OPTIMISING LOW-GWP pMDI SPRAYS FOR ENHANCED PERFORMANCE AND SUSTAINABILITY

In this article, Benjamin Myatt, PhD, Senior Product Development Engineer at Kindeva Drug Delivery, and Daniel Duke, PhD, Senior Lecturer, Mechanical & Aerospace Engineering at Monash University, explore the low-global-warming-potential propellants available and their implications for the performance of pressurised metered dose inhalers.

In response to changing legislative requirements due to environmental concerns, pharmaceutical companies are exploring switching to more environmentally friendly pressurised metered dose inhaler (pMDI) propellants. Now, the search is on to understand how these new, low-global-warming-potential (GWP) propellants affect the performance of pMDIs.

Low-GWP candidate propellants have different physicochemical and thermodynamic properties from current hydrofluorocarbon (HFC) gases, which means a change in propellant may necessitate adjustments to formulation and/or hardware.

FROM GREEN TO GREENER

The industry made a significant shift in propellant gas use with the signing of the Montreal Protocol on Substances That Deplete the Ozone Layer in 1987.[1] That agreement led to a transition from ozone-depleting chlorofluorocarbons (CFCs) to HFC-based propellants.

The current drive towards low-GWP propellants is motivated by the Kigali Amendment to the Montreal Protocol, which aims to phase down the use of HFCs with high GWPs.[1] Current pMDI propellants, HFA-134a and HFA-227, have relatively high GWP values.[2] The industry is exploring alternative propellants, such as HFA-152a and/or HFO-1234ze(E), which have significantly lower GWP values and will significantly reduce the carbon footprint of pMDIs These propellants have 90% and 99.9% lower GWP than HFA-134a, the greenest pMDI propellant currently used.[3]

THE IMPACT OF LOW-GWP PROPELLANTS ON PRODUCT PERFORMANCE

Propellant properties affect all fundamental aspects of pMDIs. The differences in thermodynamic, physical and chemical properties can all impact pMDI functionality. For example, the lower density of certain low-GWP propellants could affect the physical suspension stability of a pMDI. Similarly, the higher surface tension values of HFA-152a and HFO-1234ze(E) could impact the initial droplet size formed upon atomisation and, subsequently, the final residual droplet size that reaches the lungs. The differences in properties indicate low-GWP propellants may have a less aggressive atomisation process.

> "Understanding the properties of low-GWP propellants is essential for preserving performance."

Dr Benjamin Myatt
Senior Product Development Engineer
E: benjamin.myatt@kindevadd.com

Kindeva Drug Delivery
Building 39, Charnwood Campus
Bakewell Road
Loughborough
LE11 5RB
United Kingdom

www.kindevadd.com

Dr Daniel Duke
Senior Lecturer, Mechanical & Aerospace Engineering
Monash University

E: daniel.duke@monash.edu

www.monash.edu

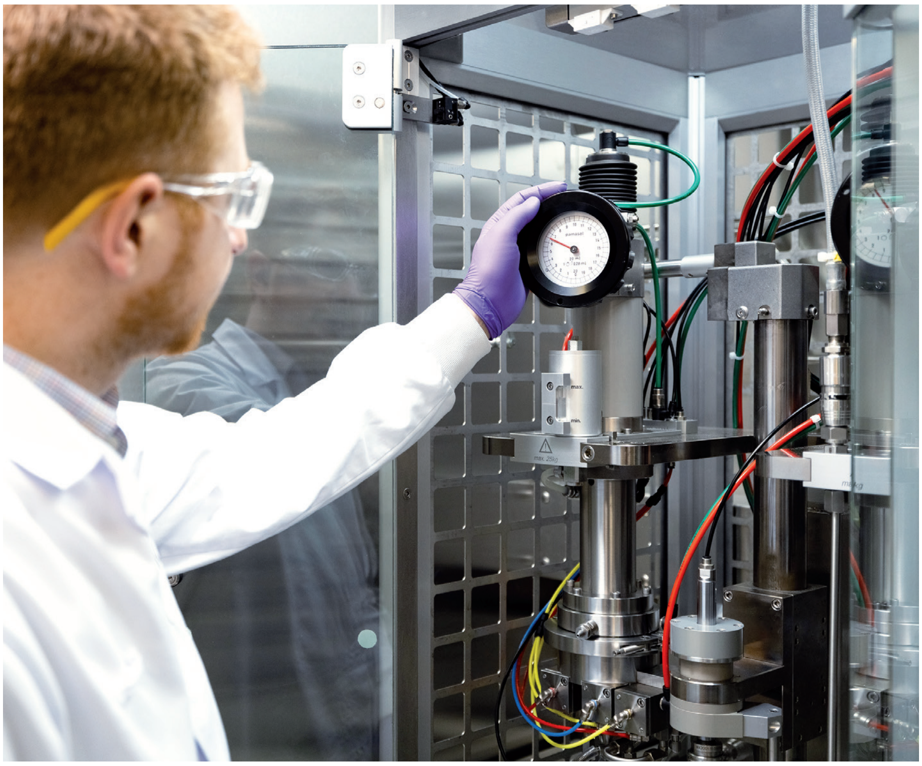

Figure 1: Evaluating low-GWP propellants.

Understanding the properties of low-GWP propellants is essential for preserving performance (Figure 1). Kindeva Drug Delivery, in partnership with Australia-based Monash University, the Woolcock Institute of Medical Research and Macquarie University, are benchmarking low-GWP propellant products against current systems. To do this, the team of research partners uses a range of novel measurement methodologies alongside compendial techniques to better understand the pMDI performance of various gases.

A COLLABORATIVE APPROACH TO UNDERSTANDING LOW-GWP PROPELLANTS

Kindeva is seeking to better understand the physics behind pMDI atomisation and how these processes change with the switch to low-GWP propellants. This research is focused on the following:

- Benchmarking to understand the differences in product performance when switching propellants
- Investigating mitigation strategies to optimise performance using current hardware and formulation toolbox parameters
- Exploring new opportunities to improve pMDI performance through novel hardware developments.

"Vapour pressure, density, surface tension, specific heat capacity and latent heat of vapourisation of low-GWP propellants may all impact pMDI performance."

Analysing the performance of pMDIs is complex due to the transient nature of the atomisation process, both inside the device and in the spray itself. The propellant liquid rapidly depressurises when a pMDI is actuated, which leads to chaotic atomisation. Vapour pressure, density, surface tension, specific heat capacity and latent heat of vapourisation of low-GWP propellants may all impact pMDI performance.

Kindeva has partnered with the team at Monash University, who have developed an ultra-high-speed imaging facility that goes beyond the resolution and capabilities of any spray pattern and plume geometry system currently available. This facility collects extremely large volumes of data from various test formulations comprising each propellant, which are then mined to extract the differences between propellants.

The facility uses a custom 100-nanosecond pulsed LED light source – a pulse of light that travels through the sprayed droplets and particles. The spray is imaged by a high-speed camera that runs at over 100,000 images per second. This device allows the dynamics of the spray to be captured, both inside the actuator and outside the device. By analysing the stability and repeatability of the spray plumes, Kindeva will gain insight into how changing the propellant alters the plume characteristics, which can then guide hardware and formulation adjustments that will optimise low-GWP pMDI performance.

Aerodynamic particle size distribution (APSD) is considered a critical quality attribute for orally inhaled and nasal drug products. When the APSD was examined with different ethanol concentrations, variations in droplet size and plume structure were found, both of which may impact drug efficacy.

A potential approach to modulate performance is to adjust the ethanol cosolvent concentration in the formulation. Additionally, the vapour pressure of mixtures of low-GWP propellant formulations with ethanol is less sensitive to the addition of ethanol than HFA-134a-ethanol binary mixtures. This suggests that, within the bounds of formulation and solubility constraints, adjusting the ethanol concentration may be one avenue to optimise pMDI performance.

Kindeva has also been experimenting with differences in pMDI hardware. Adjusting the orifice length of the pMDI alters the condition of the fluid as it exits the orifice and changes the atomisation and spray break-up process. Computer simulations have shown that, by increasing the nozzle length, the spray width can be narrowed, providing another variable for optimising pMDI performance.

RECENT ADVANCES IN SPRAY FORMATION OPTIMISATION

Kindeva's researchers are continuously working to develop new strategies for optimising spray formation with low-GWP propellants. Recent advances in this area include computational fluid dynamics to simulate the flow of propellant and medication through the MDI valve and actuator. This information can be used to optimise the design of the actuator to improve spray formation.

BUILDING A SUSTAINABLE FUTURE

The transition to low-GWP propellants in pMDIs represents a significant step towards more sustainable medical products. However, before these greener propellants are fully implemented, it is important to understand and adjust for the impact on product functionality.

Kindeva is leading the charge in this transition. It has installed pilot-scale manufacturing lines as well as two new commercial manufacturing lines capable of filling inhalers with HFA-152a and/or HFO-1234ze(E) propellants. The expansion ties in with one of Kindeva's near-term goals: to have one of the first commercial green propellant lines by 2025.

ABOUT THE COMPANY

Kindeva Drug Delivery is a global CDMO focused on drug-device combination products. The company develops and manufactures products across a broad range of drug-delivery formats, including pulmonary and nasal, injectable and transdermal. Its service offerings span early-stage feasibility through to commercial-scale drug product fill-finish, container closure system manufacturing and drug-device product assembly. Kindeva serves a global client base from its state-of-the-art manufacturing, research and development facilities located across the US and UK.

REFERENCES

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ABOUT THE AUTHORS

Benjamin Myatt, PhD, is a Senior Product Development Engineer within R&D at Kindeva Drug Delivery. His work focuses on next-generation low-GWP propellants. Dr Myatt is a chartered mechanical engineer and a member of the Institute of Mechanical Engineers. Prior to joining Kindeva, he conducted PhD research in the thermofluids and optical diagnostic groups, focusing on pMDI atomisation using non-contact laser-based and high-speed imaging techniques for investigation of pMDI internal fluid flows and spray plumes. Dr Myatt's goal is to delve into the science of pMDIs to improve pMDI drug delivery and efficiency and enable new pMDI products and ultimately improved therapeutic outcomes.

Daniel Duke, PhD, is a Senior Lecturer in the Department of Mechanical & Aerospace Engineering at Monash University (Clayton, Australia). His area of research is turbulent multi-phase fluid flows and he specialises in the development and application of synchrotron X-ray diagnostics, optical diagnostics and high-performance computing tools for studying these problems. His current work concerns the development of synchrotron diagnostics for the study of cavitation, liquid atomisation and particle formation in medical sprays. Dr Duke received his PhD in Mechanical Engineering from Monash in 2013.

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