The Future of Propellants for pMDIs

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Summary

From its first commercial appearance in the 1950's, the chlorofluorocarbon (CFC) propelled MDI enjoyed steady growth until the late 1980s, when the discovery of stratospheric ozone depletion forced a fundamental change to an alternative class of propellants, the hydrofluoroalkanes (HFAs). The conversion has been challenging, and it is only recently that the last CFC-propelled MDIs have been manufactured. pMDI remains a core treatment methodology for a number of inhaled medicines and continues to see growth worldwide. Having successfully met the ozone-depletion challenges and negotiated the HFA transition, additional environmental regulations relating to global warming potential, are coming to the fore. Although provision for continued pMDI usage has been made in the relevant environmental legislation, work is on-going to minimise the potential environmental impact associated with pMDI use including an appraisal of potential new propellant options.

The dosage form

The first pMDI appeared in the mid 1950's, made possible by the family of the then new CFC aerosol propellants, some of the members of which are shown in Table 1. All of these molecules shared the common properties of high liquid density, non-flammability and benign toxicology, reflecting their relatively low degree of chemical reactivity.

Species	Formula	B.Pt (°C)	Saturated Vapour Pressure (bara,20°C)	Specific gravity (g/cc, 20°C)	Ozone Depletion Potential	Global Warming Potential (CO_2=1)
CFC 11	$CFCl_3$	23.7	0.88	1.49	1	4660
CFC 12	CF_2Cl_2	-29.8	5.66	1.33	1	10800
CFC 114	CF_2ClCF_2Cl	3.5	1.80	1.47	1	8590
HFA 134a	CF_3CFH_2	-26.2	5.72	1.23	0	1300
HFA 227ea	CF_3CFHCF_3	-16.5	3.89	1.41	0	3350

Table 1: Properties of CFCs and HFAs used in pMDIs[1]

The CFC propelled MDI

Medihaler-iso™ was the first of these dosage forms, produced by Riker Laboratories Inc.; an MDI based presentation of isoprenaline first introduced in 1956[2]. Interestingly, it was a formulation containing CFC 12, ethanol and drug. Ethanol was later rarely used in CFC formulations, but the transition to HFA propellants has seen greater use in order to achieve satisfactory formulation performance

Glaxo set the scene for what became the most common way of formulating and filling these aerosols when they brought their salbutamol-based Ventolin™ inhalation relief formulation to the market in 1968[3]. It was a two-stage process where the drug was first slurried in a small quantity of the higher boiling CFC 11 and the concentrate filled to open aerosol cans, onto which the valves were then crimped. The second stage was to 'gas' the aerosol at the next filling point, with the lower-boiling propellant CFC 12.

It is fair to say that between the late 1960's and the early 1990's the MDI became the dominant inhaled dosage form, replacing oral and glass bulb nebulised alternatives. Dry powder inhaler (DPI) alternatives certainly existed, but their market share was only moderate. The spectrum of actives on offer to asthmatics widened to consist of β-agonist relief medications such as salbutamol, 'preventer' medications based on corticosteroids such as beclamethasone diproprionate and formulations mainly targeted at COPD sufferers based on anticholegenics such as Ipratropium bromide. Generally most formulations only contained a single drug, but there were a few combination therapies. However, as the mid-1980's arrived, so did a worrying cloud on the horizon of the MDI's future, stratospheric ozone depletion.

The identification of the ozone depletion problem, both in the lab and stratosphere, was a great scientific success of its time and is well described elsewhere[4]. This concern lead to the Montreal Protocol (MP), an unprecedented regulatory framework which mandated the phase out of the manufacture and use of certain classes of chemicals, including the CFCs. Recognising the time and difficulty associated with any reformulation or new technology development for pMDI applications, the Protocol contained a mechanism (Essential Use Allowances (EUAs)) to permit continuing use of CFCs for such essential uses beyond the phase out date for the regulated substance. It was only recently that the very final EUAs for the use of CFCs in pMDIs were approved for 2015 consumption in China.

In looking to develop alternatives to CFC-propelled medical inhalers, a number of approaches were explored including multidose DPIs and ambulatory pocket nebulisers. However, there was also a major push to develop one or more non-ozone depleting propellants for pMDI use.

HFA MDIs

From this effort, HFAs 134a and 227ea, as shown in table 1, appeared to be viable candidates but their adoption necessitated full safety studies that were carried out by two pharmaceutical company consortia, IPACT-1 and IPACT-2[5], which studied 134a and 227ea respectively. This work still provides the bedrock for current medical 134a specifications.

From a manufacturing perspective, the advancement in standards of GMP compliance expectation for these excipients also caused a move to the establishment of separate purification assets operating to cGMP, which acted to purify industrial grade HFAs to the required levels and with appropriate control measures. Typically these 'polishing plants' have been based upon high performance distillation columns, and represented a major departure from the long- established practice with their CFC forerunners, which was to just take product from the industrial plant and 'test the quality in.'

The absence of a suitable alternative for CFC 11 at the time gave rise to a number of alternative formulation and aerosol filling approaches, both single- and two-stage. Nowadays, these two principal approaches have many variants, including 3M's cold-fill process such that there is almost a continuum of options between the 'pure' versions.

The transition to HFAs 134a and 227ea presented numerous technical and formulation challenges including the risk of particles agglomerating and adhering to the can walls resulting in sub-optimal drug delivery through the life of the can. Whilst addition of ethanol can mitigate this effect, it is not without problems of its own and other techniques such as the use of inert can coatings have also been developed. 3M introduced the first HFA 134a pMDI in 1995[1]

MDIs propelled by HFAs 134a and 227ea are arguably the workhorses of respiratory medication delivery. They provide a strong platform from which virtually all of the small molecule respiratory drugs can be delivered. However, the bulk of MDI formulations these days are relatively mature with much of the latest developments in inhalation medicine and delivery focussed on DPI products and associated delivery devices, often still covered by IP. In the market, this results in pMDIs achieving around 20% of the market sales value from around two-thirds of the total standard unit sales with DPIs having around 50% of the market value from only around 25% or so of the total market volume.

The Future

There are now over 100 companies worldwide making pMDIs, with a combined 2016 output estimated at 750M units[6]. Worldwide production in unit terms is increasing at between 5-8% p.a. in the short-term, with that growth concentrated in the developing world.

However, environmental regulation is now once more on the horizon, this time as part of international efforts to minimise the rise in global temperatures as a consequence of anthropogenic enhancement of natural greenhouse warming. A standardised measure of the potential for a molecule to enhance global warming is the Global Warming Potential (GWP) with CO_2 having a GWP of 1. It is clear from Table 1 that HFA 134a already has a significantly lower GWP than CFC 12 but despite this, there are some concerns that the GWPs of HFAs 134a and 227ea are still unacceptably high taking into consideration their projected increase in pMDI consumption going forward. HFAs are already the subject of regulation in the EU via the 'F'-gas Regulation[7], and in the USA, via 'SNAP'[8]. Further, the Parties to the Montreal Protocol (MP) are discussing extending that regulatory framework to cover HFA emissions with a programme aimed at achieving a *phase-down* to around 15% of today's rate of CO_2- equivalent emission by 2035 (Figure 1). Unlike the CFCs, this will not be a *phase-out.*

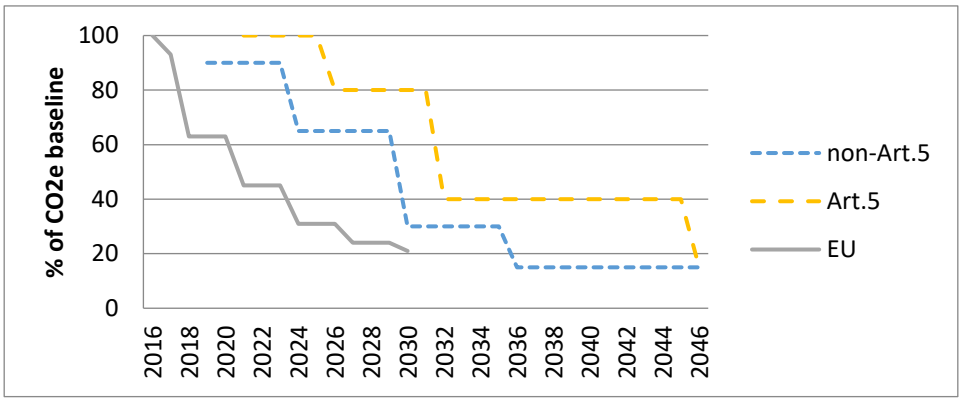

Figure 1 Montreal Protocol amendment North American Proposal and EU F-Gas Regulation schedule

The precise impact of these MP proposals on pMDI propellants is not yet clear. However, the regulations currently in place give a degree of protection for pMDI usage and the environmental regulators are of the view that there will be adequate supplies of HFAs available to support this use under the phase-down limits. Although the UNEP Technical and Economic Assessment Panel (TEAP) recognizes that any environmental benefits associated with transitioning from the existing propellants to say DPI technology would be small[9] we can still look for ways of minimising the impact of pMDI technology and perhaps to further improve performance.

Minimising the environmental impact of pMDI

There are a number of ways that the environmental impact of pMDIs can be minimised. These range from recycle schemes such as GSK's "*Complete the Cycle*" scheme where residual and unused pMDIs are collected for propellant recovery, through to the development of new reduced-GWP propellants.

As evidenced by the CFC to HFA transition, identification and implementation of a new medical propellant is no easy task and any new reduced-GWP propellant needs to:

1. Be at least as toxicologically safe as the current propellants
2. Function effectively for a range of solution and suspension pMDI drug formulations: ideally offer performance benefits
3. Be of acceptable cost and available at appropriate scale and purity
4. Be sustainable

Two candidates that have been proposed as reduced-GWP pMDI propellants are the unsaturated HFCs (HFOs) particularly HFO 1234ze(E) (*trans*-$CF_3CH=CFH$) which is already being used being used commercially as an aerosol propellant in some applications. Although HFO 1234ze(E) has GWP<4 and is regarded as safe for use across a range of non-medical applications, it has not yet been found to have acceptable toxicological safety for the more demanding inhalation medicine application sector.

Other potential reduced-GWP propellants that have been proposed are the hydrocarbons, particularly propane, butanes and pentanes and whilst these have been used successfully in formulations for some topical uses, they again have not yet been found to have acceptable toxicological safety for inhalation medicine use.

After screening over 400 candidate molecules, Mexichem has embarked on a detailed program to investigate the potential for a new medical propellant: 1,1-difluoroethane (HFA 152a). This program encompasses a number of aspects including toxicological safety, end-user safety, device component compatibility and formulation performance in vitro. Some properties of HFA 152a are illustrated in Table 2.

Although at a relatively early stage, to date, the pre-clinical safety studies are promising and have raised no grounds for concern and work continues. Like the HFOs 1234yf and 1234ze(E), HFA 152a is classed as flammable, although less so than hydrocarbons. Detailed end-user safety studies based on computational fluid dynamic simulations have shown no significant increase in end-user risk.

Property	HFA 134a	HFA 227ea	HFA 152a
BP (ºC)	-26.2	-17.1	-24.7
Vap. Press (barg, 25ºC)	5.65	2.89	4.99
Liq. Density (g/cc, 25ºC)	1.22	1.41	0.91
Flammability	No	No	LFL 3.8%
GWP	1430	3220	124
VOC	No	No	No

Table 2: Properties of HFA 152a compared to HFA 134a and HFA 227ea

On the formulation performance front, HFA 152a has shown surprisingly good performance and a number of benefits over existing formulations. For example, despite having a significantly lower density than HFA 134a, HFA 152a shows significant improvements in suspension settlement and re-suspension behaviour with salbutamol sulphate even in the absence of additional excipients:

Propellant/excipients	Time to sediment(minutes)
HFA 134a	< 0.5
HFA 134a/EtOH	1.5
HFA 134a/EtOH/Oleic acid	3
HFA 152a	2

Table 3 Turbiscan™ Salbutamol sulphate formulation sedimentation times HFA 152a versus HFA 134a

From an environmental impact perspective, initial estimates suggest that an MDI formulated with HFA 152a will have a comparable carbon footprint to many DPI devices and a more detailed environmental impact study is in progress.

It is perhaps an understatement to say that these are early days and much work remains to be done, not least on toxicological safety. However, based on the data generated so far, HFA 152a shows sufficient promise for Mexichem to continue its research and development program. If ultimately successful, HFA 152a could eventually expand the portfolio of propellants available to pMDI formulators and help to further reduce the environmental impact associated with pMDI use. If HFA 152a is found to be unsatisfactory for whatever reason, at least it is an avenue that has been explored and strengthens the case for robust maintenance of the current pMDI propellants going forward.

[1] Mexichem Chemical Safety Data Sheets. GWPs currently calculated values from IPCC AP5

[2] *50th Anniversary of the first pMDIs*, The Pharmaceutical Journal, 277, p795

[3] *Ventolin remains a breath of fresh air for asthma sufferers, after 40 years*, The Pharmaceutical Journal, 279, p404

[4] Freuh S, *Depletion of the Earth's Ozone Layer Discovery and Response*, National Academy of Science Online, 2015

[5] International Pharmaceutical Aerosol Consortium for Toxicity (IPACT) (I) and (II)

[6] Mexichem estimate derived from 2016 propellant and can usage data

[7] Regulation (EU) No 517/2014 of the European Parliament and of the Council

[8] Significant New Alternatives Program. Federal Register Vol. 80 No.138, July 20, 2015, 42870-4295

[9] *IPCC/TEAP Special Report: Safeguarding the Ozone Layer and the Global Climate System*, Chapter 8, 2005