Compatibility of P152a with pressurized metered dose inhaler materials

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Introduction

Pressurised metered dose inhalers (pMDIs) play an essential role in the portfolio of methods for delivery of therapeutic substances to the lung.

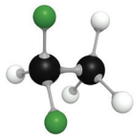
Although they have been used commercially for many years, and are regarded as a relatively mature technology, like other technologies they operate in a dynamic regulatory and market environment.

One challenging area of innovation in pMDIs is the development of a new propellant and in particular, one which has the potential for reduced environmental footprint and which maintains or improves upon the performance of existing delivery systems.

1,1-difluoroethane (P152a)

1,1-difluoroethane (P152a) is currently under investigation as a new pMDI propellant and has been shown to result in a significant reduction in carbon footprint opposite the traditional propellants, to the point where the carbon footprint of a P152a-based pMDI is comparable to that of many dry powder inhaler (DPI) products

(FIGURE 2) [1].



Carbon Footprint

Making a change from one pMDI propellant to another is not without challenges. Historically, the transition from CFC-based pMDIs to the current propellants required significant changes to the elastomers used as seals within pMDI devices [2].

P152a has been shown to have different solubility characteristics to both currently used propellants, HFA-134a and HFA-227, with respect to the solubilization of many excipient materials, such as oleic acid [3].

This work set out to begin to investigate whether or not the introduction of P152a would require any major changes to the materials used in pMDIs hardware, in particular the elastomers and engineering polymers used in the construction of the metering valve.

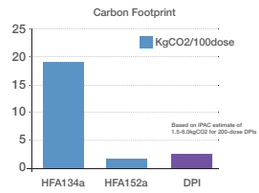


Figure 2 Carbon footprint comparison

Testing

Some of the most important parameters in assessing polymer material compatibility with pMDI formulations include:

- Change in volume (swelling/shrinkage)
- Change in hardness
- Resistance to propellant permeation
- Impact on formulation chemical stability

Changes in mechanical properties (volume, hardness) were assessed by immersing the test article in liquid propellant in a pressure vessel for a period of 28-days at 40°C. Results are illustrated in Figures 3-5:

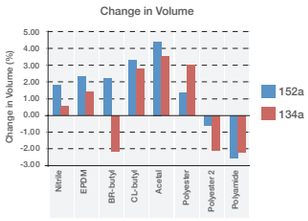


Figure 3 Changes in volume after propellant immersion (28-days 40°C)

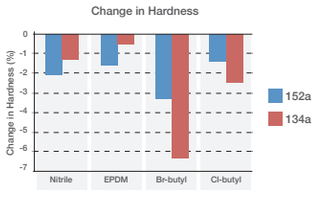


Figure 4 Changes in hardness (ASTM D 1415, IRHD-1) after propellant immersion (28-days 40°C)

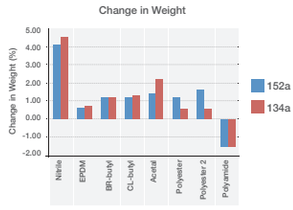


Figure 5 Changes in weight after propellant immersion (28-days 40°C)

To investigate the potential for loss of propellant through can-seal permeation, pMDIs were filled with propellant alone (approximately 10g of P152a) and the mass of the sealed pMDI monitored as a function of time under ambient laboratory conditions (25°C), or under more aggressive storage conditions (40°C @ 75% relative humidity (RH)). Results for permeation loss for selected materials are summarized in Figures 6-9:

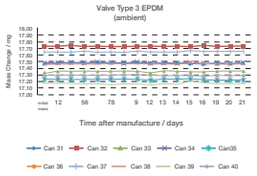


Figure 6 Permeation loss of P152a at ambient conditions for EPDM main seal

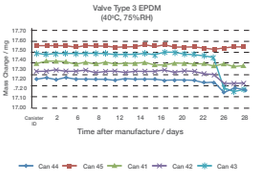


Figure 7 Permeation loss of P152a at elevated temperature for EPDM main seal

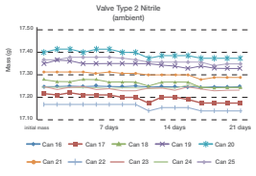


Figure 8 Permeation loss of P152a at ambient conditions for nitrile main seal

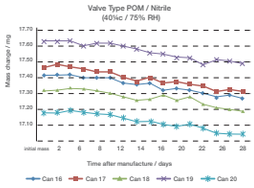


Figure 9 Permeation loss of P152a at elevated temperature for nitrile main seal

Results of a rudimentary assessment of chemical stability (storage at 40°C, 75% RH) with a model salbutamol sulphate formulation in three valve material combinations are presented in Figures 10 and 11 showing the development of two salbutamol-related impurities:

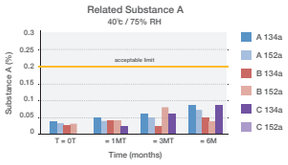


Figure 10 Salbutamol related substance 'A' development over time in P152a

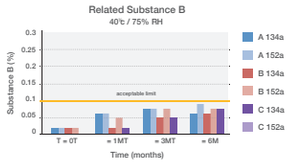


Figure 11 Salbutamol related substance 'B' development over time in P152a

Conclusion

Although further work is clearly required and the results of this work are heavily dependent on the specific materials chosen, it appears that at least some of the polymeric materials currently used in pMDI valve and seal construction are broadly compatible with P152a. Permeation losses for the particular nitrile examined as the main valve/can seal may not be satisfactory in part as a result of higher solubility of P152a in this nitrile.

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References

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