Acoustic methodology for measuring discharge rate, and predicting spray velocity effects on potential lung deposition

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Introduction

Understanding in-vitro performance of inhaler products is still a key factor in understanding or predicting in-vivo performance [1]. Rapid assessment techniques could therefore be useful for increasing the efficiency of early phase product development. Several potential techniques or diagnostic-type tests are available, such as laser techniques, accelerometers, electrostatic probes, firing force measurements [2-6].

This publication will focus on one specific area – Acoustic measurement. Actuation duration can be inferred from the sound duration ascertained via acoustic measurements [7]. For comparison of simple pMDI systems this can yield information on spray velocity, a critical characteristic in terms of lung deposition [8]. Data for spray velocity are also presented.

The spray duration trends are compared to those when using numerical modelling of propellant flow inside the pMDI metering valve [9]. The potential effect of different spray durations on lung deposition is then demonstrated via in-vitro APSD data, specifically the emitted dose post-throat (%).

Method

Acoustics

All tests were performed with a bespoke test set-up, using a microphone with USB Soundcard (ex-Maplin) linked to a PC. The microphone is positioned externally to the pMDI, adjacent to the front underside of the mouthpiece opening. Following appropriate priming of the placebo pMDIs, they were shaken and then fired into free air inside an insulated 'Sound booth' (Figure 1 - LHS image) which is situated in a separate larger booth for further noise insulation.

Sound measurements of the emitted spray were performed to determine the actuation duration, defined as when the acoustic signal (amplitude) is at least three times the noise. Noise was defined as the maximum peak-to-peak amplitude signal from 3 seconds of background measurement. Audacity® Software v2.1.1. was used.

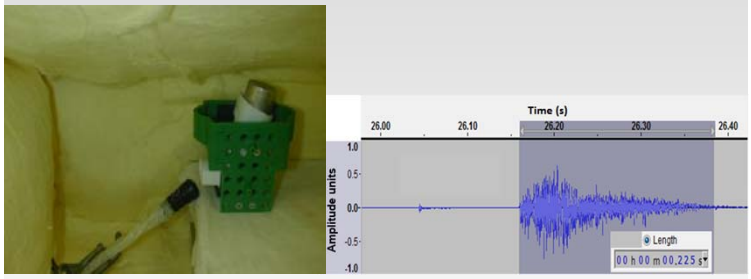

Figure 1. Acoustic measurement set-up (LHS) and amplitude data (RHS)

Internal flow model

The internal flow model is developed based on Fletcher's [10] and Clark's [11] phenomenological analysis of the flashing propellant flow inside pMDI twin-orifice systems. This model is comprehensively discussed and validated in the work of Gavtash et al [12]. The two-phase propellant mass flow through the valve and spray orifices is evaluated with the homogeneous frozen model (HFM), which assumes that no evaporation takes place along the flow path inside the orifices. Ethanol is not included in the model.

All modelling parameters were maintained as constant, except those varied in the experiments (actuator exit orifice size, propellant). Appropriate estimates of metering volume, expansion chamber volume and spray orifice were employed. Appropriate values for temperature, discharge co-efficient and liquid and vapour phase thermodynamic properties were also chosen [12, 13]. The values generated by the model are employed for trending purposes only, and are not used to claim accuracy of the acoustic measurements.

Emitted dose post-throat via Aerodynamic Particle Size Distribution (APSD) testing

Measurements were made using an NGI in accordance with USP <601> [14]. An assessment of the effect of exit orifice size was performed using a solution pMDI, with an anatomical throat (ex-Nanopharm). An assessment of the effect of propellant was performed using a suspension pMDI, with the standard USP throat.

Following appropriate priming of the active pMDIs, they were shaken and then fired into the chosen apparatus. Following collection of six actuations, sample recovery and analysis were performed with a HPLC-UV method. This method had been validated in accordance with ICH guidelines [15], for specificity, linearity and sample stability.

Spray velocity

Measurements were performed by Particle Image Velocimetry (PIV) using the Oxford Lasers EnVision Pharma system [16]. Following appropriate priming of the active solution pMDIs, they were shaken and then fired into free air. The aerosol plume particles scatter light from a pulsed monochromatic laser light sheet into a camera. The pulses of laser light "freeze" the motion of the plume particles and allow the velocity of the particles to be calculated from the distance the particles travel between successive pulses.

The average velocity of the different particles at multiple points throughout the actuation was calculated, plus a single overall average of all these time points to give a single average spray velocity per actuation.

Experiment	Formulation(s)	Actuator exit orifice diameter(s) - mm	Valve – metering chamber size
Effect of actuator exit orifice size	15% Ethanol in HFA 134a	1. 0.25 2. 0.40	A - 50 µl
Effect of propellant	1. 100% HFA 134a 2. 100% HFA 227	0.40	B - 63 µl

Table 1. Experimental summary

Acknowledgements

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Results and Discussion

Effect of actuator exit orifice size

Data from the acoustic and APSD methodologies show the anticipated effect of increased restriction from a reduced exit orifice diameter – A slower/longer spray, resulting in reduced throat deposition (See Figure 2 and Table 2). Comparison of the acoustic measurements to the flow model data show a comparable trend.

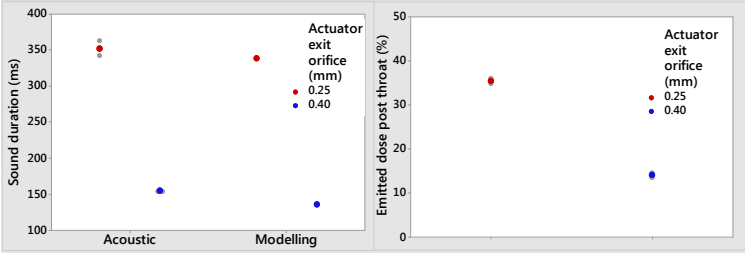

Figure 2. Measured (n=3) / modelled sound duration (LHS) and emitted dose post-throat (RHS, n=2) vs. actuator exit orifice diameter

Actuator exit orifice - mm	Average velocity - m/s
0.25	7.5
0.40	10.4

Table 2. Average spray velocity (n=1) vs. actuator exit orifice diameter

Effect of propellant

Data from the acoustic and APSD methodologies show the effect of the different propellants (See Figure 3). Again, this is as anticipated – Shorter durations, and increased throat deposition, are expected for p134a given its increased vapour pressure [13]. Comparison of the acoustic measurements to the flow model data show a comparable trend; further work is required to demonstrate the accuracy of the measurements in comparison to the flow model.

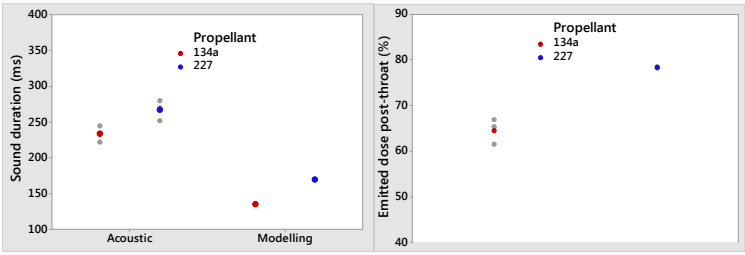

Figure 3. Measured (n=3) / modelled sound duration (LHS) and emitted dose post-throat (RHS, n=3) vs. Propellant

Conclusions

The research established acoustic measurements as a potential rapid technique for increasing the efficiency of early phase product development of pMDIs by assisting in lung deposition predictions.

The experiments showed that in order to maximise post-throat deposition, the actuator exit orifice should be minimised in order to increase actuation duration / reduce spray velocity. The data also shows that MDIs containing propellant 227 had a longer actuation duration and higher post-throat deposition than MDIs containing propellant 134a. pMDI systems with a reduced actuator exit orifice and propellant 227 may therefore yield increased lung deposition although this combination may not be suitable for all drug formulations.

Future work is required to improve the acoustic methodology to facilitate active analysis, increase measurement sensitivity and enable spectral analysis. Future work is also required to demonstrate the accuracy of the measurements in comparison to the flow model.

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