Introducing Recipharm's innovative Bespak® valve technologies for low-GWP pMDI propellants

Using its combined expertise in formulation, devices, dosing valves and clinical and commercial scale filling within its Advanced Delivery Systems business unit, Recipharm is supporting the pharmaceutical industry's transition to new low-GWP propellants.

Summary

Existing propellants for pressurised metered-dose inhalers (pMDIs) have a high global warming potential (GWP).

Legislation governing the use of these propellants is beginning to tighten, impacting their availability and cost. Although suitable low-GWP propellant alternatives are available for use in pMDIs, a transition similar to the industry's move from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) propellants will require the re-evaluation of formulations, device components and manufacturing processes to adapt to the new propellants.

History

Over the past 35 years, the pharmaceutical industry's development of pMDI devices has evolved to accommodate technical advancements and change. For example, in response to climate change and environmental policy, the propellants used in pMDIs have been completely replaced with more environmentally-acceptable alternatives.

In response to the Montreal Protocol agreed in 1987, the industry introduced HFAs (also known as hydrofluorocarbons (HFCs)) as replacements for CFCs, specifically HFA-134a in 1996, followed by HFA-227ea in 2006.[1] However, regulators have determined that these propellants will continue to impact climate change negatively, owing to their high Global Warming Potential (GWP) as greenhouse gases.[2] Under the Kigali Amendment to the Montreal Protocol, efforts are being made to phase-down high-GWP HFAs globally, across all uses, which will affect their usage within the pharmaceutical sector.[3] Diminished availability and subsequently increased cost of HFAs on the market are likely to impact pMDI cost of goods (CoGs) and production.[4] In addition, many health systems favour low-GWP inhalers and doctors are encouraged to prescribe "greener" inhalers.[5]

Next generation propellants ready for evaluation and transition

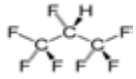
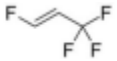
Next generation, low-GWP propellants including HFA-152a (Koura, United Kingdom) and hydrofluorolefin 1234ze (HFO1234ze) (Honeywell, USA) are actively being explored to support the development of pMDIs with a carbon footprint comparable with dry powder inhalers (DPIs).[2] pMDI devices include a valve, canister and actuator designed to facilitate the consistent delivery of a metered dose of API in particles of a specific size distribution. pMDIs require gas propellants with vapour pressures that allow them to be liquefied at ambient temperatures at pressures between 40 and 70 psi inside the canister. Propellants used in pMDIs must be certified as current Good Manufacturing Practice (cGMP) inhalation grade with high purity levels. Propellants for pMDIs must meet cGMP requirements for the methods, facilities, and controls used in manufacturing, processing, and packaging to ensure the product is safe and effective and performs as expected.[6]

In 2009 The European Medicines Agency (EMA) issued a general guideline on the demonstration of therapeutic equivalence between two inhaled products, which described a step-wise approach for the approval of generic inhalation drug products. For the formulation, the guidance states that the generic and the reference products should be the identical dosage form with the same active substance(s). Any differences in the polymorphic form of the active substance and any qualitative and/or quantitative differences in excipients should not influence the pharmaceutical performance and safety profile of the product.[6] Thus, by changing the propellant, and particularly if equivalent pharmaceutical performance is required, regional guidance can be useful to identify any regression testing and essential qualification requirements.

Guided by design principles

Regulators want to be assured that design control activities confirm there are no negative interactions between constituent parts, and also to be assured that the combined use results in a combination product that is "safe and effective and performs as expected." Switching propellants in pMDIs requires formulation, container closure system, device and manufacturing considerations to be taken into account. A range of Bespak® pMDI valves suitable for use with the emerging low-GWP propellants (HFO-1234ze and HFA-152a) is now available for evaluation from Recipharm. For the formulation, compatibility between the actives, excipients and new propellants is influenced by the physicochemical properties of the new propellants (see Figure 1) and all formulation components, for example the dosing valve.

Figure 1. Current vs. low-GWP propellant properties

Parameter	HFA227ea	HFA134a	HFA152a	HFO1234ze
Chemical Structure				
Chemical Name	1,1,1,2-Tetrafluoroethane	1,1,1,2-Tetrafluoroethane	1,1-Difluoroethane	1,3,3,3-Tetrafluoropropene
Molecular Weight	170	102	66	114
Appearance	Clear, Colorless	Clear, Colorless	Clear, Colorless	Clear, Colorless
Odor	Slightly ether like	Slightly ether like	Slightly ether like	Slightly ether like
Boiling Point (°C)	-16	-26	-25	-19
Freezing Point (°C)	-131	-101	-117	-109
Liquid Density (Kg/m³)	1408	1226	908	1293
Vapor Density (Kg/m³)	3,1	2,8	2,7	5,7
Vapor Pressure (°C)	3,90	5,72	5,12	4,27
Solubility in Water (%, w/w)	0,061	0,022	0,280	0,037
Solubility in Ethanol	Miscible	Miscible	Miscible	Miscible
Flammability	Non-Flammable	Non-Flammable	Flammable	Non-Flammable
GWP (see note 1)	3350	1300	138	1
ODP (see note 2)	0	0	0	0

Note 1: GWP (GGP5): Global Warming Potential GWP CO2=1. ***Note 2:*** ODP: Ozone Depletion Potential.

Specific pMDI transition challenges

A new propellant must have the physical and chemical properties to enable solution and suspension pMDI formulations to meet the rigorous pharmaceutical performance and stability standards set. Within a pMDI, maintaining seal integrity and achieving consistent aerosol delivery performance throughout the product's shelf life, are key; this comes down to not only the formulation, but also the container closure system that is in contact with the formulation. It is essential to ensure effective and precise dose delivery during the lifetime of the product. The properties of HFA-152a and HFO-1234ze appear to meet the required pMDI performance characteristics. To develop the corresponding, robust product and manufacturing processes, the properties of the propellants and their effect on the product must be unequivocally established.

Recipharm responds to the propellant transition challenge

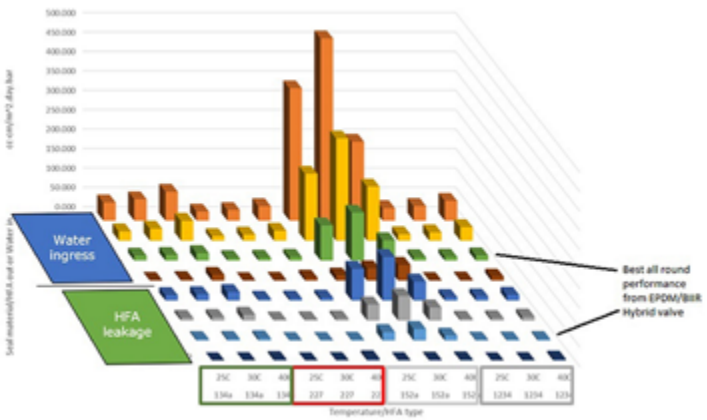
In the EU, the current F-gas Regulation in force since 2014 replaces the original F-gas Regulation adopted in 2006.[7] The current Regulation strengthened the previous measures and introduced far-reaching changes by:

- Limiting the total amount of the most important F-gases (HFAs/HFCs) that can be sold in the EU from 2015 onwards and phasing them down in steps to one-fifth of 2014 sales in 2030.
- Banning the use of F-gases in many new types of equipment where less harmful alternatives are widely available.
- Preventing emissions of F-gases from existing equipment by requiring checks, proper servicing and recovery of the gases at the end of the equipment's life.

The European Commission made a legislative proposal to update Regulation (EU) No 517/2014 (the 'F-gas Regulation') in April 2022, aiming to set an even higher ambition. Recipharm responded by convening a multi-functional team of internal and industry experts to embark upon detailed analysis and modelling, culminating in several rigorous studies, including the development of a detailed physics model for propellant containment within pMDI systems.

Recipharm modelled four valve elastomer types for pMDI leakage and moisture ingress (See Figure 2) showing predicted data for static leakage and moisture ingress for all elastomer types, comparing performance with existing versus new propellants. The model can then be used to optimise the valve performance by material type.

Figure 2. Propellant model: leakage and moisture ingress by elastomer type

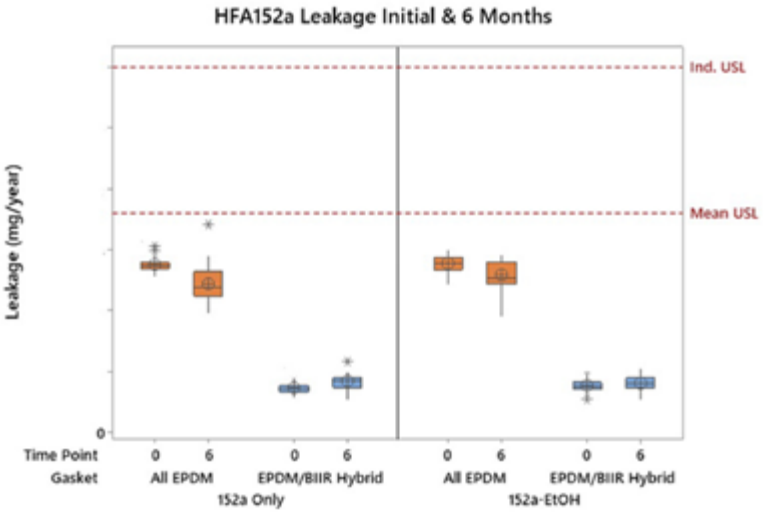


- 4 elastomer seals x 4 propellant matrix
- Permeability (D) for both water vapour and propellant vapour

Placebo stability studies of HFA-152a and HFO-1234ze in ethanol and non-ethanol formulations

Informed by the modelling, Recipharm tested EPDM (ethylene propylene based rubber) & BIIR (bromobutyl) based valves for leakage, water ingress and shot weight over 1, 3, 6, and 12-month periods and elevated temperature and humidity (see Figure 3).

Figure 3. Recipharm's Bespak® Hybrid Valve optimised for best leakage performance with new propellants (e.g. 152a)



- Testing on placebo filled packs containing 100%, 85% & 15% EtOH
- 1, 3 & 6 month testing performed on filled packs stored at 40°C/75%RH before being tested in laboratory conditions
- 12 months testing performed on filled packs stored at 30°C/65%RH then returned to laboratory conditions
- Leakage testing performed in ambient conditions over 7 days and results extrapolated

Optimised Bespak® Hybrid Valve with elastomer configuration aligned to critical performance criteria*

The results of the modelling and stability data indicated that EPDM was the best material for dynamic pharmaceutical performance and BIIR was the best material for static (e.g. leakage) performance. This high performing Bespak® Hybrid Valve (Figure 4 - patent pending) was tested for leakage (see Figure 3), water ingress and shot weight over 1, 3, 6, and 12-month periods at elevated temperature and humidity.

**Tested under cGMP validated laboratory conditions.*

Figure 4. Recipharm's Bespak® Hybrid Valve

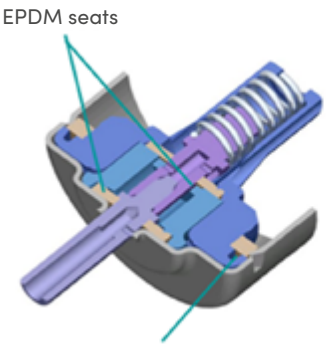
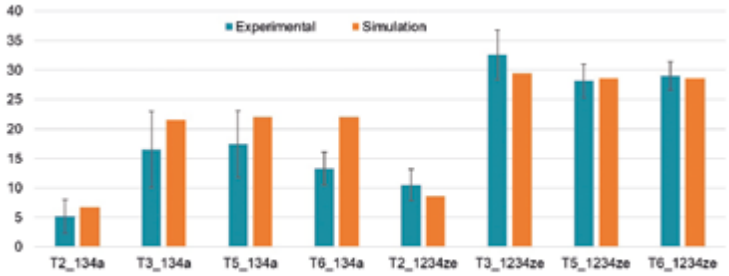


*Figure 5. Example of Recipharm's propellant model testing; discharge coefficients used in the model should be adjusted to reflect differences in the fluid flow properties of the new propellant***

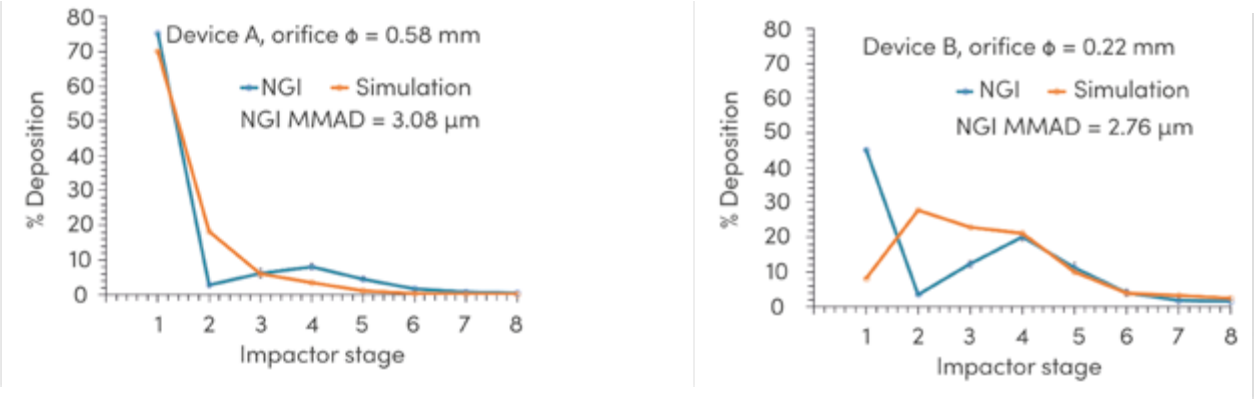


***The differences in the modelling behaviour and observed data suggests that the constants used to calculate the discharge coefficients should be adapted for different propellants.*

Simulation of propellant on pharmaceutical performance and implications on formulation & device design

Recipharm has developed and verified a model to assess the effect of device and formulation properties on spray performance (droplet size) and how equivalent performance can be achieved by changes to the formulation (e.g. by adjusting ethanol concentrations) and device characteristics (e.g. adapting the spray orifice design of the dispensing actuator). Real-world device testing data were collected and compared with the model's predictions for the current and new propellants, as shown in Figure 5 for placebo formulations. Figure 6 shows a comparison between next generation impactor (NGI) stage plate performance and model-predicted droplet sizes for two active formulations (fluticasone propionate as a suspension in R134a and as a solution in R134a with ethanol at 15 % w/w). Further work will explore the correlation between droplet and residual particle sizes to enhance its predictive capabilities.

Figure 6. Comparison of Recipharm's thermofluid mechanic model droplet size predictions vs. experimentally-measured NGI stage plate deposition for two formulations with fluticasone propionate and two actuator spray orifice diameters



Conclusions

With changes to climate legislation on the horizon, the pharmaceutical industry will need to carefully evaluate the viability of low-GWP propellant alternatives for their marketed and pipeline pMDI products. Ultimately, the selection and transition to either of the low-GWP candidate propellants must be based upon specific formulation stability and performance criteria.

Recipharm can help the pharmaceutical industry to transition successfully and quickly in the following ways

- Provide optimised Bespak® Hybrid Valves for evaluation with new propellants.
- Analyse, model, review and test formulation enhancements to achieve the required aerosol performance (e.g. spray plume geometry and device droplet size).
- Accurately simulate/predict required device performance (and potential enhancements) to achieve the critical functional performance requirements (e.g. static leakage).
- Provide stability data (12-month leakage, shot weight, water ingress) for optimised Bespak® pMDI valves – providing breakthrough valve performance data and confidence to the customer.
- As the CDMO of choice, provide formulation development, analytical method development, clinical and commercial manufacturing of pMDI products.

In summary, Recipharm can help pharmaceutical companies transition to the next generation of pMDIs by offering an integrated solution, encompassing formulation, valve optimisation and selection, analytical method development and testing, and manufacturing capabilities.

References

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F-Gas legislation is a rapidly changing area, information correct as at time of writing (March, 2023).

Recipharm