Increasing the Fine Particle Fraction of Pressurised Metered Dose Inhaler Solutions with Novel Actuator Shapes

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Abstract

In this paper we demonstrate that the use of multiple orifices can improve the fine particle fraction (FPF) of pressurised metered-dose inhaler solution formulations by up to 75% when compared to a single orifice with an equivalent cross sectional area ($p < 0.05$). While prior work has relied on metal actuator components, improvements in micro injection moulding and micro drilling now make it possible to mass produce novel orifice shapes to achieve similar FPF gains in plastic parts, with orifice diameters less than 0.2 mm. The ability to create internal features inside the actuator is also demonstrated. We show through in-vitro high speed imaging that twin orifice sprays merge quickly and act as a single, modified plume. We also show for the first time that FPF and fine particle dose (FPD) are strongly correlated with the distance at which the plume velocity decays to half its initial value ($R^2 = 0.997$ and 0.95 respectively). When plume velocity & FPF are increased, mouthpiece deposition decreases. This suggests that while smaller orifices produce

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more fine particles, higher sustained plume velocities also entrain more of the fine particles produced at the periphery of the spray due to increased shear. The effect occurs within the mouthpiece and is thus unlikely to alter the flow field in the upper airway.

Keywords: pMDI, Next generation impactor, High-speed imaging, Fine particle fraction, Fine particle dose, Solutions

1. Introduction

Optimising drug delivery from pressured metered-dose inhalers (pMDIs) has been a subject of ongoing research for over 50 years [1]. For a given formulation, this involves maximizing fine particle fraction (FPF) and fine particle dose (FPD) within the respirable size range while minimizing drug deposition in the valve, mouthpiece, and throat. These metrics are quantified via standard pharmacopeia impactor methodology [2, 3].

For pMDI solution formulations, the formation of particles is driven by the breakup of the propellant-driven liquid spray within the first few centimetres of the nozzle orifice [4]. The formation of these droplets is in turn driven by a complex relationship between formulation properties [5] and the actuator and nozzle shape [6]. The complexity of the relationship arises due to the tendency of hydrofluorocarbon (HFC) propellants to both boil inside the actuator [7–9], and flash-boil after leaving the nozzle orifice [10, 11]. Where less volatile co-solvents are used, aero-breakup of the droplets several centimetres from the nozzle also plays a role in drug distribution [12].

Choice of orifice size is a major factor influencing FPF [1]. Correlation between reduced orifice size, reduced MMAD and increased FPF has been known for decades [13], and the principle can be demonstrated from a simple dimensional analysis [14]. Like FPF and FPD, flash-evaporation of the propellant is non-monotonically influenced by orifice size [15]. The relationship between spray behaviour and FPF is therefore unclear. The underlying fluid-mechanical processes which give rise to this correlation are not fully understood [16]. This limits our ability to exploit this phenomenon to enhance drug delivery.

There are three practical considerations which limit the ability to increase FPF by reducing orifice diameter. The first is manufacturing limitations in making small holes in plastic parts, the second is the increased likelihood of clogging, and third is dosing limitations due to reduced discharge rate.
In an effort to work around these limitations, researchers have investigated the benefits of modifying orifice shape [17], orifice length [18], the presence of external features such as a ‘bowl’ or impression to aid in recirculation and droplet entrainment [19], internal geometry [20], and the effect of the mouthpiece size [6]. The end result is that the design of pMDI actuators has settled on a single circular hole with a diameter of typically 0.25 to 0.40 mm and an external bowl or impression.

In 2006, Lewis et al. [21] investigated the possibility of using multiple nozzle orifices to enhance FPF while compensating for the reduced flow rate of a single, smaller orifice. They found significant improvements in FPF by doing so, but were unable to determine the proximal cause of the improvement. They hypothesised that the increase in spray velocity caused by the reduced cross-sectional area of the nozzle orifice was a significant factor. However, it was not clear whether the laser-drilled multi hole designs they tested could be translated to plastic pMDI actuators, and repeatability was not investigated. The propensity of clogging risk in very small (0.08 mm) nozzles was also not investigated.

Without detailed near-nozzle measurements it is not yet clear how the flash-evaporation process might change when multiple nozzles are used. Flash evaporation only occurs above a critical orifice diameter [15], so having multiple smaller nozzles will not necessarily yield a proportional improvement in FPF if the effect is suppressed. Higher plume velocities may also increase mouthpiece and throat deposition [16].

This work uses the twin-hole arrangement of Lewis et al [21], but fabricates the nozzle assembly in plastic rather than metal. This allows for more complex geometries with both internal and external features. Improvements in micro-drilling technology make it possible to manufacture multiple small holes in plastics with diameters as small as 0.18 mm. Micro injection moulding also makes it possible to introduce complex internal shapes to the actuator that were not previously possible. Furthermore, improvements in high-speed optical diagnostics for sprays make it possible to study the evolution and repeatability of the plume close to the nozzle [22, 23]. When used in concert with standard impactor measurements, this can help reveal the underlying mechanisms which give rise to improvements in FPF for the delivery of solution pMDI formulations.
2. Methods and Materials

A consistent canister and valve was used throughout the study to isolate the effects of varying the nozzle orifice. Aluminium canisters (Presspart, UK) were fitted with 50 μL Bespak 357 metering valves (Bespak, UK) and filled with a mixture of 15% w/w ethanol co-solvent (Sigma-Aldrich, Australia) and the balance of HFA-134a propellant (Koura, UK). Where used, the active pharmaceutical ingredient (API) was micronised ipratropium bromide (IpBr; Vamsi Labs, India). Concentrations from 1.00 to 2.34 μg/μL were investigated. The API was chosen to facilitate direct comparison with previous X-ray measurements [12]. The high-speed imaging measurements were taken both with and without the API. No changes in plume properties were detected when the API was added to the formulation. In all experiments, the first five sprays from the canister were discharged to waste so as to provide consistent initial conditions.

2.1. pMDI nozzles and test facility

The control actuator used in the experiments was a Bespak BK632 nozzle with 0.33 mm orifice diameter [21]. This will be referred to in the results as the ‘Conventional pMDI’. For the variable nozzle geometry experiments, a pMDI testing rig was constructed with a removable front face and side panels, as shown in Figure 1. The side panels contain an integral O-ring seal and

![Figure 1: Modular pMDI test facility.](image)
allow the chamber to be cleaned and its internal volume to be adjusted. The geometry of the expansion chamber formed by these parts was designed to match the geometry of the stock Bespak nozzle, with the exception being an elongation of the stem connection to the canister to accommodate the hardware required to clamp the nozzles in place.

Replaceable nozzle inserts were manufactured from optically clear polycarbonate (3Dxtech, USA) using a micro-injection moulding machine (Babyplast 6/10P, Spain). The aluminium mould was manufactured in-house to produce template nozzles of various shapes without any orifice. Two examples of these are shown in Figures 2a & 2d. Figure 2a is an insert designed to mimic the external ‘bowl’ feature of the stock Bespak nozzle. Figure 2d contains an additional internal recess feature which has the effect of significantly reducing the length of the nozzle hole without changing the external dimensions.

The nozzle orifices were added to the templates using a micro-drill (Dumore, USA) with specialised drill bits (KEO Micro Tools, USA). The completed nozzles were inspected with a microscope for defects that might bias the results. Acceptable nozzles were installed into the front of the nozzle block with a silicone sealant and clamped in place to prevent leakage. Configurations with a single hole of diameter 0.33 mm (Figures 2b & 2e) and two vertically oriented holes with diameter 0.22 mm (Figures 2c & 2f) were investigated. The reduced hole diameter for the twin hole nozzle relative to the single nozzle results in an equivalent total cross-section area and thus equivalent discharge time for the metered volume between all cases. Combined with the internal recess feature, a total of four geometries were investigated.

2.2. Impactor measurements

The aerodynamic mass distribution of a formulation containing IpBr was evaluated using standard pharmacopeia impactor methodology. The conventional pMDI actuator was connected to the USP throat using a silicone adapter (made in house). For testing of the four novel nozzle geometries, a 3D printed rig was manufactured to accommodate the nozzle block, the pMDI canister and connect it to the USP throat (Figure 3). Aerosol mass distribution studies were conducted using the British Pharmacopoeia Apparatus E – Next Generation Impactor (Copley, UK) connected to a critical flow controller (TPK2100-R, Copley, UK) and a rotary pump (Copley, UK) operating at a flow rate of 30 L/min (calibrated using a Model 4040 flow meter; TSI Precision Measurement Instruments, Aachen, Germany).
Figure 2: Injection-moulded custom nozzle shapes tested in this study. All measurements are in millimetres.
canisters were primed to waste three times prior to analyses. The pMDI canister was then placed into the rig and actuated by depressing the canister for 4 seconds per actuation. Five actuations were performed to ensure that drug deposition on the resulting stages was above the limit of detection. Measurements were performed in triplicate for each nozzle.

After each run, the apparatus was disassembled and each stage of the NGI, the USP throat and the nozzle block/adapter were washed with a 1 mM HCl solution for drug quantification by high performance liquid chromatography (HPLC). Total delivered dose (DD, μg), fine particle dose (FPD, μg), fine particle fraction (FPF, %DD), mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were calculated for each nozzle using the Copley Inhaler Testing Data Analysis Software (CIT-DAS).

Drug content was quantified using a Shimadzu HPLC system consisting of a LC20AT pump, the SIL20AHT autosampler and an SPD-20A UV-VIS detector (Shimadzu, Sydney, NSW, Australia). Reverse-phase HPLC analysis was conducted using a μBondapak C18 (125A, 3.9 × 300 mm, Waters, Australia). Mobile phase consisted of 80% acetonitrile and 20% of phosphate buffer at pH 4 (KH$_2$PO$_4$ at 100 mM). The pH of the buffer was adjusted with phosphoric acid prior to mixture with the organic solvent. The IpBr analysis was run at 40°C for 7 min at flow rate of 1.5 mL/min. Injection volume was kept at 20 μL. The IpBr was detected at wavelength of 210 nm, and retention time around 5.4 min. Samples were quantified by interpolation in calibration curve of the standard drug prepared in 1 mM HCl solution. Linearity was
confirmed between 0.5 – 100 μg/mL with a limit of detection of 0.26 μg/mL.

Experimental results were analysed using the statistical software GraphPad Prism (version 8.2.1) and expressed as a mean ± standard deviation of three independent measurements. Mean deposition of IpBr on each stage were analysed using one-way ANOVA and compared by Tukey’s test, while aerosol performance parameters were compared to the conventional actuator using unpaired two-tailed t-test. Means were statistically different when $p < 0.05$.

2.3. High-speed imaging

High-speed diffuse backlit illumination measurements of the spray plume evolution [22–24] were conducted at the Laboratory for Turbulence Research in Aerospace & Combustion at Monash University, Australia. Key components of the experimental setup are given in Figure 4.

The canister was depressed automatically using a linear solenoid (Ledex, USA) [25] to provide a consistent metered dose and actuation timing for all experiments. The solenoid was synchronised with a Photron FastCam BC2HD high-speed camera (Photron, USA). The light source was a strobed white LED [26] (Luminus Devices, USA) with a pulse width of 2.1 μs and a repetition rate of 5 kHz. A 55mm lens and extension ring (f#8) were used to obtain an image magnification of 42.86 μm/pixel.

In order to avoid ice buildup on the nozzle, a dwell time of 1 minute was used between each recorded spray event. A minimum of $N = 50$ samples
were obtained for each nozzle configuration. The experiments were then repeated with multiple similarly manufactured nozzles in order to control for the effects of nozzle manufacturing variability. Measurements were also repeated with multiple canisters to control for any variability in formulation preparation.

High-speed images were analysed by removal of the background intensity $I_0$ before the spray, and normalisation to extinction $C_{\text{ext}}$:

$$C_{\text{ext}}(t, y, x) = 1 - \frac{I(t, x, y)}{I_0(x, y)}.$$  \hspace{1cm} (1)

Data were masked where the background light intensity was less than 1%. Sample extinction images for two of the four sprays are shown in Figure 5. The co-ordinate system is defined with $x$ as the distance from the nozzle and $y$ the transverse distance from the nozzle centreline. The field of view begins at 1.44 mm from the nozzle exit due to the shape of the bowl (see Fig. 2) and extends 44 mm downstream.

For each spray event, the time region where the spray was ‘steady’ was determined by integrating the extinction over a region $1.9 \text{ mm} < x < 2.6 \text{ mm}$ and determining the time period in which the spatially integrated extinction exceeded $2/3$ of the peak value. All subsequent statistical analysis is restricted to this time period. The plume centreline was located by least-squares fitting a straight line to the peak extinction locations at each pixel in $x$. This avoids bias in the results due to variable steering of the plume with different nozzles. In Figure 5b for example, the plume is angled slightly upward. The mean and temporal standard deviation of the extinction for each spray event were interpolated along the plume centreline to yield an extinction decay profile.

The width of the spray plume was measured by calculating the full-width at half-maximum (FWHM) of the extinction profile either side of the interpolated centreline position, denoted $w(x)$. From this, the cone angle of the spray may be readily determined:

$$\theta = \tan^{-1}\left( \frac{dw}{dx} \right).$$  \hspace{1cm} (2)

The spray velocity was estimated near to the nozzle during the ‘steady’ time period using an image cross-correlation technique [27] which measured the average displacement of the visible liquid structures in the spray from one frame to the next. All measurements were replicated with sample sizes.
Figure 5: Sample high speed extinction images of pMDI sprays.
Table 1: Aerosol performance summary for all nozzles. Means were compared to the conventional pMDI using unpaired two-tailed t-test. *p < 0.05, **p < 0.01.

of 50 < N < 55. Ensemble statistics were used to determine temporal ensemble average values, and the standard deviation contributions due to both temporal fluctuations and shot-to-shot variation (repeatability).

3. Results and Discussion

Deposition measurements from the Next Generation Impactor are shown in Figure 6. There are 8 stages in the NGI: stage S1 is for particle sizes > 11.7 μm, S2: 6.4 - 11.7 μm, S3: 3.99 - 6.4 μm, S4: 2.3 - 3.99 μm, S5: 1.36 - 2.3 μm, S6: 0.83 - 1.36 μm, S7: 0.54 - 0.83 μm and MOC. The inset figure shows the relatively small deposition in the first three filter stages with a reduced vertical scale.

From the NGI data, the total dose, calculated delivered dose, FPD, FPF, mass aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated. The results are expressed in Figure 6 and Table 1. The correlation coefficients in Table 1 represent the quality of fit for the log-Probit scale used to calculate GSD and MMAD. Good repeatability was obtained for all nozzles. No statistically significant changes in MMAD or GSD were observed.

The FPF significantly changed between the conventional and the twin hole nozzles (Figure 8). The changes were statistically significant, as determined by an unpaired two-tailed t-test (p < 0.05). The conventional pMDI has the highest total delivered dose, but the lowest FPF and highest amount of throat deposition. The ‘Single nozzle’ (red bar) using the design shown in Fig. 2b shows a 40% improvement in FPF. The difference between this single-orifice nozzle and the conventional pMDI is an increase in the nozzle length and internal canister stem length.

When the twin orifice nozzle is used (green bar), a 75% increase in FPF is observed relative to the conventional pMDI (p < 0.05). This increase is
consistent with the aluminium laser-drilled actuator tests of Lewis et al [21] accounting for the reduction in orifice diameter. The total dose is reduced by 15% for the twin nozzle, such that the increase in fine particle dose reported in Table 1 is not statistically significant. Throat deposition is also significantly reduced such that the deposition on the stages representing the lower lung (S4, S5, S6 and S7) are significantly increased.

Adding the internal recess feature (blue bars) to both the single and twin-hole designs had the effect of reducing FPF and FPD proportionately. The internal recess significantly reduces the length of the nozzle. This result suggests that larger length to diameter ratios are advantageous, in agreement with Symth et al. [18].

In order to understand the cause of the large changes in FPF, high speed imaging measurements were performed. The time-average, ensemble-average extinction profiles during the steady period of the spray for all the nozzle configurations are shown in Figure 8. They are listed in order of increasing FPF matching Table 1 and Figure 7. The spray width of the new nozzle configurations is clearly less than the conventional pMDI and the centreline extinction values decrease more rapidly, but there are no clear trends evident.
A key feature of note in Figures 8c & 8e is that the twin hole nozzle produces only a single jet. The flow from both orifices merges rapidly upon exiting the nozzle. The merging region is not visible as it occurs inside the ‘bowl’ feature on the front face of the nozzle (see Fig. 2c). The behaviour of flash-evaporating multi-hole nozzles has been extensively investigated in the field of automotive engineering [28]. Above a threshold degree of superheat and at sufficiently low ambient pressures, closely-spaced jet plumes have been observed to rapidly merge in a phenomenon known as ‘spray collapse’ [29]. It is hypothesised that expansion of vapour in the core of each jet causes a rapid initial expansion which causes the plumes to overlap and mix. Once merging occurs, the expansion slows and a single dilute spray is formed. The same phenomena may be occurring here, as the HFA propellant is sufficiently superheated at room conditions for the effect to occur. It can be problematic for internal combustion engines, but may be advantageous for the operation of pMDIs as it produces a single spray with a higher FPF but otherwise similar macroscopic properties.

From the extinction data, the spray FWHM was calculated; this is shown in Figure 9a. The solid lines represent the ensemble-average, temporally averaged spray width with distance from the nozzle on the horizontal axis. The shaded regions around each solid line represent the temporal standard deviation; the variation in width due to unsteadiness in the spray. The hatched
region around the outside of the shaded region represents the ensemble standard deviation; the increase in sample standard deviation due to shot-to-shot variations between sprays. The uncertainty is primarily dictated by temporal variations. Shot-to-shot variation between sprays was relatively small.

We observe from Figure 9a that the sprays with higher FPF (green and red lines) have correspondingly narrower FWHM. From these data, the average spray cone angle and plume width at the mouthpiece were calculated. These are given, along with their correlation to the FPF data in Table 2. The relatively low correlation coefficients between plume angle, origin, width and FPF suggest that these parameters, while indicative of device performance, are not strongly linked to the determination of FPF.

In subsequent analysis, the spray plume average velocity was also esti-
Figure 9: Ensemble temporal average spray width and velocity decay with distance from the nozzle orifice. The shaded regions represent the standard deviations from temporal variations (solid area) and shot-to-shot variability (hatched area).
If we assume that within the imaging region the propellant evaporation process is completed and the plume density is approximately constant, then the average velocity will decay with increasing distance from the nozzle proportionately to the cross-sectional area of the plume. If we assume that the spray is axisymmetric, then the plume width can be used as a proxy for spray diameter and the cross-sectional area estimated. If the initial velocity \( U_0 \) is known at the location where the plume width is \( w_0 \), then the average streamwise velocity of the plume can be estimated:

\[
U_x(x) \approx U_0 \frac{w_0^2}{w(x)^2}
\]  

In our analysis, we estimate \( U_0 \) from cross-correlation of the liquid structures in the plume. The resulting estimates of streamwise velocity are shown in Figure 9b. We note that the nozzles with less deceleration (higher plume velocity at a given distance) correspond to higher FPF. However, there is no clear correlation between the nozzle exit velocity \( U_0 \) (Table 2) and FPF.

We subsequently measured the distance \( x_{1/2} \) at which the velocity decays to a value of \( 0.5U_0 \). Following equation 3, this measurement is independent of any error in estimating \( U_0 \) and only depends on the plume width \( w(x) \). Remarkably, the half-velocity decay distance \( x_{1/2} \) correlates to FPF with \( R^2 = 0.997 \) despite the broad assumptions regarding spray symmetry and density outlined above. The correlation between \( x_{1/2} \) and FPD is also significant, with \( R^2 = 0.95 \). The relationship is plotted in Figure 10 with the error bars indicating the sample standard deviation and the dashed line indicating a least squares line of best fit. Corresponding values are shown in Table 2.

<table>
<thead>
<tr>
<th>Spray cone angle (degrees)</th>
<th>Conventional pMDI</th>
<th>Single nozzle + internal recess</th>
<th>Twin nozzle + internal recess</th>
<th>Single nozzle</th>
<th>Twin nozzle</th>
<th>Correlation with NGI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone angle virtual origin [mm]</td>
<td>-14.54 ± 0.04</td>
<td>-4.82 ± 0.04</td>
<td>-17.38 ± 0.04</td>
<td>-7.35 ± 0.04</td>
<td>-5.73 ± 0.04</td>
<td>( R^2 = 0.63 ) (FPF)</td>
</tr>
<tr>
<td>Plume width at mouthpiece [mm]</td>
<td>6.35 ± 0.04</td>
<td>5.00 ± 0.04</td>
<td>5.93 ± 0.04</td>
<td>3.88 ± 0.04</td>
<td>3.80 ± 0.04</td>
<td>( R^2 = 0.78 ) (FPF)</td>
</tr>
<tr>
<td>Nozzle exit velocity [m/s]</td>
<td>77 ± 6</td>
<td>69 ± 7</td>
<td>72 ± 5</td>
<td>84 ± 6</td>
<td>82 ± 4</td>
<td>( R^2 = 0.59 ) (FPF)</td>
</tr>
<tr>
<td>Distance to 50% velocity decay [mm]</td>
<td>1.51 ± 0.04</td>
<td>3.14 ± 0.04</td>
<td>5.02 ± 0.04</td>
<td>5.75 ± 0.04</td>
<td>9.13 ± 0.04</td>
<td>( R^2 = 0.997 ) (FPF)</td>
</tr>
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Table 2: High speed imaging analysis summary for all nozzles.
The unusually high degree of correlation between two independent measurements suggests that higher spray velocities in the region $10 < x < 40$ mm from the nozzle may be directly responsible for entraining a larger fine particle dose into the plume. Fine particles at the edge of the plume will follow the diverging streamlines of the rapidly expanding propellant vapour and some will impact the walls of the mouthpiece. If the spray velocity is increased, then shear between the ambient air and the plume will also increase. Fine particles at the periphery of the plume are therefore more likely to be entrained back into the plume and transported through the mouthpiece rather than settling out. This hypothesis requires further investigation.

4. Conclusions

In this paper we have investigated the performance of novel pMDI orifice shapes manufactured in polycarbonate plastic parts with a standard solution formulation of 15% w/w ethanol co-solvent and HFA-134a propellant. A standard canister was used and all results were compared to a conventional Bespak actuator as the control.

We have shown that switching from a single 0.33 mm diameter orifice to
two 0.22 mm diameter orifices can increase FPF by up to 75%. This increase is consistent with those from metal actuators [21]. The lack of a statistically significant change in FPD is likely driven by reduced total dose, which is a consequence of the reduction in nozzle diameter. The addition of an internal feature which reduces the length of the nozzle reduces the FPF correspondingly, indicating that larger length-to-diameter ratios are beneficial for pMDI nozzles. The test facility also has the capacity to test the effect of changing the expansion chamber volume so as to optimise it along with the nozzle orifice; this will be investigated in future work.

Analysis of high speed images of the plume in the mouthpiece region reveal that both FPF and FPD are strongly correlated with the distance at which the plume velocity decreases to approximately half its initial value. This is measured by determining the distance at which the square of the FWHM of the plume is 50% of that at the nozzle. This suggests that not only do smaller orifices produce higher FPF, but that entrainment of fine particles at the periphery of the plume play a critical role in deposition. It is important to note that while plume velocities can vary significantly within the mouthpiece across the designs considered, the power-law decay of the peak velocity with increasing distance from the nozzle will result in little difference in flow velocity once the particles leave the mouthpiece.

Although the benefits of multiple nozzles have been investigated in the past, these measurements are the first to demonstrate the efficacy of this approach in plastic components suitable for mass manufacture. The required reduction in orifice diameter is also less extreme than those reported in previous studies [21], which will likely correspond to less risk of clogging. No discernible differences in plume evolution or ensemble variance were observed in our measurements when the experiments were repeated with and without the API. This suggests that for the IPBr solution formulation used in this study, clogging of the smaller orifices did not occur. However, further research into the risk of clogging in novel actuator designs for a wider range of formulations will be required beyond this preliminary study.

Correlation between spray deceleration and FPF has not been previously reported. While it is generally appreciated that internal fluid mechanics are important to the operation of the pMDI, our results reveal that the fluid mechanics of the plume evolution within the first few centimetres from the nozzle play an outsize role in determining the fine particle fraction. These effects are somewhat independent of other macroscopic properties such as plume cone angle, width, or initial velocity. This insight may prove useful in
aiding the rapid development and testing of novel pMDI actuators for new propellants and formulations.

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Nomenclature

- $C_{\text{ext}}$: Extinction coefficient
- $D$: Nozzle orifice diameter
- $f$: Frequency
- FPD: Fine particle dose
- FPF: Fine particle fraction
- FWHM: Full width at half maximum
- GSD: Geometric standard deviation
- HFA: Hydrofluoroalkane
- $I$, $I_0$: Intensity of spray image and background image (grey scale value)
- IpBr: Ipratropium Bromide
- MMAD: Mass median aerodynamic diameter
- NGI: Next Generation Impactor
- pMDI: Pressurised metered dose inhaler
- $t$: Time after actuation
- $U$: Spray velocity
- $U_0$: Nozzle velocity
- $w$: Spray width
- $x$: Distance from nozzle
- $x_{1/2}$: Distance from nozzle where velocity is half the initial value
- $y$: Transverse distance from nozzle centerline
- $\theta$: Spray cone angle
References


