In-Vitro Evaluation of pMDI Spray Development of HFA134a, HFA152a and HFO1234ze(E)

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Summary

To assist the transition to alternative low GWP pMDI propellants, the current study performed high-speed imaging and droplet sizing of the near-orifice spray development of HFA-152a and HFO-1234ze(E) based formulations. Conventional HFA-134a propellant was tested as the control. Placebo (pure HFA/HFO) and model solution (2 mg/mL drug dissolved in 8% w/w ethanol) formulations were measured, for each propellant. The results indicate larger droplets produced by HFA-152a and HFO-1234ze(E) based placebo formulations at the near-orifice locations. HFA-152a also showed a wider and denser spray profile as compared to that of HFA-134a due to its low vapour pressure and density. The temporal spray development was also less stable and repeatable. HFO-1234ze(E) showed a similar spray profile and a more stable spray development compared to that of HFA-134a, however with reduced spray repeatability. The impact of changing propellants on spray development was reduced in model solution formulations. Both HFA-152a and HFO1234-ze(E) showed comparable spray profiles and measured droplet size to that of HFA-134a. The issue of low spray stability and repeatability persists in solutions, particularly for HFA-152a. These early results indicate that the transition to low GWP propellants is feasible, but further optimisation of the actuator design and formulation composition is needed.

Key Message

HFA-152a and HFO-1234ze(E) show higher similarity with HFA-134a in spray width and extinction profile, and droplet size in model solution-based formulations than propellant placebo models of suspension formulations. The two alternative low GWP pMDI propellants also show reduced spray stability and repeatability. Between the two, HFA-152a is more different from HFA-134a.

Introduction

The pharmaceutical industry is now transitioning toward low GWP propellants, given the high global-warming potential (GWP) of current HFA propellants. In this regard, HFA-152a and HFO-1234ze(E) are two promising candidates [1]. However, with measurable differences in their thermodynamic and physicochemical properties, little is known about the formulation spray development as driven by these alternative propellants. Meanwhile, the droplet evolution heavily depends on the spray development and directly changes the delivered dose [2]. For example, the variation in propellant vapour pressure and density alters the spray mixing through variation in spray velocity and spread angle [3]. The current study aims to bridge this gap by performing direct comparisons among HFA-134a (control), HFA-152a and HFO-1234ze(E) based pMDI formulations via highspeed imaging and droplet sizing of the sprays.

Methodology

Two formulations were tested for each propellant - a placebo (pure propellant) and a model solution formulation - 2 mg/mL dissolved drug (an inhaled corticosteroid as model molecule) in 8% w/w ethanol co-solvent (Univar, Australia), to generally model a suspension and a solution pMDI formulation. Propellants were pressure-filled into identical canisters (Kindeva, UK), and crimped with 50 µL metering valves (Bespak, UK) using a Pamasol (Laboratory Plant 2016/100). A conventional pMDI actuator of 0.3 mm orifice diameter, 0.8 mm orifice length, and 14 mm³ sump volume was employed (Kindeva, UK). With a particular interest in the near-orifice spray development, optical access was achieved by removing the mouthpiece and a portion of the actuator body, as shown by the example in Figure 1a.

The current optical diagnostic setup is illustrated in Figure 1(a) by the simplified schematic. A 28 L/min air flow at 21°C and 50% humidity was supplied through the actuator. The ambient temperature was kept constant at 21°C. Canister actuation was achieved via a pneumatic actuator, synchronised to the
high-speed camera trigger. To prevent icing, a custom-made heater probe was inserted behind the actuator to maintain a constant actuator stem block temperature of 30°C. Note that the temperature gradient between the actuator and ambient air was shown to have a negligible impact on the pMDI spray [4] – latent heat of propellant boiling dominant over the heat transfer through the plastic actuator body. A high-speed camera (Photron SA-Z) and LED (Luminus Devices, USA) system were used to capture back-illuminated images of transient spray development, at 50 kHz and 350-ns exposure time (Figure 1(a)). The camera field of view, with a 30 μm/pixel resolution, is illustrated by the raw spray image in Figure 1(b). Separate laser diffraction measurements were performed for the same formulations to obtain droplet size distribution data using a Malvern Spraytec (Malvern Instrument Ltd., UK).

Image post-processing was performed only during the quasi-steady period of the spray development, which was determined based on the detected spray area and centreline direction for all captured events, per formulation. An average of 6000 image frames were processed per spray, corresponding to a 120 ms period. For each image, spray width at 10 equally spaced locations along the spray axis was measured based on the detected spray area (Figure 1(b)). A pixel-wise extinction measurement, i.e. the calculation of the amount of light absorbed/scattered as compared to the background (no spray) image, was also conducted based on background correction, as shown in Figure 1(c).

![Figure 1. Schematic diagram showing the experimental setup and actuator configuration (a), the imaging field of view (b) and image post-processing (c)](image)

**Result and Discussion**

Measured spray widths as a function of horizontal distance to the orifice are shown in Figure 2(a). The various formulations are distinguished by the line style and colour. Mean extinction profiles of the same formulations are shown in Figure 2(b). The spray width and extinction profile were calculated by temporal averaging of the quasi-steady processing period of each spray, followed by ensemble averaging of all 16 captured sprays per formulation. For the placebo formulations (dashed lines), similar spray width and
extinction profiles were measured for HFO-1234ze(E) and HFA-134a sprays. HFA-152a shows a larger spray width than that of HFA-134a, indicating a potential higher tendency of droplet deposition (e.g., device and oropharyngeal). The extinction profile of the HFA-152a spray (Figure 2(b)) is also larger and at an overall higher extinction level, indicating higher droplet number density. This difference in the HFA-152a spray development is likely caused by its relatively low density and vapour pressure, which reduces droplet momentum. For the model solution formulation, broader and denser spray structures were observed compared to placebo. This is expected given the reduction in vapour pressure and density due to the addition of ethanol as a cosolvent [5]. The modulation effect of ethanol is also evident in Figure 2. Sprays of HFA-134a and HFA-152a based model solution formulations show almost identical spray widths, which were slightly larger than that of the HFO-1234ze(E) spray. Different propellants show consistent/comparable extinction profiles.

Figure 3. The measured droplet size distribution for the placebo (left) and solution (right) formulations.

Results of droplet size measurements are shown in Figure 3. The sizing location of the current study is close to the orifice (30 mm downstream), where the effect of propellant variation is expected to be the largest. At this location, the measurement indicates the primary droplet size at the orifice rather than the final size of respiratory droplets/particles. In Figure 3, sprays of placebo formulations of HFA-152a and HFO-1234ze(E) are skewed toward larger sizes (>10 μm) compared to HFA-134a. The size distribution of HFA-152a is distinctly different from the other propellants. The Sauter mean diameters (SMD - mean diameter estimating volume to surface area ratio of measured particles) support this observation; 19.8 μm and 19 μm for HFA-152a and HFO1234-ze(E) compared to 14.9 μm for HFA-134a.

The droplet size of the model solution formulations was smaller than the propellant placebo. SMD was 11.1, 14.8 and 11.4 μm for HFA-134a, HFA-152a, and HFO1234ze(E). The ethanol/API content in the droplets is likely to enhance evaporation at near-orifice locations, acting as a heat sink during evaporative cooling. However, at downstream locations, the reduction in droplet evaporation due to non-volatile contents is expected to be dominant, causing larger respiratory droplets/particles for solution formulation. Further studies are needed to clarify. The moderated impact of changing propellants in solution formulation is demonstrated in Figure 3, consistent with the high-speed imaging results (Figure 1). The SMDs and size distribution of low GWP propellants show higher similarity to the case of HFA-134a for model solution formulations, as compared to the placebo formulations. This is most apparent with HFO-1234ze(E) solution for the comparable SMD and distribution profile compared to HFA-134a.

Spray stability and repeatability are critical factors influencing pMDI efficiency [2]. The stability of a spray indicates the fluctuation in its temporal development, which will influence sensitivity to inhalation timing.

Figure 4. Spray stability and repeatability contour maps of HFA-134a placebo formulation (a and b). The difference heat maps as compared to that of HFA-134a for low GWP propellants (c-f).
and delivered dose. Repeatability is a measurement of the variation between different sprays, which will influence dose-to-dose repeatability. For the current study, the spray stability is quantified by the ensemble average of the standard deviation of the extinction signal of each spray, as shown in Figure 4(a) for the HFA-134a placebo formulation. The repeatability is defined as the standard deviation among spray-mean extinction profiles (Figure 4(b)). In the control, locally unstable and less repeatable spray development is found at the orifice exit for HFA-134a. To make a direct comparison, difference heat maps for the alternative propellants relative to HFA-134a are shown in Figure 4(c-f). Blue and red colours correspond to higher and lower stability/repeatability compared to HFA-134a. The HFA-152a placebo formulation is consistently less stable (Figure 4c) and less repeatable (Figure 4d). HFO-1234ze(E) shows improved spray stability (Figure 4e) but a larger spray-to-spray variation (Figure 4f).

Figure 5. Spray stability and repeatability contour maps of HFA-134a solution formulation (a and b). The difference heat maps as compared to that of HFA-134a for low GWP propellants (c-f).

As shown in Figure 5(a,b), HFA-134a solution formulations show improved spray stability and repeatability compared to the placebo formulations, particularly at the spray centreline. This is expected given the reduced formulation vapour pressure. Compared to HFA-134a, HFA-152a shows an apparent reduction in stability (Figure 5c) and overall reduced repeatability (Figure 5d). This is less problematic for HFO-1234ze(E) yet localised less-stable/repeatable regions within the spray are still visible. This suggests that HFA-152a may be more susceptible to poor dose consistency and repeatability in solution and suspension formulations. Conversely, HFO-1234ze(E) does not demonstrate this behaviour.

Conclusion

This study assessed alternative Low GWP propellants for use in pMDI formulations using near-orifice high-speed imaging. HFA-152a and HFO-1234ze(E) show promise as replacements for solution formulations due to their similar spray width, extinction, and droplet size distributions compared to HFA-134a. Implementation in suspension formulations may prove more challenging, based on our measurements of pure propellant placebos, as evidenced by larger droplet size distributions. Low GWP propellants show reduced spray stability and repeatability than sprays of HFA-134a. This may lead to high susceptibility to variation in delivered dose consistency, but more data is required to determine this. Among the two low GWP propellants, HFO-1234ze(E) showed a greater similarity to HFA-134a in terms of near-orifice spray development. Our current findings suggest the need for further design/formulation optimisation of the pMDI [6] to assist the transition towards these alternative propellants, particularly for HFA-152a formulations.

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References

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