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Environmentally friendly metered dose inhaler propellants: Challenges for inhaler design

Timely conversion to low-GWP propellants involves a number of tradeoffs but the challenge is surmountable.

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Introduction

The pressurized metered dose inhaler (pMDI) has undergone many changes in its 68-year history. Some of the most significant in pMDI formulation and design have been driven by regulatory restrictions on the liquefied gas propellants that the pMDI relies upon to produce a fine aerosol [1]. Starting thirty years ago, the substitution of chlorofluorocarbon (CFC) propellants with hydrofluoroalkane (HFA) propellants was undertaken in response to the Montreal Protocol's phase-out of ozone-depleting CFCs [2]. To achieve this goal, many complex challenges had to be overcome, such as the replacement of seals, canister coatings, new toxicity studies and product reformulation due to changes in propellant chemistry and interactions with drugs and hardware components. Despite many changes to materials and formulations, the chemico-physical properties of the new HFA propellants were such that the pMDI actuator geometry did not need to change significantly, remaining relatively similar to its original design [3].

The transition to CFC-free propellants was completed in 2001, and now a second major shift in pMDI propellants is already underway due to the need to phase out HFA propellants with high global warming potential (GWP). The most popular HFA pMDI propellants are potent greenhouse gases; 1 kg of HFA-134a is equivalent to 1,430 kg of CO_2, and 1 kg of HFA-227 is equivalent to 3,220 kg of CO_2. The Kigali Amendment to the Montreal Protocol, which was ratified in 2016 and came into force in 2019, manages the phase-down of HFA usage to reduce greenhouse emissions from these fluorinated products ("F-gases"). The European Union is leading the phase-down with the goal of reducing consumption to 20% of 2014 levels by 2030. Although the metered dose inhaler industry only accounts for about 2.3% of worldwide F-gas emissions, a combination of regulatory pressures, economic pressures and changing customer priorities are driving the inhaled drug delivery market towards more environmentally friendly alternatives [4].

Some high-GWP pMDI products may be replaced by dry powder inhalers and soft mist inhalers, but a low-GWP propellant-option may be justified for some pMDIs that cannot be transitioned to these platforms for technical, medical and economic reasons. A discussion of these factors, along with the history of the CFC-HFA transition and lessons that can be learned from that process, is neatly summarized in a recent review by Buttini, Glieca, Sonvico and Lewis [5].

Propellant manufacturers have developed two primary low-GWP alternatives that are currently in clinical trials. HFA-152a (difluoroethane) from Koura Global (Boston, Massachusetts, US) is a low molecular weight hydrofluoroalkane with chemico-physical properties similar to HFA-134a [6]. HFA-152a contains fewer fluorine atoms than the HFAs it replaces, affording it a lower GWP (124 kg CO_2-equivalent). However, its low specific gravity, 25% less than HFA-134a [7], makes formulating suspensions challenging due to insoluble sedimentation of the active pharmaceutical ingredient (API) in the time between shaking and inhaling. There are some concerns around flammability. HFA-152a is less flammable than hydrocar-

bon aerosol propellants, but requires additional safety considerations during filling and transport compared to propellants previously commercialized in pMDIs [8]. HFA-152a has demonstrated analogous material compatibility and similar plume properties compared to current HFAs. It is also a favorable solvent for lipophilic drugs [9].

The second propellant of note is HFO-1234ze(E) (tetrafluoropropene) from Honeywell International, Inc. (Charlotte, North Carolina, US). Unlike the HFAs discussed above, this propellant is a hydrofluoroolefin; a different class of molecule. It therefore has different chemical behavior and interactions compared to the propellants it proposes to replace. Its carbon-carbon double bond gives it a GWP approaching that of CO_2, while retaining a high liquid density likely to facilitate suspension stability [10]. However, it has a lower vapor pressure (similar to HFA-227ea) and a higher surface tension than HFA-134a, and is therefore likely to produce a narrower aerosol plume with larger droplets if delivered using equivalent actuator hardware [11]. There are also some concerns regarding its breakdown products once emitted into the upper atmosphere, and its viability due to perfluoroalkyl (PFAs) restrictions currently under consideration [12].

Given the long lead time required for new products to come to market, the development of entirely new low-GWP products within the HFA phase-down period will prove challenging. The rapidly shifting economics of HFA production in response to the accelerated phase-down timelines proposed by the European Union, and the desires of consumers to reduce their carbon footprint drive the need for a faster response [13]. This may be achieved by alternative development pathways to demonstrate *in vitro* equivalence via the weight of evidence approach, which may include tests such as spray pattern, plume geometry and droplet size and velocity [14].

We have investigated how the change from current-generation to next-generation pMDI propellants might affect the technical performance of currently used pMDI hardware, with a particular focus on actuator designs that assist with the achievement of *in vitro* equivalence.

In-canister performance: X-ray fluorescence spectroscopy

When considering the *in vitro* performance of novel pMDI propellants, we can divide our studies into three broad categories as illustrated in Figure 1. The first category is consideration of performance inside the canister. This includes factors such as API solubility (for solutions), sedimentation or creaming time (for suspensions), material compatibility, and adhesion or loss of the drug onto the canister valve and wall surfaces (both physical forms).

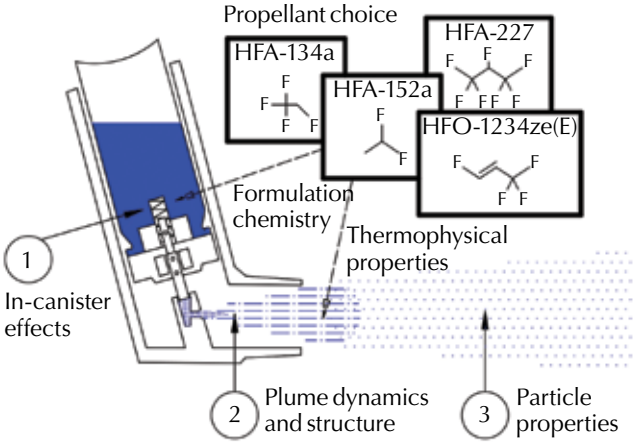
The latter two categories in Figure 1 involve the external aerosol, previously described as Phase I and II of the aerosol maturation process by Stein and Myrdal [15]. The second category concerns the performance of the spray plume beyond the orifice, which drives spray pattern, plume geometry, droplet size and velocity. It is dominated by atomization, mixing and evaporative processes. The third category is the performance of the matured aerosol particles, as measured by their delivered dose and size distribution. All three of these categories represent a complex interaction of hardware, propellant and formulation chemistry. In our studies, we have not considered varying ambient conditions, preferring to hold these constant in order to investigate the effect of the propellant change.

Investigating in-canister stability, sedimentation and adhesion (among other factors) often requires the use of transparent vials or destructive testing of samples. This limits the amount of information that can be obtained. In response to this challenge, we have developed a non-destructive, confocal X-ray fluorescence technique capable of measuring API distribution for both suspended and dissolved surrogate drugs in a model formulation through the wall of an aluminum canister. This allows us to study formulation interactions with canister, valve and actuator components.

For example, we can evaluate API deposition in the actuator orifice. In previous work, we demonstrated the use of synchrotron X-ray fluorescence to measure the distribution of ipratropium bromide in a pMDI spray plume [16]. In this new work, we used a higher X-ray beam energy (42 keV compared to 15 keV) capable of penetrating the aluminum canister wall. To obtain a strong signal, potassium iodide (KI) was used as a surrogate API to make a model solution formulation. The characteristic X-ray fluorescence emis-

Figure 1

Schematic diagram of a pressurized metered dose inhaler showing regions that could be affected by propellant choice.



sion from the iodine atom has sufficient energy to escape the aluminum canister. For suspension formulations, a similar approach can be obtained through the use of insoluble, micronized, barium sulfate particles. With appropriate corrections for reabsorption in the formulation and canister wall, its concentration can then be measured and spatially mapped [17]. A suitable tracer element is required to perform the measurements, so its behavior is first characterized in glass vials to determine solubility and settling time. This ensures that its behavior is similar to that of conventional APIs of interest. Selection of dopants with appropriate size and solubility characteristics provides insight into the ways conventional APIs may be expected to perform.

In the results shown in Figure 2, a Kindeva actuator with 0.3 mm exit orifice diameter was used. pMDI units consisting of 50 µL metal metering valves (Kindeva Spraymiser with retaining cup, Loughborough, UK) and FEP-coated aluminum canisters with standard wall thickness were used for all tests. All canisters were pressure-filled to 200 nominal doses. Figure 2 shows a series of X-ray images inside the canister-valve closure region of an aluminum canister with a solution formulation of 2 mg/mL KI in 8% w/w ethanol, comparing the current HFA-134a to novel propellants HFA-152a and HFO-1234ze(E). The left color panels show the local concentration of API in the highlighted region of the canister, where red indicates high concentration and blue indicates low concentration. Measurements were taken after 5, 45, 85, 125 and 165 actuations (out of 200 nominal doses). From these measurements, a total volume-integrated concentration of API deposited in the canister-valve closure region can be obtained; this is shown in the right panel. The X-ray measurements are integrated along the beam path (z axis) and have units of length, so the volume-integrated concentration is defined as:

$$C_V = \frac{1}{V} \iint c(x,y)\, dx\, dy$$

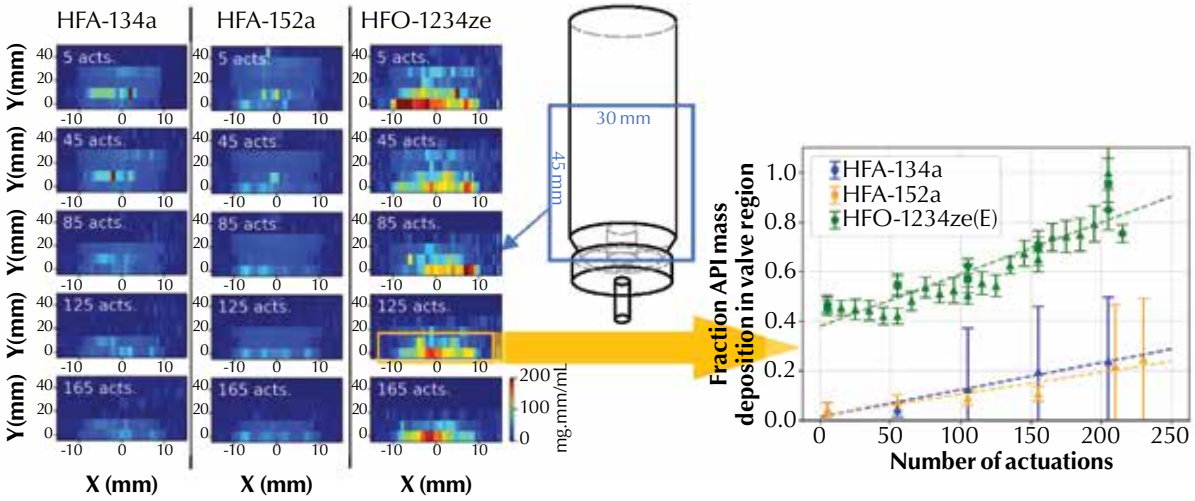
Early results in model solution and suspension formulations indicate higher levels of both valve deposition and precipitate formation in HFO-1234ze(E) beyond that observed in glass vials. These effects can be separated by observing the spatial distribution of the X-ray fluorescence signal. The resolution of the measurement technique permits us to identify where the tracer is adhered to the valve components or settled as precipitates near the valve seal, as opposed to remaining in solution in the bulk formulation. This indicates that solubility and wall-interactions are altered in HFO propellant and must be accounted for when reformulating with these propellants. These observations correlate with observed changes in water solubility and reduced polarizability. The data shown in Figure 2 were obtained with a constant 8% w/w ethanol co-solvent but without other excipients.

Plume performance: High-speed imaging

The properties of the droplets produced by a pMDI (as characterized by their size, velocity and distribution, for example) depend on the chemico-physical properties of the formulation. Such properties include saturated vapor pressure, density, latent heat of vaporization and surface tension, among others. No single physical property of a propellant is predictive of plume metrics. However, the properties believed to be most important are shown in Table 1.

Figure 2

X-ray fluorescence profiles of the canister valve and closure region for various propellants, comparing the level of sedimentation and deposition over unit life. The error bars in the right panel represent a 99.7% confidence interval about the mean mass fraction of deposited API in the integrated volume indicated by the yellow box.



These properties determine the amount of evaporation and expansion that occur as the formulation passes through the orifice and forms the initial spray. These key chemico-physical properties can vary considerably when the propellant or co-solvent level is altered. As the droplets break apart and coalesce, droplet size tends to an equilibrium that depends on surface tension [15]. Complex thermal and turbulent droplet mixing effects are also involved.

One of the major challenges in the implementation of low-GWP propellants for pMDIs is that each has a unique set of chemico-physical properties, with at least one or of more of these being suboptimal when compared to current-generation propellants. For example, HFA-152a has a high vapor pressure but a low liquid density relative to HFA-134a, which allows the spray to expand more widely, resulting in increased mouthpiece deposition [18]. Conversely, HFO-1234ze(E) has a low vapor pressure but high density relative to HFA-134a, which produces a narrow plume, leading to fewer and larger droplets [10, 19].

The structural differences between pMDI plumes with different propellants can be subtle, as they occur close to the orifice where the fluid is moving with high velocity [20]. In this region, the relevant length and time scales are on the order of microns and microseconds. To investigate the flow at such scale, high-magnification imaging systems capable of collecting large amounts of time-resolved data are required. We have undertaken a large-scale parametric study of pMDI plume dynamics utilizing an ultra-high-speed imaging approach [19]. In the data shown in this article, a conventional Kindeva actuator with 0.3 mm orifice and conventional FEP-coated aluminum canisters with 50 µL Bespak metering valves were used (King's Lynn, Bergen Way, UK); these were identical across all tests. A range of formulations were studied containing 0%, 8% and 15% ethanol co-solvent with 2.1 mg/mL beclomethasone dipropionate (BDP) in propellant HFA-134a, HFA-152a or HFO-1234ze(E).

A sub-microsecond pulsed LED backlight was used to uniformly illuminate the near orifice region of the pMDI spray, which was accessed by cutting a viewing window into the side of the mouthpiece. A high-speed camera recorded video with a magnification of 31 µm/pixel at up to 140,000 frames per second. A sample high-speed image is shown in the upper panel of Figure 3. Spray measurements were repeated 15-60 times with 2,000-14,000 frames per spray, resulting in more than 100,000 images per formulation, in order to achieve sample size-independent statistics. From this large, multi-terabyte database, statistical analyses of plume structure were undertaken to obtain both the temporal stability across the

Table 1

Key chemico-physical properties of various propellants, and typical APSD results obtained with model suspension and solution betamethasone dipropionate (BDP) formulations made with them. Background color density indicates relative improvement (green) or deterioration (orange) relative to HFA-134a. Adapted with permission from reference 19.

		HFA-134a	HFA-227	HFA-152a	HFO-1234ze(E)
GWP, kg CO_2-equivalent		1430	3220	124	7
Saturated vapor pressure at 25° C (SVP)		6.7 atm.	4.7 atm	5.6 atm.	4.6 atm.
Specific gravity (liquid phase at 25° C)		1.21	1.41	0.91	1.17
Theoretical stable droplet size at 25° C		5.7 µm	4.9 µm	9.7 µm	7.5 µm
Fine particle fraction	0.05 mg/mL BDP in propellant only	88.5%	-	70.7%	93.6%
	2.0 mg/mL BDP in 8% w/w ethanol	55.7%	-	51.3%	60.7%
	2.0 mg/mL BDP in 15% w/w ethanol	54.2%	-	50.1%	56.6%
Actuator, coupler, and throat deposition	0.05 mg/mL BDP in propellant only	32.3%	-	40.5%	30.8%
	2.0 mg/mL BDP in 8% w/w ethanol	51.7%	-	64.7%	52.6%
	2.0 mg/mL BDP in 15% w/w ethanol	50.3%	-	54.1%	46.8%
Spray pattern area at 60mm	0.05 mg/mL BDP in propellant only	589 ± 82 mm^2	-	610 ± 68 mm^2	474 ± 31 mm^2
	2.0 mg/mL BDP in 15% w/w ethanol	526 ± 24 mm^2	-	573 ± 22 mm^2	466 ± 26 mm^2

spray event and the shot-to-shot repeatability from one spray to the next for a range of formulations.

The results of our preliminary analysis are shown in Figure 3 for BDP solution formulations with 8% w/w ethanol co-solvent as described above. The schematic (top left) shows the region of the actuator observed in the high-speed images (top right). The colored panels in the lower portion of the figure show the average plume structure, temporal stability and shot-to-shot repeatability of the spray plumes (top row to bottom row, respectively). These were obtained from statistical analysis of the high-speed imaging data. The column headings name the propellants. All other hardware, formulation and ambient properties were held constant across the tests. Our data show that the average plume structure does not vary greatly with propellant change, and the presence of co-solvent acts to moderate the differences between propellants. However, the higher-order statistics reveal more interesting differences. HFA-152a formulations show more unstable plume behavior over time than HFA-134a. This is likely due to the lower density of the gas and its high vapor pressure. These act together to enhance entrainment of the surrounding air and turbulent mixing in the spray, increasing the likelihood of mouthpiece and actuator deposition. In recent work (not shown), we have demonstrated that HFO-1234ze(E) formulations show greater plume variability from shot to shot [21], which we attribute to reduced mixing of the spray with ambient air.

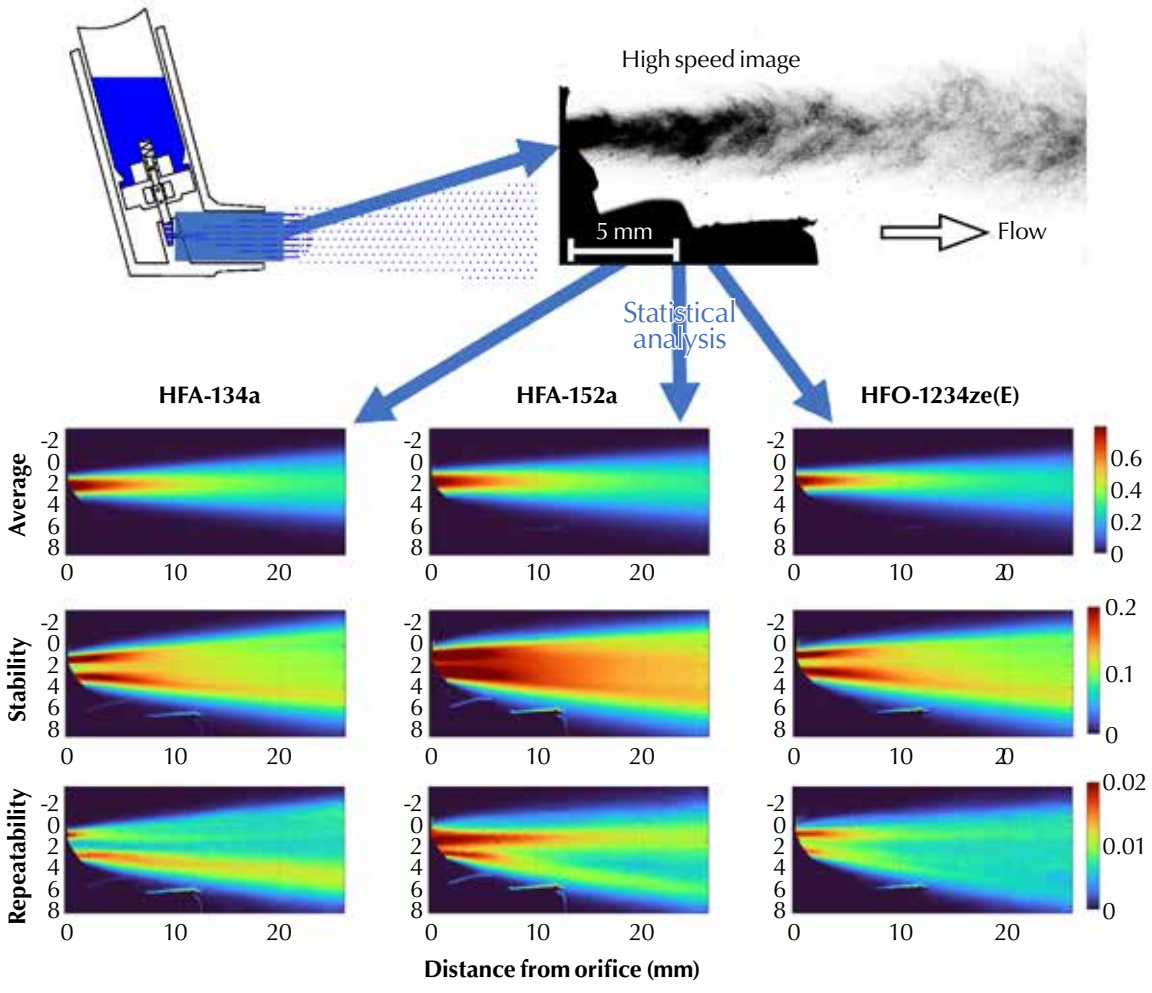
Other recent work has shown that spray stability changes are primarily initiated at the orifice [21]. Most importantly, we have also observed in simulations that the stability and repeatability challenges observed in these experimental studies can be minimized by making minor modifications in orifice geometry (such as orifice length or diameter), providing a route to adjustment of low-GWP pMDIs toward equivalence with existing formulations [22].

Matured aerosol performance

The most important consequence of propellant choice is its effect on the matured aerosol since

Figure 3

High-speed analysis of ex-orifice plume structure for matched hardware with various formulations. The formulations contained 8% w/w ethanol and 2.0 mg/mL BDP in each propellant. The horizontal and vertical axes are given in mm relative to the location of the orifice.



this influences drug deposition characteristics. In recently published work, we have undertaken a suite of cascade impaction measurements of various model BDP formulations in a range of propellants and compared several outcomes [19]. An ultra-low concentration of 0.05 mg/mL BDP without co-solvent was used as a model co-solvent-free solution. This was compared to solution formulations of 2.0 mg/mL BDP at various ethanol concentrations. The results are shown in Table 1 [19, 23]. Data are given as the average of N = 3 replicates ±1 standard deviation. Each aerodynamic particle size distribution measurement consisted of n = 24 repeated actuations (for co-solvent-free formulations) and n = 5 actuations (for 8% and 15% ethanol solutions).

We found that HFA-152a formulations showed consistently lower fine particle fraction and higher actuator, coupler and USP throat deposition compared to analogous formulations with HFA-134a. HFO-1234ze(E) formulations showed improved performance with respect to these metrics. The low density and higher velocity of HFA-152a results in a less stable and wider spray (as indicated by spray pattern area). This likely results in greater mouthpiece deposition and loss in the USP throat. Conversely, the high density and lower pressure of HFO-1234ze(E) can lead to narrow plumes. While it reduces mouthpiece, coupler and throat deposition, the narrower spray and reduced mixing causes maturation to occur further from the orifice.

Conclusions: Novel ways to accelerate the transition to low GWP propellants

Existing *in vitro* test results on HFA-152a and HFO-1234ze(E)-based formulations suggest that neither propellant is a drop-in replacement for HFA-134 or HFA-227ea, and that one does not have a decisive advantage over the other. HFA-152a has similar molecular and chemico-physical properties to the current-generation of HFAs and may be well suited to a range of solution formulations where solubility or stability in HFO propellant is poor. However, its low density makes reformulation of suspensions challenging and it produces a less stable spray that can lead to a lower fine particle fraction than HFA-134a in equivalent hardware. Its GWP is still more than 100 times that of CO_2. HFO-1234ze(E) is an ultra-low-GWP replacement whose higher density makes it well suited to suspension formulations, but whose lower vapor pressure (and therefore spray velocity) can lead to narrower sprays with larger droplets and longer maturation length and time scales.

The key finding of the preliminary *in vitro* studies described in this paper is that the changes required to convert pMDI formulations from current HFAs to low-GWP alternatives require careful evaluation, but do not represent an insurmountable barrier. The *in vitro* methods shown here may provide a means of measuring and demonstrating equivalent or improved in-canister formulation stability, plume performance and aerosol size distributions through the following means:

- For solution formulations, adjustment of co-solvent concentration. Small changes in co-solvent level can alter the vapor pressure and density of the formulation to compensate for some changes in chemico-physical properties.
- For solution or suspension formulations, adjustment of the spray orifice. Changes in vapor pressure and density lead to changes in spray duration, stability and spreading rate, which can be compensated for by small alterations in diameter, length and shape.
- For solution or suspension formulations, adjustment of the mouthpiece. Less stable sprays, such as those produced by HFA-152a propellant, lead to increased mouthpiece deposition. Altering the shape and length of the mouthpiece may be able to compensate for these effects. (This is a matter of ongoing research).

The above modifications open up a range of new possibilities in the realm of actuator design that were not necessary and therefore not widely investigated during the CFC to HFA transition era. The ability to take advantage of these optimizations requires a deep understanding of the physics of pMDI sprays, and tools that can provide the high-resolution data required to do so.

Many challenges remain for the development of low-GWP pMDIs beyond simply matching aerosol performance. These will be driven by regulatory and formulation needs rather than engineering considerations [5]. However, with additional engineering design variables at our disposal, the metered dose inhaler can continue to be adapted to serve the needs of clinicians and patients for decades to come.

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