MATERIALS COMPATIBILITY TESTING OF HONEYWELL'S NEW LOW GLOBAL WARMING POTENTIAL PROPELLANTS

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INTRODUCTION

Honeywell previously introduced three new low GWP (global warming potential) fluids which could, potentially, be used as propellants in metered dose inhalers. Each of these candidate compounds has a global warming potential of less than 10 (vs. CO_2) on a 100-year integrated time horizon, which is substantially lower than the GWPs of currently used propellants. Each also exhibits a very low order of toxicity. Two of these compounds are now commercially available: HFO-1234ze(E) (hydrofluoro-olefin) is being used in non-pharmaceutical aerosols, while HFO-1234yf is being used in mobile air conditioning systems. Key properties of these two propellants are shown in Table 1, for comparative purposes CFC (chlorofluorocarbon) propellants p11, p12 and HFA (hydrofluoro-alcane) propellants p134a, p227 are also referenced.

(all measures at @ 20 °C)	HFO-1234ze(E)	HFO-1234yf	HFA-134a	HFA-227ea	CFC-11	CFC-12
Molecular weight (g/mol)	114	114	102	170	137	121
Liquid density (g/cc)	1.12	1.09	1.22	1.41	1.48	1.32
Vapour density (g/cc)	0.02 - 0.03	0.03 - 0.04	0.032	0.008	0.006	0.037
Heat of vaporization (kJ/kg) @ NBP	197.4	178.2	217	131.4	181.4	166.1
Surface tension (dyn/cm)	8.55	7.11	8.11	10.24	17.95	8.65
Dipole Moment (debye)	1.443	2.543	2.058	0.940	0.450	0.510
Boiling point (°C)	-19	-29	-26	-16	24	-30
Flash point (°C)	None	None	None	None	None	None
Lower/upper flame limit (vol. percent in air)	None	6.5 - 12.3	None	None	None	None
Global warming potential	6	4	1,430	3,220	4,600	8,100
Solubility of Water in Propellant (PPM)	225	260	1300	-	-	-

Table 1. General Propellant Properties

An important part of the development of a propellant for use in MDIs «Metered Dose Inhalers» is an evaluation of the compatibility of that propellant with commonly-used packaging materials. Aptar Pharma is currently conducting a long-term compatibility test with HFO-1234ze(E) and HFO-1234yf.

Compatibility Test Programme

Compatibility testing was performed within Aptar Pharma's R&D department with the purpose of evaluating the behavior of materials used in Aptar Pharma's Drug Delivery Devices (metering valves for pMDIs) when immersed in Honeywell's two novel propellants HFO-1234ze(E) and HFO-1234yf at different temperatures. Table 2 outlines the experimental design. Various tests were performed to verify if the mechanical properties of the materials after being immersed in HFOs 1234ze(E) and 1234yf had significantly changed when compared with the same materials immersed in the HFA 134a and 227 propellants for the same period of time.

MATERIALS AND METHODS

Two propellants from Honeywell, HFO-1234ze(E) (trans-1,3,3,3-tetrafluoroprop-1-ene) and HFO-1234yf (2,3,3,3-tetrafluoroprop-1-ene) were evaluated in comparison with HFA 134a (1,1,1,2-tetrafluoroethane) and HFA 227ea (1,1,1,2,3,3,3-heptafluoropropane).

Different materials from Aptar Pharma's drug delivery devices (valves for pMDIs) were placed into 90ml. aluminium canisters, which were then fitted with 1" valves. The canisters were then filled with sufficient propellant so that all pieces were completely submerged. Filled canisters were then stored in upright position for 1 month, 3 months, 6 months and 12 months for plastic and metallic components, and for 1 week, 2 weeks, 3 weeks and 4 weeks for elastomeric materials. Storage was carried out at room temperature and under accelerated conditions. Both HFAs and HFO-1234ze(E) were stored at 40°C / 75%RH, while HFO-1234yf was stored in specific explosion-proof oven at 45°C (no control of humidity) for safety reasons.

The mechanical properties of the different components immersed in HFOs were then compared to results obtained after immersion in HFAs, for the same storage conditions and period of time.

The components to be analyzed were chosen according to a risk analysis that enhanced the critical pieces of the valve, they were upper and lower stems, bodies, rings, springs and elastomers.
For metallic and plastic materials, various tests were performed in order to represent the forces and stress that are actually applied to the valve on a finished pMDI product. These tests included, but were not restricted to: crimping tests, friction and force evaluation and spring compression.

For elastomeric compounds, mechanical properties including hardness, swelling and elongation at rupture were evaluated.

The different components used and the tests performed are represented in the following table (table 2).

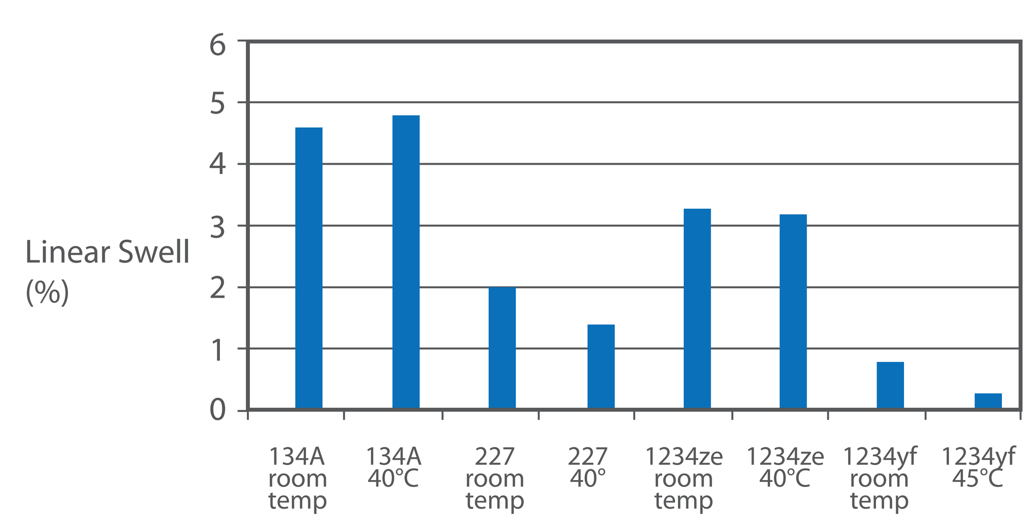
For each propellant (1234ze, 1234yf, HFA134a, HFA227)							
Component type	storage time	Plastic parts: dimensional testing	Plastic parts: mechanical properties	Metallic parts: corrosion	Springs: compression	Elastomer: swelling	Elastomer: mechanical properties
POM Plastic	1,3,6,12 months	X	X				
PBT Plastic	1,3,6,12 months	X	X				
Polyamide Plastic	1,3,6,12 months	X	X				
Polyethylene Plastic	1,3,6,12 months	X	X				
Aluminium components	1,3,6,12 months			X			
Springs	1,3,6,12 months			X	X		
EPDM gaskets	1,2,3,4 weeks					X	X
Nitrile gaskets	1,2,3,4 weeks					X	X
Chloroprene gaskets	1,2,3,4 weeks					X	X
Butyl gaskets	1,2,3,4 weeks					X	X
TPE gaskets	1,2,3,4 weeks					X	X

Table 2. Compatibility Testing Matrix
(Storage Conditions: Ambient temperature and 40°C / 75%RH (or 45°C))

RESULTS

Elastomeric materials:
Mechanical resistance: the results obtained are similar for both Honeywell propellants HFO-1234ze and HFO-1234yf comparing with the HFA-134a and HFA-227 reference propellants.

Swelling of the elastomers: the measured swell rates of elastomers after immersion are all within acceptable range values, irrespective of propellant used. However, we can observe some differences from one propellant to the other. For nitrile e.g. (see Graph 1) we observe an extremely low level of swell after immersion in HFO-1234yf, whereas results for HFO-1234ze(E) are observed to be between those values obtained for HFA propellants p134a and p227.



Graph 1. Swell rate of nitrile in propellants

Plastic materials:
Regardless of the tests conducted, no notable differences could be observed irrespective of the propellant in which the components were immerged:
- Crimping test on immersed body components did not show any broken bodies after 6 months immersion in the different propellants.
- Force resistance test on immersed body components did not show any broken parts or deformation on the pieces evaluated after 3 months immersion. Moreover force/displacement curves show similar trend (example below in Figures 1 & 2 for POM body material immersed in HFA 134a and HFO-1234ze).

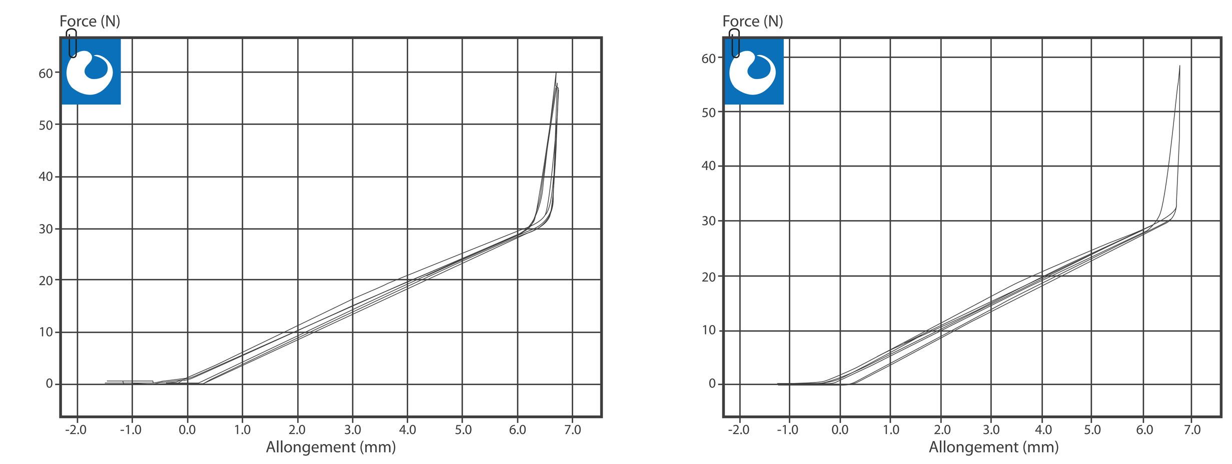


Figure 1& 2. Force/displacement curve for body POM at 40°C/75%RH in HFO-1234ze (left) and HFA 134a (right)

- Radial test on immersed stems didn't lead to any leakage after 3 months immersion.
- Force resistance test on immersed stem components (see Figure 3 below for schematic representation) did not show any broken parts after 3 months at 40°C/75%RH and 6 months at room temperature.

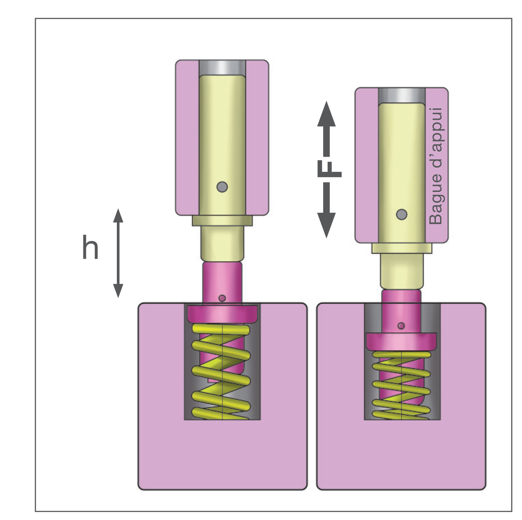


Figure 3. Force resistance test on stem components

Springs:
- After 6 months immersion, no corrosion could be observed on the springs immersed in the different propellants.
- Compression rate measurements are all equivalent, irrespective of the propellant and the storage conditions (see Table 3, values P are for the weight (in g) necessary to compress the spring to a defined length, to evaluated its rigidity).

P	HFA 134a		HFA 227		HFO-1234ze		HFO-1234yf	
(in g)	RT	40°/75RH	RT	40°/75RH	RT	40°/75RH	RT	45°
n=	10	10	10	10	10	10	11	10
mini	1450	1512	1456	1489	1493	1488	1510	1469
maxi	1575	1596	1564	1575	1593	1556	1556	1582
mean	**1538**	**1536**	**1528**	**1523**	**1530**	**1518**	**1540**	**1539**
SD	36	24	35	28	29	20	14	39

Table 3. Compression rate for springs after 6 months immersion

Rings:
- After 6 months immersion under accelerated conditions, there is no influence on the dimensions of the rings (3 designs and 2 materials of rings evaluated).
- Crimping test on immersed rings did not show any broken parts after 6 months immersion in the different propellants.

CONCLUSIONS

Based on the test results generated to date, no notable differences have been observed between the mechanical properties of the materials immersed in Honeywell propellants in comparison with the materials immersed in HFAs p134a and p227. From a technical perspective, based on these results, the Honeywell propellants do not appear to present any incompatibility in use with Aptar Pharma Drug delivery devices.

References

1. RDD 2010: *"A New Generation of Aerosol Propellants for Metered Dose Inhalers"*, Knopeck, Decaire, Ghelani, Honeywell Specialty Chemicals