PRESSURISED METERED-DOSE INHALER SPRAY STRUCTURE

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ABSTRACT

Sprays with and without ethanol issuing from a pressurised metered-dose inhalers (pMDI) are studied with Mie scattering, particle image velocimetry and laser extinction. Preliminary PIV measurements in the sagittal plane show that axial velocities are lower immediately downstream of the mouthpiece for ethanol-containing sprays at 50 ms after the start of actuation; further downstream, the velocity appears equal for both formulations. Vertical profiles of axial velocity collapse to a single curve when non-dimensionalised by peak velocity and distance from the atomising nozzle, suggesting that outside the mouthpiece the mean spray behaves like a self-similar turbulent jet. High turbulence intensities for the axial and vertical velocity fluctuations are measured, and found to decay with increasing axial distance from the nozzle. Laser extinction measurements downstream of the mouthpiece reveal an intermittent high amplitude fluctuation in spray density, an observation consistent with conjectures from prior studies of pMDIs with less temporal resolution. Propellant-only sprays are found to have higher fluctuations in absorption, indicative of a higher amplitude pulsation taking place in the nozzle.

BACKGROUND

The pressurised metered-dose inhaler is an extensively used drug delivery device and is predominantly used for the treatment and management of respiratory diseases. In a pMDI canister, a drug is kept in solution or suspension in a propellant liquid, often with a cosolvent to aid stability. When the canister is depressed, the liquid suspension or solution is forced out of the canister by the vapour pressure of the propellant and is expelled from an atomising nozzle, forming a spray that is inspired by the user. Evaporation of liquid propellant and cosolvent as the droplets convect downstream results in the formation of an aerosol of drug particles, which are intended to deposit in the lung. Efficiency of pMDIs is typically low, with the majority of the delivered drug depositing in the mouth of the user. This is the result of droplets with large aerodynamic diameters and high initial velocities, which cannot trace the inspired flow into the lung of the user. Ivey *et al.* (2014*b*) reviews research into the effects of device and formulation parameters on pMDI performance. Ethanol is a cosolvent typically used to improve drug solubility in hydrofluoralkane propellants, however its effect on atomisation and deposition can be significant and detrimental to efficient delivery (Stein & Myrdal, 2006).

Sprays from pMDIs have been observed to have a pulsatile behaviour, with large variation of ejected spray density and cone angle at a frequency of around 1000 Hz. This frequency has been estimated in prior studies by observing the distance between large pulsatile bursts in the spray (Ju *et al.*, 2012) or from high-speed visualisations (Dunbar *et al.*, 1997; Versteeg *et al.*, 2006). Visualisations of a transparent expansion chamber showed the formation of large bubbles, with the pulsation attributed to their formation and collapse (Versteeg *et al.*, 2006). However, only a single formulation was tested, and the expansion chamber and nozzle used were scaled up from typical pMDI geometries.

Prior studies have attempted to characterise the velocity field of the spray with particle image velocimetry (Crosland *et al.*, 2009; Harang, 2013) amongst other techniques, including phase doppler anemometry (Dunbar *et al.*, 1997). These studies noted the high value of turbulent fluctuations, with estimates of peak turbulence intensity greater than 50% (Harang, 2013).

We present measurements using particle image velocimetry to characterise the velocity field for ethanol-containing and ethanol-free formulations. Time-resolved laser extinction measurements are used to explore pulsatile spray behaviour.

EXPERIMENTAL METHODOLOGY

Particle image velocimetry measurements were performed with a double shutter camera, dual cavity pulsed laser and a simple Mie scattering arrangement, as shown in Figure 1. Velocity measurements were performed by cross correlating images of the droplets issued from the pMDI, with no additional tracer particles added. This introduces a difficulty in estimating velocity in regions where turbulent fluctuations give rise to intermittent spray presence. For this reason, velocity measurements are only shown for regions where the spray is consistently present. Experimental and processing parameters are summarised in Table 1. For the cross-correlation, errant vectors were determined using a maximum displacement difference of 5 pixels between windows, and were replaced by interpolation. Images were preprocessed with a dynamic histogram clipping technique, removing the highest 2.5% of pixels.

Table 1. Imaging and processing parameters for particle image velocimetry measurements.

Parameter	Value
Camera	PCO 4000
Laser	PILS Nd:YAG
Interframe time (μs)	10
Magnification $\left(\frac{\text{px}}{\text{mm}}\right)$	52
Field of view (mm x mm)	77 x 51
Aperture	f2.8, f4
Focal length (mm)	105
Window size (px x px)	48 x 48
Window overlap (px)	16

Laser extinction was used to obtain time-resolved information about fluctuations in spray density. Where multiple species are present, the intensity drop is the product of the contributions from each component. An estimation of the absorption coefficient is made difficult by the change in concentration of the propellant and ethanol as evaporation occurs at different rates. The laser extinction results are presented as an 'effective mass' M, the non-dimensional ratio of mass per unit area $\frac{\mathrm{d}^2 m}{\mathrm{d}x\mathrm{d}y}$ $\left(\frac{kg}{m^2}\right)$ normalised by the absorption coefficient μ $\left(\frac{m^2}{kg}\right)$:

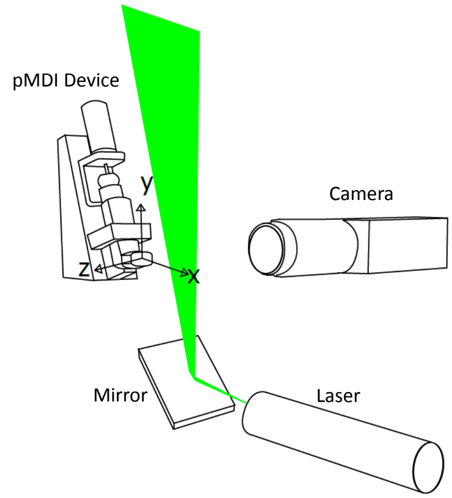

Figure 1. Schematic of the experimental apparatus for Mie scattering, consisting of PILS laser, 45 degree mirror, automated pMDI device and PCO 4000 camera. Coordinate system shown is used for the PIV and laser extinction measurements.

$$M = \frac{1}{\mu} \cdot \left(\frac{\mathrm{d}^2 m}{\mathrm{d}x\mathrm{d}y}\right) = -\log_\mathrm{e}\left(\frac{I}{I_0}\right) \tag{1}$$

Details of the data acquisition parameters are summarised in Table 2. The laser sheet was aligned with the centreline of the spray axis. A region of interest of 360 by 12 pixels in the axial and vertical directions was used. A reference intensity I_0 image was obtained by ensemble averaging 100 images in which no spray was present. After normalising the obtained image sequence by the reference intensity image, the sequence was binned in the vertical direction to provide a line measurement of extinction. Uncertainty on absorption measurements in optically dense sprays is considered to be comparatively high, as much of the attenuation of the incident light is a result of scatter and refraction from phase boundaries rather than direct absorption (Kastengren & Powell, 2014). For the present results, laser extinction is used as a visualisation technique and not as a tool for measuring spray mass.

Four placebo formulations were used for the measurements, two of which contained only propellant and two of which contained a mixture of propellant and ethanol (EtOH), which is a common cosolvent used in commercial pMDIs. Propellant-only canisters consisted of either 100% HFA134a or HFA227. Effects due to the presence of the drug are considered negligible for this study. Table 3 details the formulations used, their vapour pressures p_v and liquid densities ρ_l in the canisters. The vapour pressures presented for the ethanol-containing formulations are molar-weighted averages of the constituent vapour pressures (Ivey *et al.*, 2014*a*).

Two spray devices were used for measurements. A linear solenoid-driven pMDI actuator was used for PIV

Table 2. Imaging parameters for laser extinction measurements.

Parameter	Value
Camera	MotionPro X3
Exposure time (μs)	10
Frame rate (FPS)	40,000
Magnification $\left(\frac{\text{px}}{\text{mm}}\right)$	28.9
Field of view (mm x mm)	12.5 x 0.4
Aperture	$f2.8$
Focal length (mm)	105
Radiometric resolution	8-bit

Table 3. Placebo formulations used in the study.

Formulation (w/w)	p_v $\left(\text{Pa} \times 10^5\right)$	ρ_l $\left(\frac{\text{kg}}{\text{m}^3}\right)$
HFA 134a	5.76	1206
HFA 227	3.90	1408
HFA 134a 85% EtOH 15%	4.16	1116
HFA 227 85% EtOH 15%	2.39	1258

measurements, and has previously been used to study the spray plume from a pMDI using schlieren (Buchmann *et al.*, 2014). Canisters were installed in a Bespak inhaler body, which had a nozzle diameter of 0.3 mm and a distance of 20 mm from the nozzle to the end of the mouthpiece. The inhaler was actuated by an externally triggered linear solenoid, and was held at a 15 degree angle to the vertical to orient the mouthpiece in the horizontal plane. An electronic metering inhaler (EMI) (Lewis, 2013) with expansion chamber attachment was used for laser extinction measurements. The EMI uses an unmetered canister capable of continuous operation and an electric solenoid capable of dispensing microlitre liquid quantities. The expansion chamber attachment was used with a Bespak 0.3 mm diameter nozzle. No coflow was used for the presented measurements.

VELOCITY MEASUREMENTS

Particle image velocimetry measurements were obtained for each of the canisters, however for brevity we present results for canisters with and without ethanol, for a single propellant. The ensemble average velocity magnitude fields for HFA134a canisters at 50 ms after actuation are shown in Figure 2.

Several features are observable for the mean velocity magnitude field. The spray is inclined to the horizontal axis. Prior studies (Buchmann *et al.*, 2014) have shown that a coflow directs the spray downward; in the absence of a coflow, we find the spray from the Bespak inhaler to be directed upward at an angle of 5 degrees. The velocity magnitudes are higher for the propellant-only canisters, which is expected to be a result of the higher vapour pressure.

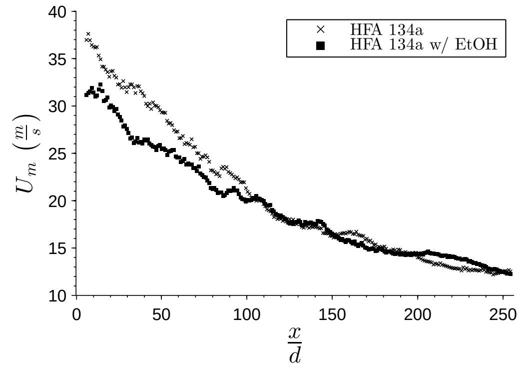

Figure 3. Maximum mean axial velocity against axial distance for the HFA 134a spray, 50 ms after actuation.

For the presented velocity fields, the maximum mean axial velocity is obtained for each axial location of the velocity field, and is shown in Figure 3. U_m appears to follow a relation $U_m \propto \frac{c}{x+a}$ for some constants c and a, which is consistent with the self-similar turbulent jet described by Abramovich (1963). Notably, these values are approximately a factor of three higher than those obtained at 50 ms after actuation with propellant-only HFA 134a sprays by Harang (2013), however this may be the result of different apparatus delays, resulting in measurements being taken at different times in the spray.

To test whether the velocity field outside the mouthpiece is self-similar, vertical profiles of axial velocity U are normalised by the maximum axial velocity U_m for each x. Self-similar velocity profiles collapse with a characteristic width of the spray, typically the half-width or full-width half-maximum (Rajaratnam, 1976), which is proportional to the axial distance from the nozzle if a constant cone angle θ is assumed. Figure 4 shows the velocity profiles for the two formulations, normalised by U_m and the axial distance $(x+a)$ where $a = 20mm$ which is the distance from the atomising nozzle to the mouthpiece exit. The horizontal axis for the velocity profiles is $(y-b)$, where b is the vertical location of U_m.

The vertical profiles of velocity, when appropriately non-dimensionalised, collapse onto each other, suggesting that the spray behaves like a self-similar turbulent jet in the region studied. Non-dimensional profiles are similar for the ethanol-containing and ethanol-free cases, suggesting that mean spreading rates are comparable with and without ethanol.

A further property of a self-similar turbulent jets is a constant turbulence intensity along the line of U_m, such as that found over the range (x/d) = 50-97.5 for a Reynolds number on the order of 10^5 by Wygnanski & Fiedler (1968). Axial and transverse turbulence intensities for the spray from the ethanol-containing canister are shown in Figure 5. As x/d increases, ${u'_{rms}}/{U_m}$ has a gradual decaying trend while ${v'_{rms}}/{U_m}$ increases, suggesting that the spray does not satisfy this criterion. This trend towards lower turbulence intensity may be an artifact of the measurement technique. Larger droplets have a disproportionate influence on the cross-correlation used in PIV, and it is possible that further from the mouthpiece where the finely atomised droplets have evaporated, comparatively large droplets remain and the velocity measurement is biased towards droplets with

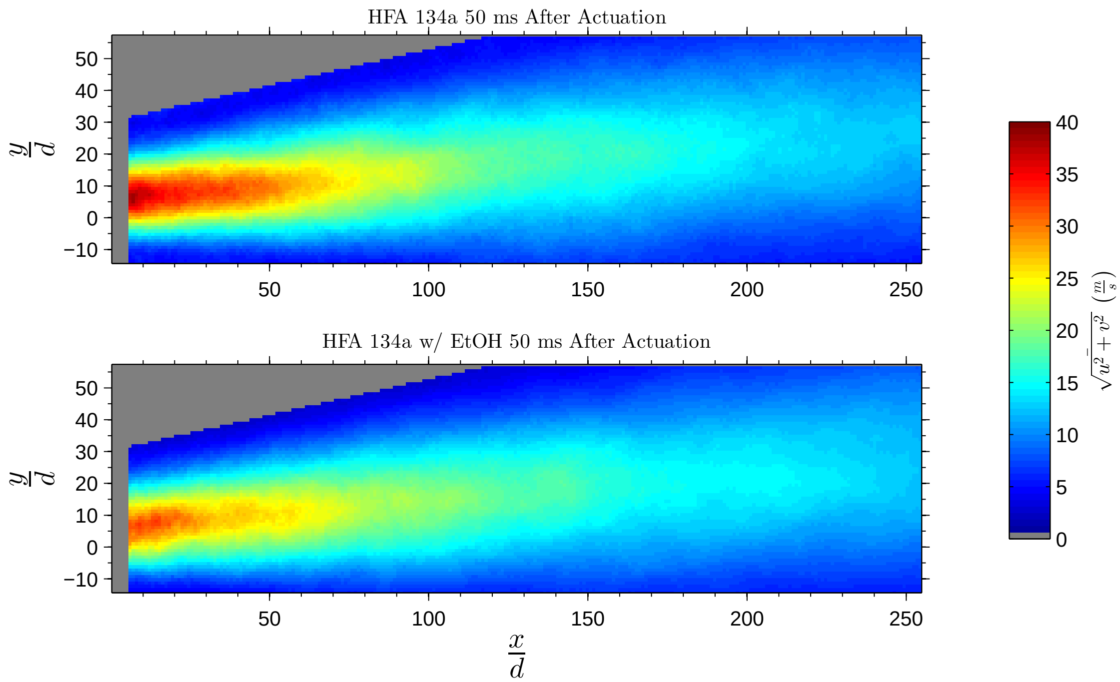

Figure 2. Ensemble average velocity magnitude field 50 ms after actuation for HFA 134a (top) and HFA 134a with ethanol (bottom) sprays. Mean fields are generated from 121 velocity fields. Masking is applied in regions where the spray is inconsistent (shown in gray).

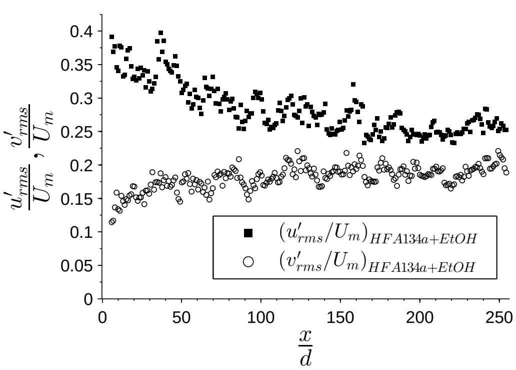

Figure 5. Axial and vertical turbulence intensities for HFA 134a & ethanol spray, downstream of the mouthpiece at 50 ms after actuation.

high inertia and poor flow tracing ability.

ABSORPTION MEASUREMENTS

Mean absorption $x-t$ plots were generated from 20 separate spray events for each formulation presented. As there appeared to be high frequency fluctuations, a centreline mean absorption $\overline{M}(t)$ was generated by applying a simple moving average with a kernel width of 2.5 ms, or 100 samples, to the mean effective mass at the centre of the region depicted. For each formulation, effective masses M are normalised by the maximum value of the centreline mean absorption $\overline{M}_{max}$.

Figure 6 shows plots of the mean effective mass $\overline{M}(x,t)$, the centreline mean effective mass $\overline{M}(t)$, the effective mass for an individual spray event $M_i(x,t)$ and its centreline residual $\left(M_i(t)-\overline{M}(t)\right)$, all normalised by the maximum centreline mean effective mass $\overline{M}_{max}$. The normalised residual is only plotted for regions where $\left({\overline{M}(t)}/{\overline{M}}\right) > 0.25$.

Prior studies have treated the spray as consisting of three main phases: a start-up transient, a steady state spray, and a decay for the end of the spray. Our results with unmetered canisters show that a steady state case is reached rapidly, relative to typical metered dose discharge times. The propellant-only case does not reach its steady state as rapidly as those with ethanol. The effective mass is seen to peak for the ethanol-containing formulations around 50-60 ms, and maintains at a quite constant value. For the ethanol-containing formulations a steady state spray is achieved by approximately 40 ms; the propellant only spray develops more slowly, reaching a steady state around 70 ms.

The measurements for individual spray events exhibit very large fluctuations in absorption, and the convection of these structures is observed in the (x,t) plots as diagonal lines. The normalised residuals are much larger for the propellant-only case, indicating that ethanol serves to reduce the magnitude of density fluctuations in the spray. The measurement is integrated across the width of the spray in the z-direction, consequently large fluctuations in the measurement are likely to be coherent across the cross-section of the spray.

To observe whether the variation is laser extinction is related to pulsatile ejection from the nozzle or a turbulent fluctuation about the centreline of the spray, crossplanar Mie scattering images of sprays from the pMDI are shown in Figure 7. At 50 ms after actuation and 5 mm downstream of the nozzle mouthpiece, the Mie scattering images vary greatly in their intensity, indicating the large differences in spray density that occur in the spray. Reductions in inten-

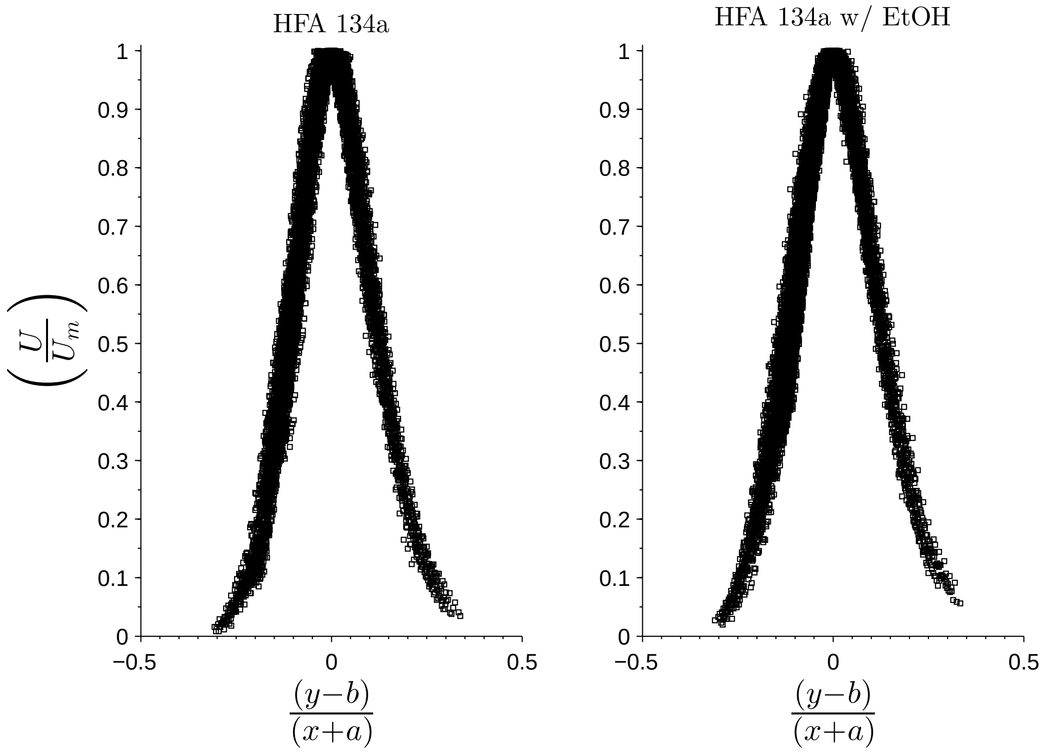

Figure 4. Non-dimensional velocity profiles for sprays from HFA 134a canisters with and without ethanol (left and right, respectively). The collapse of velocity profiles onto a single curve demonstrates self-similarity of the mean axial velocity for the region of interest studied.

sity in the laser extinction measurements are the result of reductions in spray mass across the entire cross-section of the spray, rather than a fluctuation in the spatial distribution about the spray centreline.

CONCLUDING REMARKS

Sprays from pressurised metered-dose inhalers were studied with particle image velocimetry and laser extinction. Propellant droplets are observed many diameters downstream of the nozzle, and can be used to obtain velocity measurements with particle image velocimetry. Large fluctuations in velocity are observed, however mean axial velocity profiles appear to be self-similar. Laser extinction showed that density fluctuations in sprays from a propellant-only formulation are higher than sprays containing ethanol. Mie scattering showed that the absorption fluctuations in the extinction measurements appear to be the result of large axial variations in cross-sectional mass, rather than a turbulent fluctuation about the jet centreline.

Acknowledgements

The authors gratefully acknowledge the support given to the project by the Australian Research Council.

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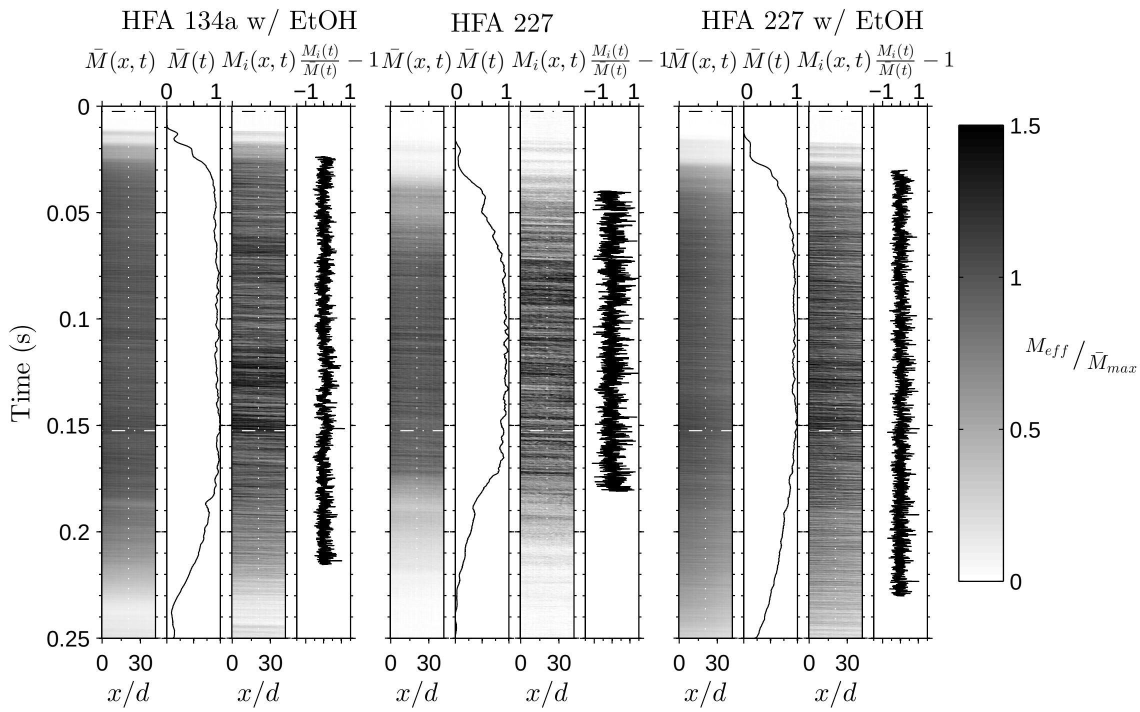

Figure 6. Ensemble average and individual $x-t$ spray images from the electronic metering inhaler with HFA 134a & ethanol (left), HFA 227 (center) and HFA 227 & ethanol (right). The start and end of spray actuation from the electronic metering inhaler are indicated by horizontal dash-dot lines, and the line used for the mean and single shot is indicated by a vertical dotted. All plots are normalised by $\bar{M}_{max}$ for the formulation.

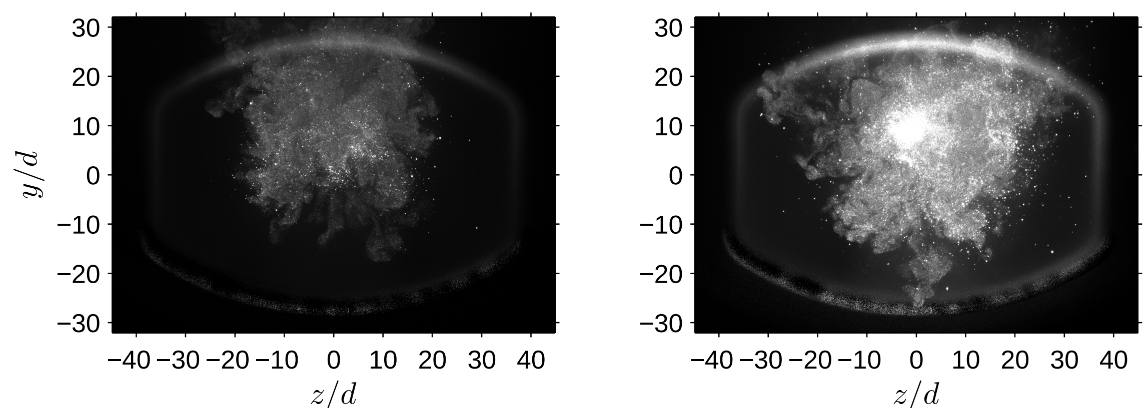

Figure 7. Instantaneous Mie scatter images from a pure HFA 134a canister sprayed from the pMDI, 5 mm downstream of mouthpiece 50 ms after actuation. Images are background subtracted, and the mouthpiece is illuminated by scattering from the spray.

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