

MDI PROPELLANTS – IS THE POPULARITY OF HFA 227EA SET TO GROW?

In this piece, Tim Noakes, PhD, Medical Propellants Commercial Manager, Mexichem Fluor, predicts a rise in demand for HFA 227ea – a less common MDI propellant than the better-known HFA 134a.

Inhalation aerosols, usually called Metered Dose Inhalers (MDIs), provide an effective, easy-to-use method of delivering medication in an atomised form.

These products require the use of a propellant to deliver the dose and there are two approved propellants in use today, both belonging to the class of hydrofluoroalkanes (HFAs). These are HFA 134a

produce something which, when emitted from the aerosol can as a dose, will contain the right amount of the drug in a highly dispersed form so that it can be inhaled, throughout the entire shelf life of the product – commonly a period of two years and sometimes longer.

To achieve this, the chemist has to meet the following requirements:

“The most important difference between the two HFAs for an MDI formulation is the liquid density. The difference between approximately 1.2 and 1.4 may not look like much, but many drugs that are used in MDIs have crystal densities in this range so the choice of the HFA can determine whether a particular drug crystal floats, is neutrally buoyant, or quickly sinks to the bottom”

1. The drug should not chemically decompose under possible conditions of storage
2. The suspended drug particles should not change their particle size distribution, in particular there should not be any loss of fine particles and growth of coarse particles, by any recrystallisation processes
3. The suspended drug may well settle to the bottom of the can when not in use, but it is important that a single shake will re-suspend it in the propellant, so that a good dose can be taken out of the can when the unit is used.

(1,1,1,2-tetrafluoroethane) and HFA 227ea (1,1,1,2,3,3,3-heptafluoroethane), both of which have been in use since passing extensive toxicology studies in the 1990s. HFA 134a is currently the most widely used but in this article I wanted to focus on its specialist cousin HFA 227ea – a product which we believe will significantly grow in use in the near future.

In use, medical HFAs need to deliver a complicated balance of properties. Most MDI formulations consist of an insoluble finely ground drug, suspended in liquefied, pressurised HFA propellant, possibly with other ingredients such as small amounts of alcohol added as well. This formulation is held in a small aerosol can with a metering valve, such that when the valve is pressed a metered dose is atomised out of the nozzle and into the patient’s respiratory tract.

The key goal for the formulation chemist in developing these medications is to

It is in addressing these three requirements that the need for the specialist properties of 227ea arises. Figure 1 contrasts the key properties of HFA 227ea with those of HFA 134a.

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Dr Tim Noakes
Medical Propellants
Commercial Manager
T: +44 1928 514 840
F: +44 1928 518 818
E: zephexsales@mexichem.com

Mexichem Fluor
The Heath Business & Technical Park
Runcorn
Cheshire
WA7 4QX
United Kingdom

In some cases, the polarity of HFA 134a can make the recrystallisation problem worse as indeed can the higher level of moisture affinity. This also has a very serious impact on chemical stability, as uptake of moisture is one of the most common reasons for decomposition of drugs on storage in these aerosols.

Although generally speaking problems of this nature with HFA 134a are few and far between, in some cases HFA 227ea has proven the better choice in addressing these issues. Recognition of this has seen its adoption for a small but growing number of formulations, including some highly successful products. One example is AstraZeneca's Symbicort formulation, a blend of formoterol (long-acting beta agonist) and budesonide (second-generation corticosteroid).

Mexichem expects that demand for HFA 227ea is likely to grow in part because formoterol is being used in an increasing range of MDI formulations, and HFA 227ea has proved invaluable in maintaining its stability for an effective shelf life.

One factor limiting the adoption of HFA 227ea in the past has been the perceived weakness in the 227ea supply chain.

Property	HFA 134a	HFA 227ea
Boiling point (oC)	-26.2	-16.5
Liquid pressure at 25 oC (bar)	5.65	3.54
Liquid density at 25 oC (g/cc)	1.21	1.39
Polarity (solvent power)	Polar, like a weak alcohol	Less polar, more ether-like.
Moisture affinity (ppm water saturation, 20 oC)	~1000	~500

Figure 1: Comparison of key properties of HFA 134a and HFA 227ea.

Production as a medical grade – purification under rigorous quality control in compliance with key pharmaceutical industry codes such as current Good Manufacturing Practice

HFA 227ea through the acquisition of DuPont's medical HFA 227ea business.

Mexichem is the largest supplier in the medical propellants business and a major

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(cGMP) – is reliant on wider industrial production. In the case of HFA 134a there is a large global supply for industrial HFA 134a for refrigeration and foam blowing applications but the volume and range of applications is lower for HFA 227ea. Mexichem has now strengthened its supply chain for

manufacturer in the wider fluorochemicals industry, from the extraction of the mineral fluorspar through to production into many fluorochemical products. As such Mexichem's recent investment in HFA 227ea ensures that it can offer a reliable source of HFA 227ea as demand increases.



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email: andrea.james@management-forum.co.uk

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