Development of HFA-152a as an environmentally sustainable propellant for pressurized metered dose inhalers

The next step in the evolution of pMDI technology

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The drive for alternative propellants

Pressurized metered dose inhalers (pMDIs) are a common drug delivery platform for the treatment of asthma and COPD. Including breath-actuated devices and those used in conjunction with spacers, pMDIs are widely acknowledged as perhaps the most universal and often most cost-effective platform for delivery of respiratory-related medical products.[1]

The adoption of the Montreal Protocol in 1989 initiated the development of the propellants currently used in pMDIs: HFA-134a (1,1,1,2-tetrafluoroethane) and HFA-227ea (1,1,1,2,3,3,3-heptafluoropropane) that replaced the ozone-depleting chlorofluorocarbons (CFCs), CFC-12 (dichlorodifluoromethane) and CFC-11 (trichlorofluoromethane). Although focused on reducing the impact on atmospheric ozone depletion, the introduction of the hydrofluoroalkane (HFA) propellants also resulted in almost an order-of-magnitude reduction in the global warming potential (GWP) associated with pMDI usage, based on the reduction of GWP from CFC-12 (GWP = 10,900) to HFA-134a (GWP 1,430).[2,3]

Despite this, there is now growing concern regarding the GWP of many hydrofluorocarbons, which has led to additional regulations in a number of parts of the world, for example the F-Gas Regulation in Europe and the Kigali Amendment to the Montreal Protocol. While these regulations currently do not place restrictions on the use of HFA-134a or HFA-227ea for pMDIs, they have the potential to adversely impact the supply chain through rationing or loss of industrial product feedstocks used as inputs for medical product manufacturing. Further, individuals and companies are seeking ways to reduce their environmental impacts, with carbon footprints being a particular focus. This broad drive to reduce carbon footprints provides motivation to adopt alternative propellants and propellant-free delivery systems, if practicable. There is a need for concern about the environment, yet the interests of the patient must be foremost in any approach to change.

Environmental sustainability is only one factor; developing a new pMDI propellant requires a candidate that satisfies a number of essential criteria including:

- Safety—at least as safe for extended inhalation use as current propellants
- Functionality—effective for a range of solution and suspension pMDI drug formulations and ideally offering performance benefits over current propellants or other technologies
- Economics—of acceptable cost and available at the appropriate scale and purity

A number of materials have been considered[3] as potential propellants in pMDIs, including hydrocarbons (isobutane) and unsaturated hydrofluorocarbons (HFO-1234ze(E) (1,3,3,3-tetrafluoropropene). In addition, HFA-152a (1,1-difluoroethane) is under investigation in an extensive research and development program and, to date, has shown an attractive combination of environmental and formulation performance properties.

Environmental impact: Life cycle analysis (LCA)

The carbon footprints of a number of inhalers have been reported previously by the United Nations Environmental Programme (UNEP)[4] and by Goulet, et al.[5] In the UNEP report, studies indicated that the carbon footprint per dose of medication delivered,

expressed as the equivalent number of grams of CO_2 (gCO2eq), is in the range of 200-300 gCO2eq for an HFA-134a-propelled pMDI, 600-800 gCO2eq for an HFA-227ea-propelled pMDI and 8-60 gCO2eq for dry powder inhalers (DPIs). The study by Goulet, et al[5] estimated 97 gCO2eq for an HFA-134a-propelled pMDI. The difference between the UNEP and Goulet estimates relates to the differing product formulations, where the UNEP value was based on a formulation that used approximately 60% of the propellant per dose of that used in the UNEP study. This is an important consideration when comparing product environmental performance because each technology platform has a range of impacts. For example, three common salbutamol sulphate pMDI products currently on the market, each specified for 200 actuations, employ 18 g, 6 g and 8.5 g of HFA-134a propellant in total, respectively, yet have approximately proportional carbon footprints. Therefore, in the same way that not all pMDI products are equivalent, there is a range of footprints associated with the diverse DPI products on the market.

Detailed life cycle analysis (LCA) to ISO 14040/14044 methodology, in effect an assessment of the cradle-to-grave impact across a range of environmental metrics, has shown that using HFA-152a as an alternative propellant to HFA-134a results in a greater than 90% reduction in carbon footprint with an equivalent formulation propellant:active pharmaceutical ingredient (API) ratio.[6] HFA-227ea has a GWP of 3,220, which is greater than that of HFA-134a. Therefore, the proportional percentage reduction in carbon footprint would be significantly higher if an HFA-227ea-based product were replaced by an equivalent HFA-152a product. This magnitude of reduction would place an HFA-152a pMDI squarely within the range of the DPI products reported in the UNEP reference.

In their study, Jeswani and Azapagic[7] compared the environmental impacts of pMDIs using HFA-134a, HFA-227ea and HFA-152a with those of a particular DPI device (Diskus®, GlaxoSmithKline, Brentford, UK). The pMDI products were assessed using a weighted average representing prescription use in the United Kingdom, while the particular DPI device was at the lower end of the range of reported DPI carbon footprints. This study confirmed that, of all of the environmental metrics investigated, carbon footprint is the most significant parameter for both pMDI and DPI devices and that HFA-152a performs favorably across all of the metrics examined.

Data from a number of sources,[7, 8] can be used to compare the carbon footprint per dose of medication across a number of devices. Figure 1 summarizes carbon footprints for pMDI devices using HFA-134a, HFA-227ea and HFA-152a, as well as a propellant-free DPI (Diskus) and a fine mist inhaler (FMI) (Spiriva® Respimat®, Boehringer Ingelheim, Ingelheim am Rhein, Germany). For pMDI devices, two puffs per dose were assumed.

Scenarios for propellant change

Recognizing that inhaled medications represent a target for carbon footprint reduction in the healthcare system, what is the best way to achieve a reduction? Based on the inhaler usage data from the United Kingdom National Health Service (NHS), Jeswani and Azapagic[7] considered the environmental impact of a number of inhaler-use change scenarios (Figure 2). Focusing on the scenarios predicted to have the greatest carbon footprint mitigation, the first scenario, (A), is replacement of all pMDIs by DPIs. Scenario (B) substitutes the current propellants HFA-134a and HFA-227ea with new like-for-like formulations based on HFA-152a. The pMDI/DPI proportion in use remains unchanged and current product propellant:API ratios are maintained, subject to correction for the liquid density reduction associated with HFA-152a.

As noted, scenario (A) is based on the replacement of all pMDIs by DPIs but it is widely recognized, by the UK's National Institute for Health and Care Excellence (NICE) and others, that DPIs are not universal in their patient applicability.[3] Consequently, the magnitude of carbon footprint reduction envisaged by scenario (A) is unlikely to be achievable or even desirable. The proportion of patients requiring or preferring pMDI treatment varies significantly across countries and is dependent on a number of different factors that are beyond the scope of this article.

Sweden, which has a long history of restrictions on the use of hydrofluorocarbon (HFC) products across a range of applications, is likely the country having the lowest proportion of pMDI usage. Yet even in Sweden, approximately 10-20% of inhalers prescribed are pMDIs. For comparison, approximately 70% of inhalers prescribed in the United Kingdom and the United States are pMDIs. Scenario (C) replaces pMDIs with DPIs but approximately 20% of inhalers remain pMDIs with the current HFA-134a or HFA-227ea propellants. Scenario (D) replaces the current pMDI propellants with HFA-152a, with formulations using a reduced (60%) propellant charge and with end-of-life recovery of propellant and device components. The reduction in carbon footprint as a percentage of the current UK NHS position for each of these scenarios is presented in Figure 2.

In addition to the carbon footprint reductions achieved in each of the scenarios, it is essential to consider the potential consequences for patients and healthcare providers. Scenarios (B) and (D) maintain the current treatment platform for patients, minimizing the requirements for technique retraining associated with a shift in delivery platforms. By changing the propellant charge per dose, it is possible that scenario (D) may have some effect on patient perception.

Figure 1

Carbon footprint per dose for pMDI and propellant-free delivery platforms

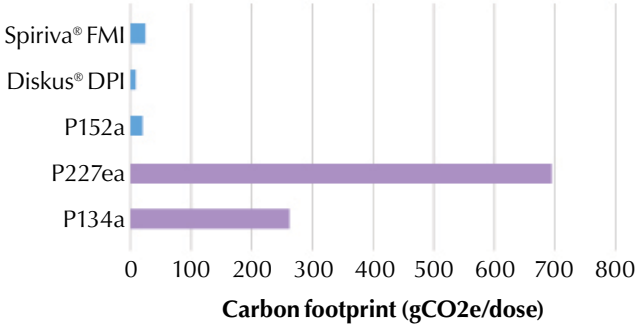
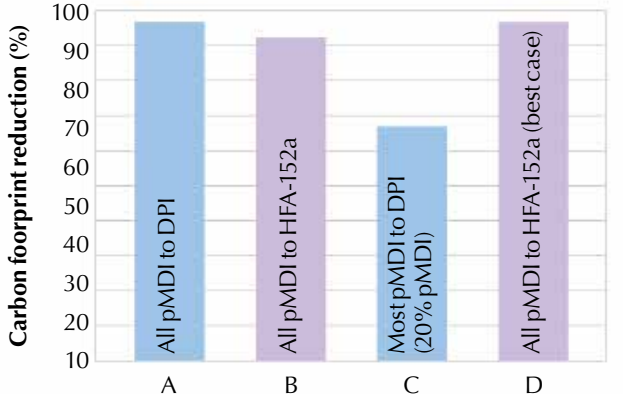


Figure 2

Reduction in current UK NHS carbon footprint from inhaler use; comparison by scenario



Similarly, all other things being equal, the change in propellant itself (to HFA-152a) may also be perceived to be different by patients (in scenarios (B) and (D)). Scenarios (A) and (C) would both require significant numbers of patients to change delivery platforms from pMDIs to DPIs, requiring investments of time and money in retraining and has the potential for an increase in exacerbations with consequential cost and health impacts.[9]

Going forward, it appears that pMDIs using HFA-152a can provide significant reductions in the carbon footprint associated with inhaler usage. Furthermore, these environmental savings can likely be achieved without significant disruptions to patients, possible consequences for loss of disease control, and consequent morbidity and mortality from obstructive airways diseases such as asthma, which might result from a widespread imposed transition to an alternative platform.[10]

Flammability considerations

Traditionally, lack of flammability was seen as a prerequisite for a pMDI propellant. Unlike HFA-134a and HFA-227ea, HFA-152a is flammable. Consequently, there are two scenarios to consider when considering the flammability of pMDI propellants: end-user safety and pMDI manufacturing safety.

While HFA-134a itself is non-flammable, many pMDI formulations on the market contain significant levels of ethanol (which is flammable) and have been used for many years without significant patient safety impact. Unlike the continuous flow valves used in many consumer aerosol products, the metered emissions from a pMDI are small and result in a very low level of risk. Quantitative risk assessment (QRA) studies, conducted by Koura in 2017, indicate that the flammability associated with HFA-152a is also unlikely to have significant impact on patient safety.

HFA-152a flammability is likely to require reconfiguration of many pMDI manufacturing and filling facilities to ensure safe manufacture and needs to be addressed on a site-specific basis. Such reconfiguration would be expected to have cost and scheduling implications and therefore may not be an immediately attractive option in some existing manufacturing facilities. Measures required to mitigate flammability hazards are well understood in the industrial and consumer aerosol sectors but would need to be translated to a cGMP-manufacturing environment. However, pharmaceutical manufacturing capabilities using flammable propellants already exist, albeit for topical products.

Safety regulations for transport, storage and use of flammable materials, including building regulations and insurance codes, are already in place but are complex and beyond the scope of this article. In addition, many of these national and international standards are on fixed review cycles and can take several years to amend. This review process is ongoing.

As noted previously, other potential low-carbon propellants have been proposed, including the hydrofluoroolefin HFO-1234ze(E) (1,3,3,3-tetrafluoropropene).[4] HFO-1234ze(E) may be labeled as non-flammable, an apparent potential advantage when it comes to using existing facilities for pMDI manufacturing.

In the refrigerants sector, the quest for reduced GWP fluids has shown that it is difficult to achieve the lowest GWP targets yet maintain non-flammability and many of the alternative products developed for refrigeration are flammable to some degree. In various respects, the atmospheric chemistry associated with rapid refrigerant breakdown can be thought of as analogous to the chemistry involved in combustion. Refrigerant flammability and toxicity is characterized by the American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE). Information is shown in Table 1, where numbers relate to flammability and letters relate to toxicity.

Unlike HFA-134a and HFA-227ea, both part of Group 1, HFA-152a is flammable (part of Group 2),

Table 1

ASHRAE Standard 34 (ISO817:2014) refrigerant safety classification

	Safety Group	
Higher Flammability	A3 (Butane)	B3
Lower Flammability	A2 (HFA-152a)	B2
	A2L (HFO-1234ze(E))	B2L (Ammonia)
No Flame Propagation	A1 (HFA-134a, HFA-227ea)	B1
	Lower Toxicity	Higher Toxicity

although less so than hydrocarbons such as butane (in Group 3). In contrast to a simple binary flammable/non-flammable classification, this approach provides for more nuanced application across a range of use scenarios. Yet even in the ASHRAE system, it was felt to be more useful to introduce an additional flammable class (2L) that enabled further differentiation between products. HFO-1234ze(E) falls into Group 2L along with HFO-1234yf (2,3,3,3-tetrafluoropropene), HFA-32 (1,1-difluoromethane) and ammonia. The additional relatively high toxicity of ammonia places it in Group B.

Incorporation of the 2L classification across the range of standards is not yet complete. For example, Material Safety Data Sheets (MSDSs) use the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, published by the United Nations and adopted in the European Union by the Classification, Labelling and Packaging (CLP) regulations (EC/1272/2008) as the agreed-upon international standard for classification. HFO-1234ze(E) is an anomalous product in that it is non-flammable at the test temperature (20°C) defined under the GHS but becomes flammable by 30°C, a temperature relevant for ASHRAE 34 testing. This is why a "non-flammable" propellant can have published flammability concentration limits. Even HFA-152a is not uniformly "flammable" since under the US Consumer Products Safety Commission (CPSC 1500.3(c)(6).16CFR), HFA-152a aerosols are classified as non-flammable.

The unique and anomalous classification position of HFO-1234ze(E) has been recognized and, like all other flammable fluids including HFA-152a, rigorous assessment of hazard and mitigation measures is strongly recommended for HFO-1234ze(E).[11] In this way, it should be treated with the respect required for safe use of other flammable fluids. (Additional data for both propellants is shown in Table 2.)

Table 2

Flammability of HFA-152a and HFO-1234ze(E)

	Method	Limits in Air (by volume)
HFA-152a	ASHRAE 34	4%-17%
HFO-1234ze(E)	ASTM E681-04 (21°C)	Non-flammable
	ASHRAE 34	7%-12%

Formulation and device development

The transition from CFC propellants to HFA propellants presented a number of technical challenges with respect to differences in formulation behavior and materials compatibility. Testing of HFA-152a to date has highlighted potential benefits with some active pharmaceutical ingredients and excipients.[6]

From their use in the refrigeration and insulation foam application sectors, there is a basic understanding of the behaviors of HFA-152a and HFO-1234ze(E) in contact with elastomers and polymers.[12] HFO-1234ze(E) is reported to have good compatibility with a number of materials used in pMDI valve construction.[13] In recent research, HFA-152a also appears to have good compatibility with existing valve materials[14] and designs. There also may be scope for further performance optimization, for example in plume behavior, as formulations based on HFA-152a are developed and refined. This is clearly a welcome development given the complexity, costs and time associated with the design and manufacture of a new pMDI valve.

Inhalation safety studies

While environmental sustainability is clearly an attractive goal for any commercial product, a new pMDI propellant must not be achieved at the cost of any significant compromise to patient inhalation safety. A medical-grade formulation of HFA-152a, from Koura, has been the subject of an extensive suite of inhalation safety tests with the chronic two-year study already beyond the halfway point. Although the program is still in progress, results to date on both acute and sub-chronic safety tests have been very encouraging, with HFA-152a behaving in a manner similar to HFA-134a. So much so that the US Food and Drug Administration has raised no objections to propellant-only clinical trials.[15] If, as expected, the safety program continues according to plan, it is anticipated that sufficient data will be available in the HFA-152a Drug Master File (DMF) to support the registration of HFA-152a-formulated products in the year 2022, in much the same way as the current DMFs for HFA-134a and HFA-227ea.

While HFO-1234ze(E) has a low GWP, good compatibility with the materials used in pMDI valve construction and low acute toxicity, and is acceptable for use in industrial applications, some questions remain, including the effects of chronic exposure at the levels relevant to pMDI inhalation. In a series of rat studies,[16] focal and multifocal mononuclear cell infiltrates in the heart, often an indicator of inflammatory response, were observed after only 14 days. This type of cardiac effect may be common to other propanes and propenes having halogen on C-1 and a trifluoromethyl-C-3 group.[16] The clinical relevance of these observations would require significant further investigation before HFO-1234ze(E) could be considered suitable for pMDI use.

Anticipated next steps

HFA-152a manufactured to cGMP is already available in small quantities for research purposes. Although it is expected that the DMF for HFA-152a will be finalized in 2022, there will still be much work to be done before a commercial pMDI based on HFA-152a can be made available. In the interim, pharmaceutical companies can make use of the availability of cGMP HFA-152a to develop acceptable formulations and devices but once developed, there are a number of familiar regulatory hurdles to be overcome before a new product could be placed on the market.

This development and regulatory stage is anticipated to go some years beyond the 2022 propellant timescale. However, it is hoped this will be the start of a transition from many existing HFA-134a and HFA-227ea-based pMDIs to those with an HFA-152a propellant. The viability of HFA-152a as a pMDI propellant has been endorsed by Chiesi, who announced their intention to launch HFA-152a pMDI products in 2025.[17] In addition, Koura has announced a major investment in the construction of a facility for commercial manufacture of medical HFA-152a.[18]

Registration of new formulations based on HFA-152a may also provide an opportunity for device manufacturers to introduce more recent product or device innovations that, in their own right, might otherwise struggle to overcome the inertial and cost hurdles associated with product change.

In summary

A program for development of HFA-152a as a sustainable propellant for use in pMDIs has made significant progress over the last few years. By reducing the environmental impact of pMDIs to levels comparable to other propellant-free delivery technologies, adoption of HFA-152a may address many of the environmental concerns that have surrounded the pMDI delivery platform and help maintain the long-term availability of an essential treatment option.

Engineering safety studies by Koura indicate that manufacture and filling of pMDIs with HFA-152a is viable, although there may be costs and time associated with reconfiguration of many of existing manufacturing facilities. Extensive inhalation safety studies conducted with medical-grade HFA-152a indicate high levels of safety and as a result, the US FDA has no objections to propellant-only clinical trials. These trials are expected to provide essential support for pharmaceutical companies that move forward with development and regulatory approval processes for formulated pMDI products based on HFA-152a. While these processes take time and are not without commercial risk, at least one company has announced their intention to launch pMDI products based on HFA-152a in 2025.

Acknowledgements

The author would like to acknowledge Simon Gardner, Paul Watkinson and Tim Noakes for helpful discussions in preparation of this article.

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