PREDICTION OF THE AEROSOL PERFORMANCE OF ACTIVE AND SUSPENSION FORMULATION PMDIS USING A 1-DIMENSIONAL THERMOFLUID-MECHANIC MODEL

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INTRODUCTION

- The simulation of pressurised metered dose inhaler (pMDI) device performance could accelerate the development time for new products, which is pertinent for the introduction of new, low-global warming potential (GWP) propellants[1] and novel formulation developments[2]
- Predicting the aerosol performance of devices and linking this to impactor stage performance could assist with facilitating a reduction in development time.

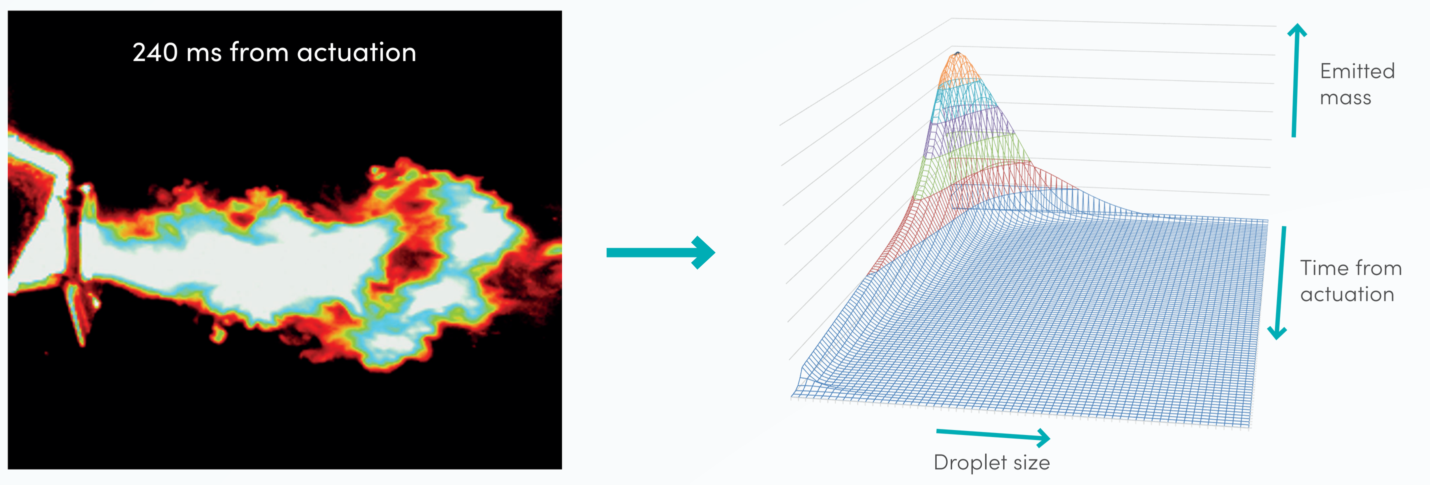
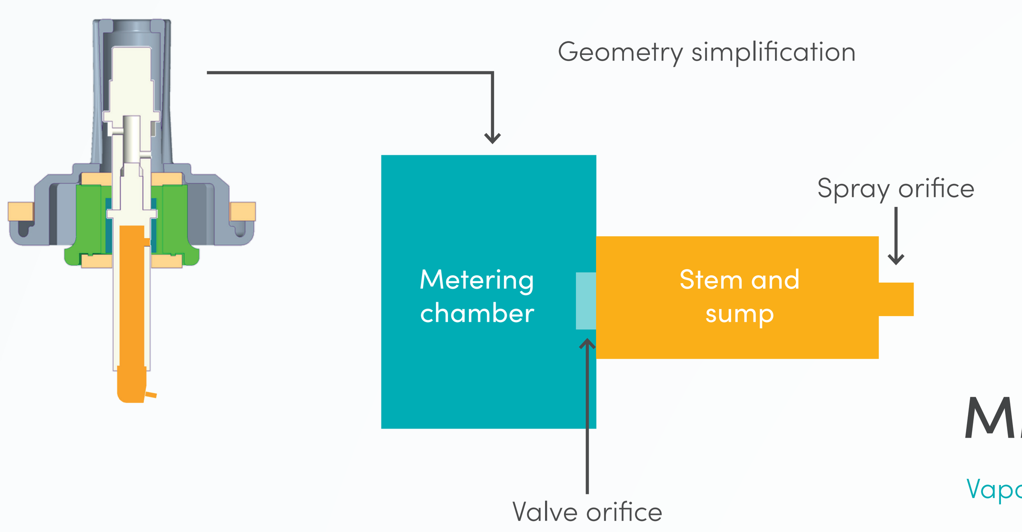


Figure: 1 R134a spray plume in still air and predicted droplet size distribution from our simulation.

AIMS AND OBJECTIVES

- Validate our thermofluid-mechanic model against experimental, laser-diffraction aerosol droplet size data
- Investigate whether measured droplet sizes link to next generation impactor (NGI) residual particle sizes
- Explore the link between droplet size and drug delivery efficacy to the lungs.

MODEL DESCRIPTION



Sump pressure

$$\text{MMD} = \frac{1.82}{q_{ec}^{0.56}\left(\frac{P_{ec}-P_{atm}}{P_{atm}}\right)^{0.46}}$$

Vapour quality

Figure 2: Flowchart of the modelling process.

- An iterative, time-stepped, 1-dimensional simulation in Matlab performs a mass and enthalpy balance across the two orifices, throughout discharge, to simulate the pressure and vapour fraction at the spray orifice
- These are used as inputs into Clark's equation[3] to calculate the mass median droplet diameter (MMD) at each time step of 0.1 ms
- A Rosin-Rammler curve fit was then used to estimate the droplet size distribution at each step, fitted around the MMD
- Model enhanced from those presented by Clark[3] and Harang[4].

EXPERIMENTAL DESIGN

- All packs contained 0.07 % w/w fluticasone propionate (FP) as the active substance. Solution formulations also contained ethanol at 15 % w/w. Two actuator orifice diameters were used; 0.22 mm and 0.58 mm
- Droplet size measurements were taken 60 mm downstream of the actuator mouthpiece, in still air, using a Sympatec Helos laser diffraction system. Three replicates were taken at each condition. Residual particle sizes were measured using an NGI at 30 l/min airflow, with subsequent analysis using a validated HPLC method[5]. Five replicates were taken at each condition.

RESULTS

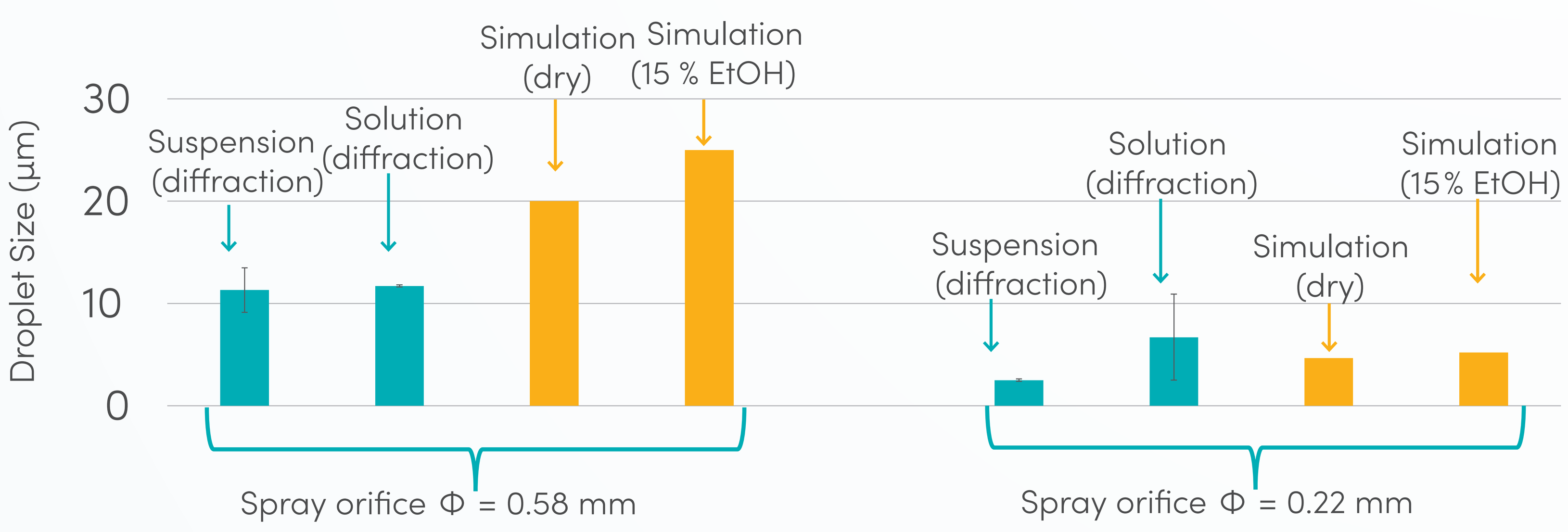


Figure 3: Laser diffraction and simulation mass median diameters for two actuator spray orifice diameters; solution and suspension.

RESULTS

- Figure 3 shows that the simulation data are in excellent agreement with the solution formulation experimental droplet size and in good agreement for the ethanol-free formulation for the smaller actuator orifice
- A lower level of agreement is observed for the larger orifice diameter case, particularly in conjunction with ethanol. Differences in fluid flow properties and the discharge coefficient applied to the orifice may be responsible for this.

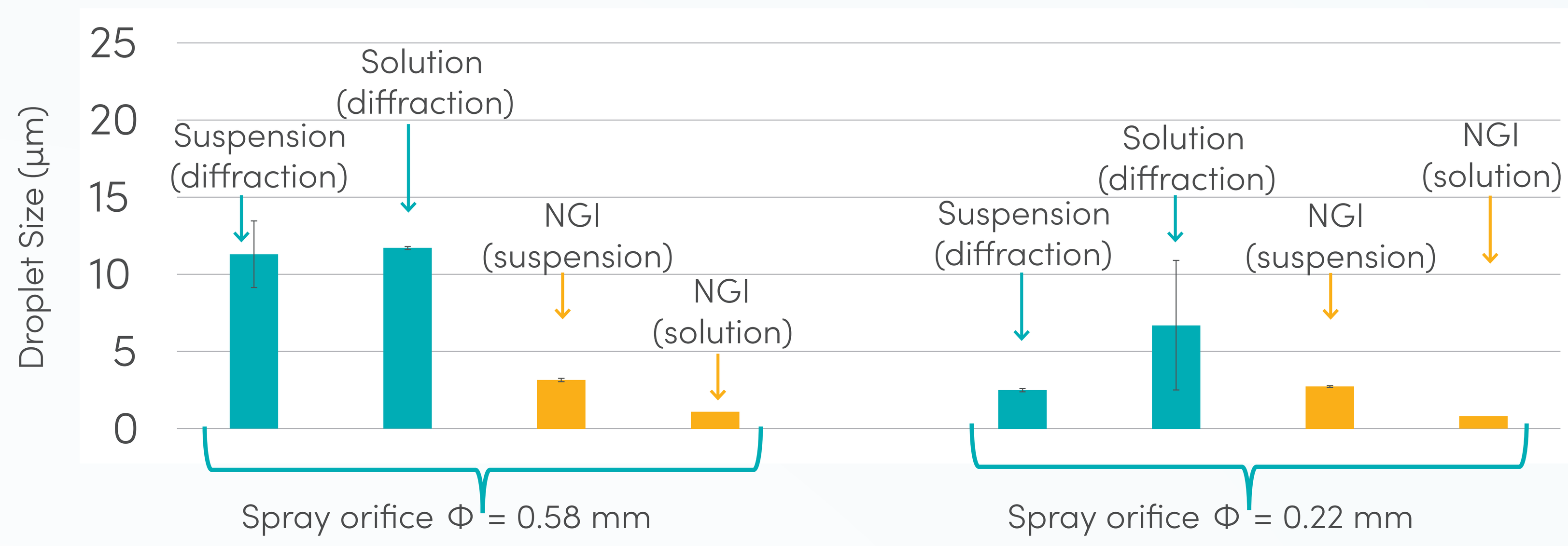


Figure 4: Laser diffraction-derived volume mean diameters and NGI particle mass median aerodynamic diameters for the two actuator spray orifice diameter casesa.

- The larger spray orifice clearly leads to larger droplet sizes. The residual particle sizes for both the suspension and solution are relatively unaffected
- The initial, micronised API particle size in the suspension formulation acted as a size limit for the residual particle size; the solution residual particle sizes were not constrained in this way, potentially leading to the smaller particle size observed for the solution formulation
- In this case, droplet size is not a good proxy for overall residual particle size; more information may be gleaned from a full impactor stage split analysis.

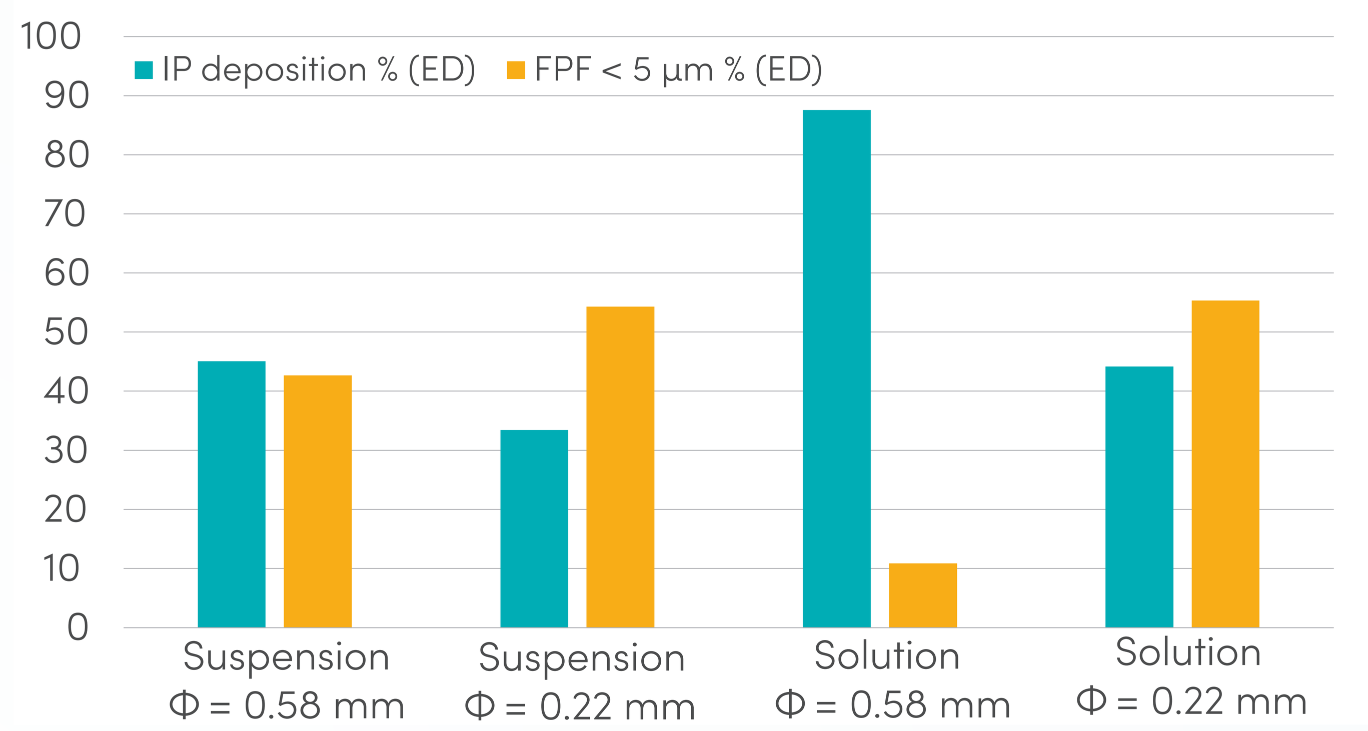


Figure 5: NGI induction port (IP)/throat deposition and fine particle fraction (FPF) < 5 µm of the emitted dose (ED) for the device configurations in Table 1.

- Spray orifice diameter appears to be a significant influencer of both induction port deposition and fine particle fraction, for both suspension and solution formulations
- The large spray orifice coupled with ethanol gives the highest throat deposition and lowest FPF, due to the large droplets created and the impaction of these in the NGI "throat".

CONCLUSIONS

- Our simulation reflected the change in aerosol droplet size brought about by the actuator spray orifice diameter, with the discrepancy between the experimental and simulation data increasing with actuator spray orifice diameter. This is to be investigated in future work
- Droplet size was not found to be a good indicator of residual particle size; a full impactor stage split analysis may reveal more correlation
- Larger actuator spray orifice diameters are linked with larger droplet sizes are lower fine particle mass/higher throat deposition as measured with the NGI.

ACKNOWLEDGEMENTS

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