DEVICE AND FORMULATION PARAMETERS INFLUENCING PRESSURISED METERED DOSE INHALER (pMDI) AEROSOLS USING HFO1234ZE PROPELLANT

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INTRODUCTION

Meeting next generation impactor (NGI) stage plate performance requirements for inhalers using low global warming potential (GWP) propellants is an important area of interest for pressurised metered dose inhalers (pMDIs)[1]. Accurately simulating this using computational tools as illustrated in Figure 1 could reduce development time for new and generic pMDI products.

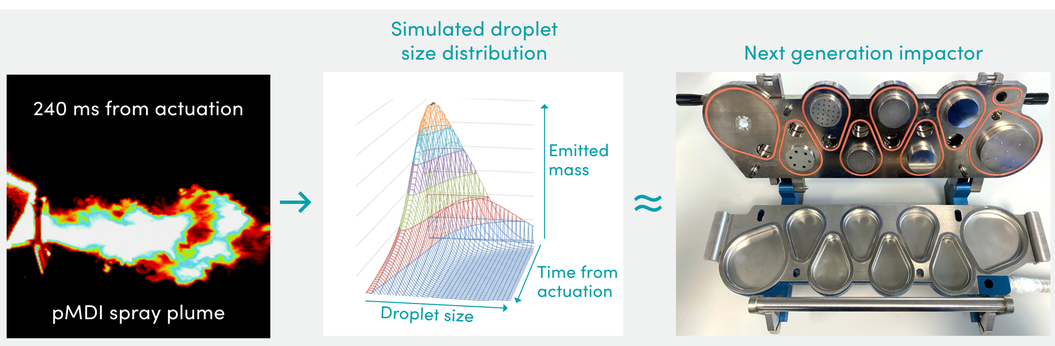

Figure 1. Schematic indicating how our model could be used to predict the droplet from a pMDI spray plume.

AIMS AND OBJECTIVES

Compare simulated aerosol droplet sizes for two devices containing fluticasone propionate (FP) in HFO1234ze propellant, with laser diffraction and NGI data to ascertain if the simulation data provide a good indication of NGI performance for a low-GWP propellant.

MODEL DESCRIPTION

The pMDI device is simplified into two volumes as shown in Figure 2 – the metering chamber and the "expansion" chamber, separated by the valve stem orifice. The propellant thermodynamic properties were calculated at each 0.1 ms time step.

From the expansion chamber pressure and vapour fraction, Clark's equation[2] was used to calculate the mass median droplet diameter (MMD). The droplet size distribution was estimated by fitting a Rosin-Rammler distribution to the MMD.

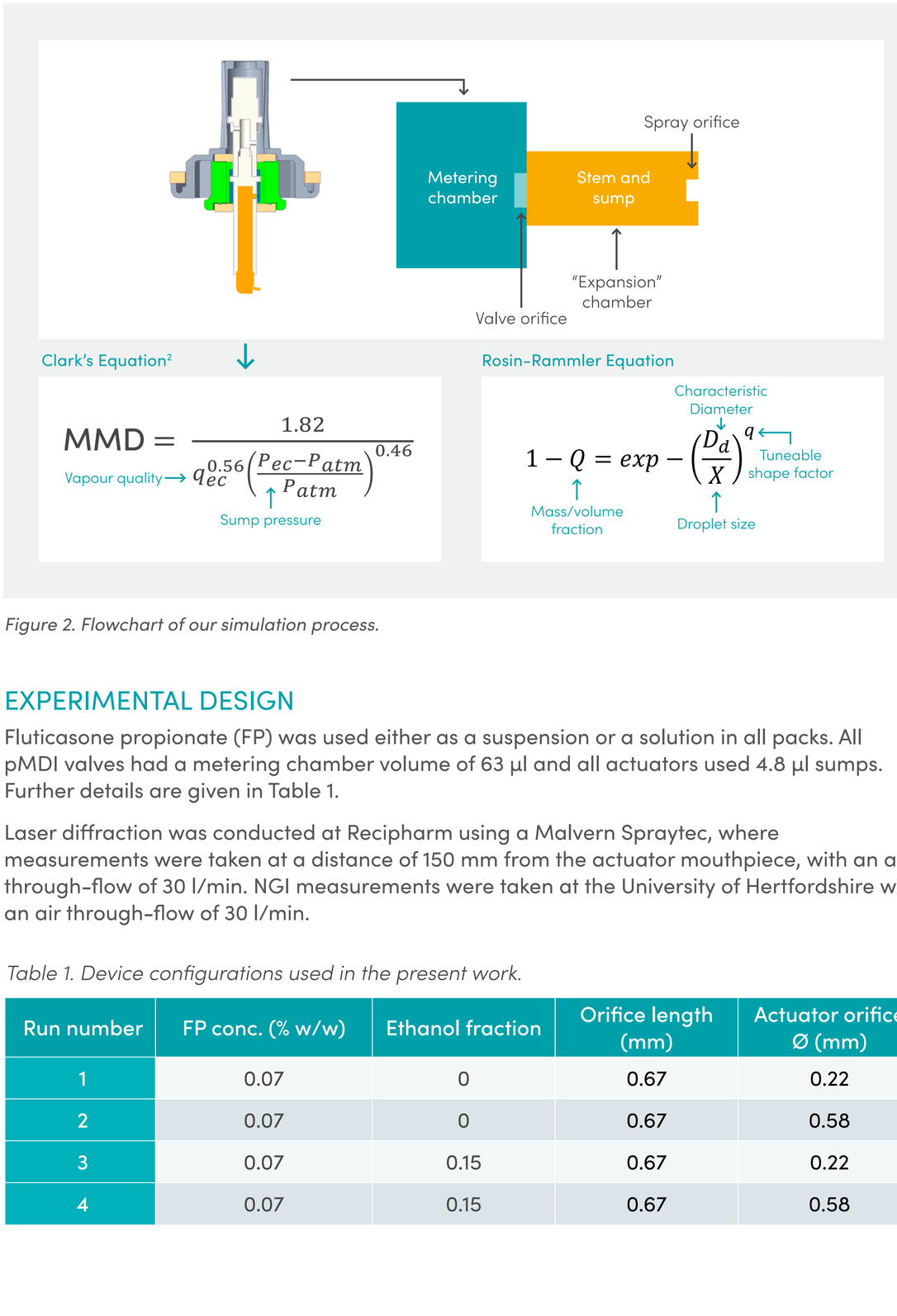

Figure 2. Flowchart of our simulation process.

EXPERIMENTAL DESIGN

Fluticasone propionate (FP) was used either as a suspension or a solution in all packs. All pMDI valves had a metering chamber volume of 63 µl and all actuators used 4.8 µl sumps. Further details are given in Table 1.

Laser diffraction was conducted at Recipharm using a Malvern Spraytec, where measurements were taken at a distance of 150 mm from the actuator mouthpiece, with an air through-flow of 30 l/min. NGI measurements were taken at the University of Hertfordshire with an air through-flow of 30 l/min.

Table 1. Device configurations used in the present work.

Run number	FP conc. (% w/w)	Ethanol fraction	Orifice length (mm)	Actuator orifice Ø (mm)
1	0.07	0	0.67	0.22
2	0.07	0	0.67	0.58
3	0.07	0.15	0.67	0.22
4	0.07	0.15	0.67	0.58

RESULTS

The simulation estimates the ex-actuator droplet size distribution before significant droplet evaporation has occurred as shown in the left hand graph in Figure 3.

Spray orifice diameter had the largest effect on predicted droplet size, with ethanol fraction having a smaller influence. The presence of ethanol had the largest impact on laser diffraction measured droplet size shown in the right-hand graph of Figure 3.

For suspensions and solutions, smaller spray orifices resulted in smaller droplet sizes at 150 mm. However, this effect was most pronounced for solution formulations suggesting that suspensions had evaporated to final particle size by the measurement window at 150 mm.

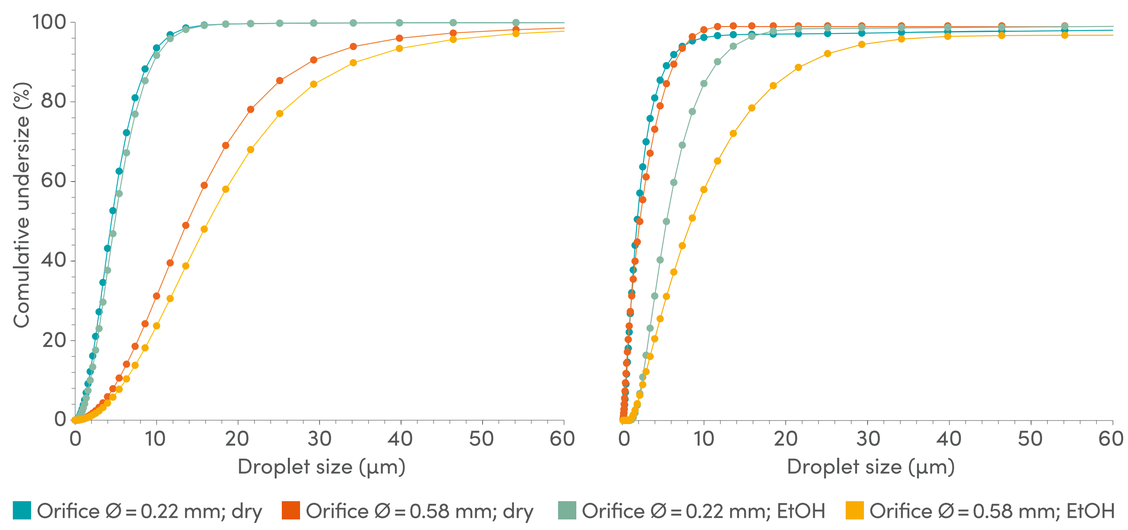

Figure 3. Simulated (left) and laser-diffraction measured (right) cumulative undersize pMDI droplet sizes.

Figure 4 illustrates that USP Throat deposition was highest for the 0.58 mm spray orifice (56 ± 3% and 86 ± 1% for suspension and solution formulations, respectively) resulting in lower stage deposition and fine particle mass than the 0.22 mm spray orifice (throat deposition of 41 ± 3% and 49 ± 2% for suspension and solution respectively).

Although of lower fine particle mass, the aerodynamic diameter (MMAD) of solution formulations was lower for the 0.58 mm compared to the 0.22 mm spray orifice product; the cumulative undersize plot supports this. There was no statistically significant impact of orifice diameter on the MMAD of suspension products (2.81 vs 2.85 µm)

The mechanism responsible for higher MMAD with the 0.22 mm orifice requires investigation, but may be caused by capture of small droplets in the throat moving at higher velocity than those from the 0.58 mm orifice.

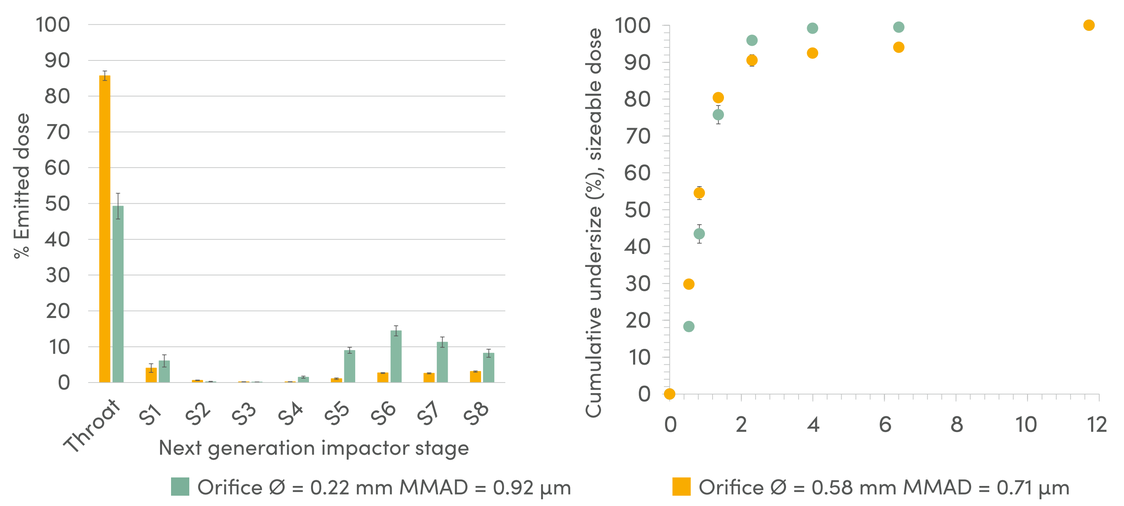

Figure 4. NGI data obtained for solution formulations using two spray orifice diameters.

CONCLUSIONS

Larger spray orifices yield larger droplets, where the presence of ethanol further increases the evaporation time and impaction in the NGI throat.

However, the larger spray orifice yielded smaller residual particles within the NGI for solution formulations as observed by the sizeable dose, but not for suspension formulations, the cause of which is to be explored further.

ACKNOWLEDGEMENTS

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1. Pritchard, J. N. (2020): "The Climate is Changing for Metered-Dose Inhalers and Action is Needed" Drug design, development and therapy, 14, 3043–3055.

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