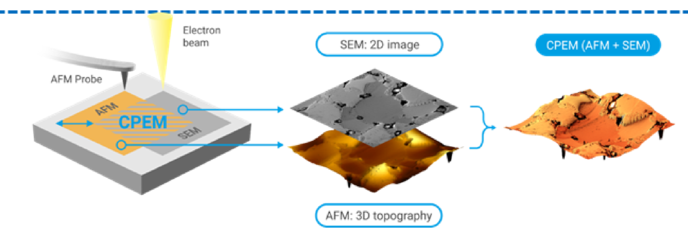
Requirements are met if:
- Average leakage per year ≤ 525 mg
- Maximum individual value ≤ 750 mg

FATTY ACID METHOD

The samples are analyzed after a reaction (derivatization) in order to add a chromophore function to fatty acid and allow quantification by HPLC/UV

TOPOGRAPHY

Neck gasket topography was evaluated using:
- Scanning electron microscope (SEM)
- Coupled with an atomic force microscope (AFM)



Results and Discussion

Static Leakage & Fatty acids

To visualize the difference in leakage rates, the following graph (Figure 1) illustrates the mean yearly loss for various propellants in both COCE and nitrile valves. Table 1 summarises the fatty acid extractable levels from different propellant and elastomer systems.

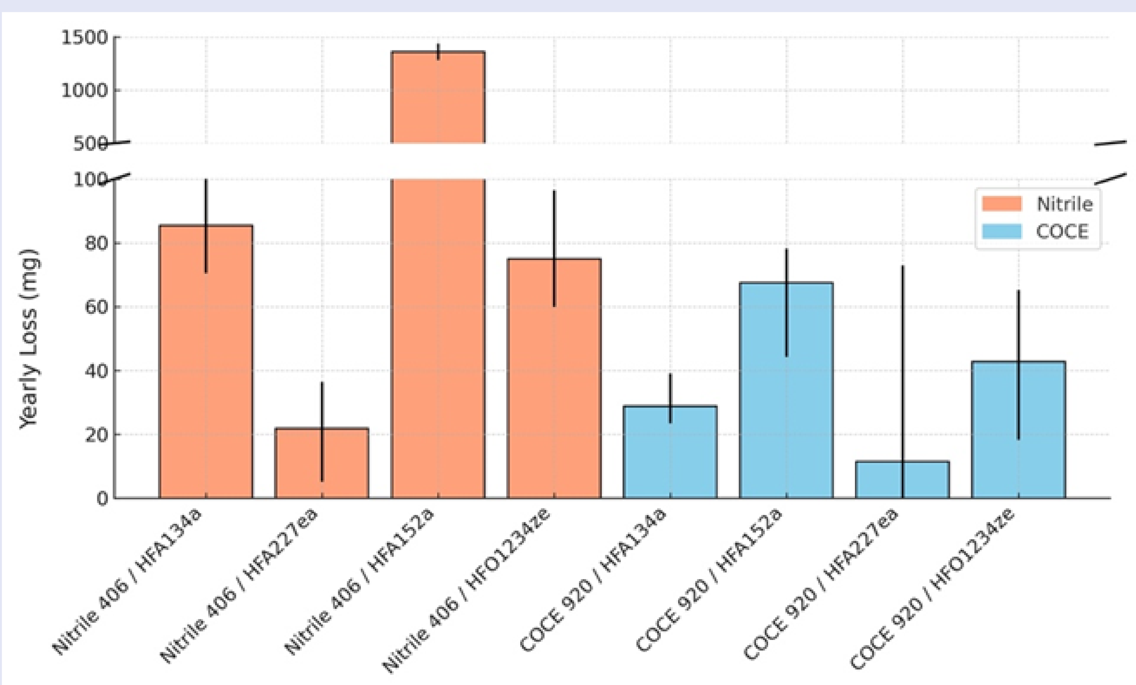


Figure 1 – Yearly loss distribution (mg) for different propellants, comparing Nitrile and COCE neck gaskets. Bar graph shows mean ± standard deviation (N=20)

The data presented indicate that nitrile valves show significantly higher mean yearly loss rates for various propellants. For example, the mean yearly loss for HFA 152a was extremely high at 1358.1 mg, compared to 85.4 mg for HFA 134a. This high permeability is attributed to the higher dipole moment of nitrile (1.85 debye) and the presence of polar nitrile groups, which enhance interaction with polar molecules like HFA-152a. HFO-1234ze had lower leakage in both elastomers, but

Conversely, COCE valves exhibited much lower leakage rates. The mean yearly loss for HFA 152a in COCE valves was 67.5 mg, significantly lower than in nitrile valves. COCE's lower dipole moment and less polar structure result in reduced interaction with polar permeants, thus lowering permeation rates. Additionally, COCE's intrinsic properties, such as low permeability, chemical resistance, and structural stability, contribute to its effectiveness in preventing gas and vapor transmission.

Moreover, fatty acids extracted from COCE valves are lower than ones from nitrile valves (see typical values obtained from both configurations in the Table 1). This level of fatty acids that can be extracted from the valve is an important factor to consider when selecting valve raw materials. Indeed, fatty acids can directly impact MDI performance or leachables obtained.

	mg/valve	
	Nitrile valve	COCE valve
Total fatty acids	2.5	0.1

Table 1 –Typical fatty acid values obtained

Integrated SEM/AFM (Scanning Electron Microscope/ Atomic Force Microscope) imaging data

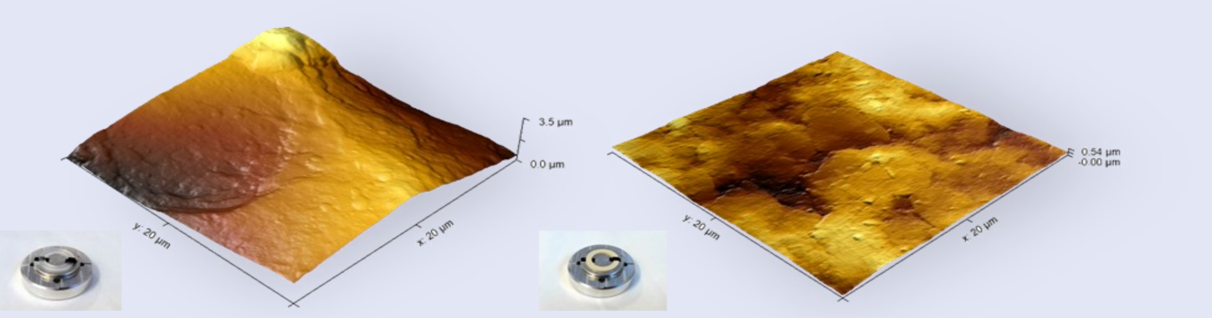


Figure 2 – Surface topography images analysed by integrated SEM/AFM technology of COCE neck gasket (left) and nitrile neck gasket (right).

Integrated SEM/AFM imaging data revealed significant differences in the surface topography and material properties of the two gaskets, directly correlating with their leakage performance (Figure 2). The nitrile gasket exhibited a rough, scale-like surface structure, leading to increased surface area and greater interaction with gas molecules, which contributed to its higher permeation rates. In contrast, the COCE gasket displayed a more corrugated but smoother surface, which reduced the effective contact area between the gasket and the gas molecules. This limited direct interaction with propellants, combined with the material's higher stiffness, minimised molecular diffusion and reduced gas permeation. These surface characteristics may explain the observed lower leakage rates for COCE compared to nitrile, demonstrating COCE's superior performance in applications requiring minimal leakage and high barrier properties.

Conclusions

- The study highlighted the differences in propellant leakage observed between nitrile and COCE valves. The lower dipole moment and less polar structure of COCE appear to reduce its interaction with polar permeants, leading to significantly lower permeation rates. Additionally, the measured differences in total fatty acid content between nitrile and COCE valves highlight the product quality implications with valve selection when manufacturing MDI products with different propellant formulations.
- The data suggests that using COCE as a valve material can result in measurable reductions in the loss of propellants, such as HFA 152a and HFA 134a, thereby which may enhance the overall efficiency and reliability of the drug delivery system. This finding is particularly relevant for the development of next-generation inhalers and other delivery devices where minimizing drug loss is essential.

Acknowledgements

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