PDA and High Speed Image Analysis of HFA/Ethanol pMDI Aerosols: New Findings.

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Summary

The pressurised metered dose inhaler is one of the most popular devices for producing a respirable cloud of droplets or particles for inhaled therapy of respiratory conditions. The primary atomisation mechanism of a pMDI is relatively poorly understood. This work aims to further develop this fundamental understanding by conducting and analysing phase Doppler anemometry (PDA) and high speed imaging studies.

We report the findings of a PDA study of aerosol plumes generated by a commercial actuator of HFA134a placebo formulations containing ethanol up to 20% w/w. Data for the temporal variation of aerosol velocity and droplet size 25 mm from the spray orifice exit is presented alongside internal flow images of the expansion chamber obtained from custom made transparent models. With increasing ethanol concentration, the spray plume velocity remained broadly constant, but the number mean diameter increased. Internal flow imaging has revealed marked differences in the flow regimes within the expansion chamber between formulations. Previous studies have suggested that the aerosol velocity and droplet size are strongly linked with the formulation vapour pressure, a function of ethanol concentration. The variation of flow regime with ethanol concentration and mean droplet diameter increase observed in this study suggest that other physical properties (e.g. surface tension and/or viscosity) play more significant roles in governing the drop size than previously acknowledged.

This study demonstrates that increasing the concentration of ethanol in the formulation increases the droplet size produced. However, the ethanol concentration does not have a discernible effect on the aerosol plume velocity.

Introduction

The pressurised metered dose inhaler (pMDI) is one of the most popular devices for producing a respirable cloud of fine droplets or particles for inhaled therapy of respiratory conditions such as asthma and COPD. However, understanding of the primary atomisation mechanism of a pMDI is relatively poor[1]. One significant weakness of the pMDI is the high level of oropharyngeal deposition due to high spray plume velocities leading to turbulent mixing of the plume with the surrounding air and inertial impaction[2]. This unwanted deposition leads to low drug delivery efficiency of less than 20%[3] as measured by gamma scintigraphy[4]. Important variables that directly affect the deposition of drug within the lung and therefore the effectiveness of the device include the geometric properties of the actuator, its resultant droplet size distribution and plume velocity as well as the composition of the formulation [5 6].

This work aims to further develop the fundamental understanding of the atomisation process by conducting and analysing a phase Doppler anemometry and high speed imaging study of three placebo formulations based on HFA134a/ethanol mixtures with ethanol concentration up to 20% w/w. The range of variation of ethanol concentration causes considerable reduction of the vapour pressure of the formulation as noted by Vervaet & Byron[7] and Mason, Lewis and Gavtash[8]. This enables us to explore the relationship between formulation vapour pressure, the observed internal flow processes, and plume velocity and droplet diameter, which are known as critical parameters determining drug deposition within the lung.

Experimental methods

A bespoke, high power, high resolution PDA system at Loughborough University was employed to survey the spray plume emitted by a Bespak 630 series actuator 25 mm downstream of the spray orifice. PDA provides temporally resolved droplet velocity and diameter at a location close to the spray source before interaction with the surrounding environment enabling understanding of the atomisation process to be gained in a way that cascade impactor measurements cannot. This knowledge allows for improved design to control the primary atomisation process, subsequent aerosol plume transport and patient interaction. A robust experimental methodology was developed using results of initial studies showing that data from 30 actuation events with 1 minute delay between successive actions was required in order to obtain spray metrics to within 1% variance, spray to spray.

The design of the PDA system was detailed by Wigley, Hargrave and Heath[9]. The actuator was held within a custom-built pneumatic rig for repeatable actuation and mounted to a three-axis traverse. Actuation was fully automated using a programmable controller for number of actuation events and time delay between successive actuations. High speed images of the expansion chamber through custom made transparent models were recorded at 5000 frames per second with a Photron® FASTCAM APX RS camera with diffused LED illumination.

Results

Graphs of temporal axial velocity, number mean and Sauter mean diameters are found in Figure 1 to Figure 3. Internal flow images of the expansion chamber are found in Figure 4. The end point of the spray event was determined as the time at which 95% of the mass was measured. Table 1**Error! Reference source not found.** summarises the event averaged spray metrics as calculated over this duration.

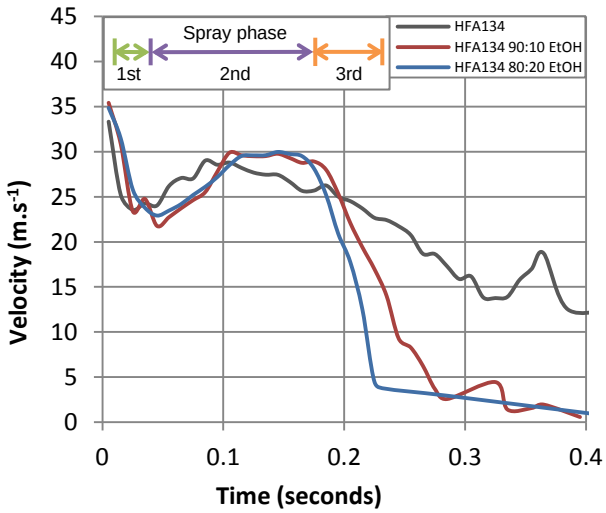

Figure 1 – Temporal variation of axial velocity of HFA134a/ethanol formulations

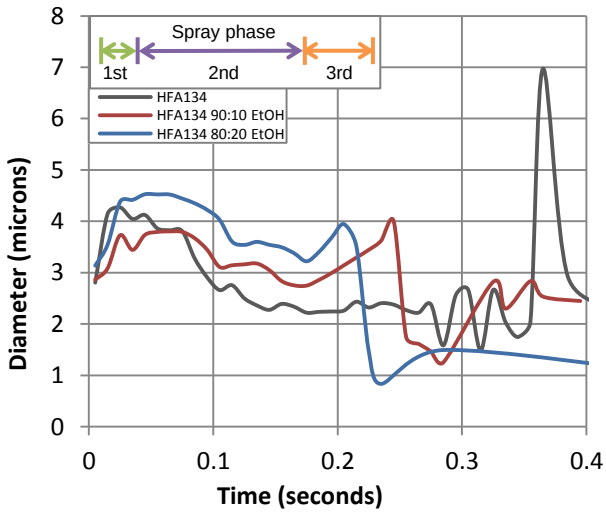

Figure 2 – Temporal variation of number mean diameter of HFA134a/ethanol formulations

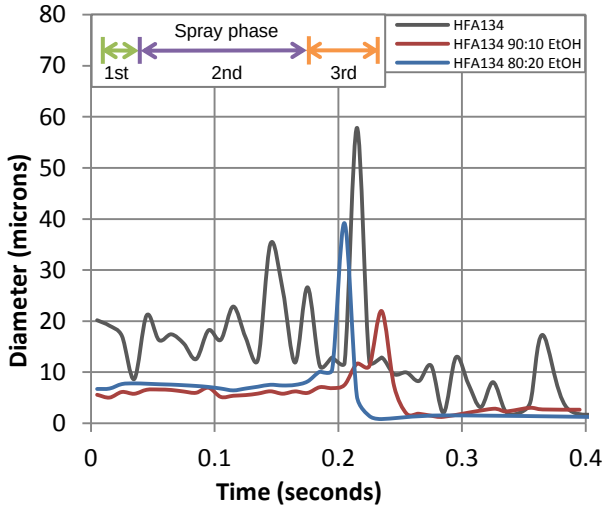

Figure 3 – Temporal variation of Sauter mean diameter of HFA134a/ethanol formulations

Table 1 - Ensemble averaged PDA spray metric data by formulation (over 95% measured mass)

	Axial velocity ($m.s^{-1}$)	Mean diameter (µm)	Sauter mean diameter (µm)	Spray plume duration (ms)
HFA134	24.8	2.80	16.92	188
HFA134 90:10 EtOH	27.5	3.26	6.06	175
HFA134 80:20 EtOH	27.3	3.88	7.62	171
Average	26.5	3.31	10.20	178

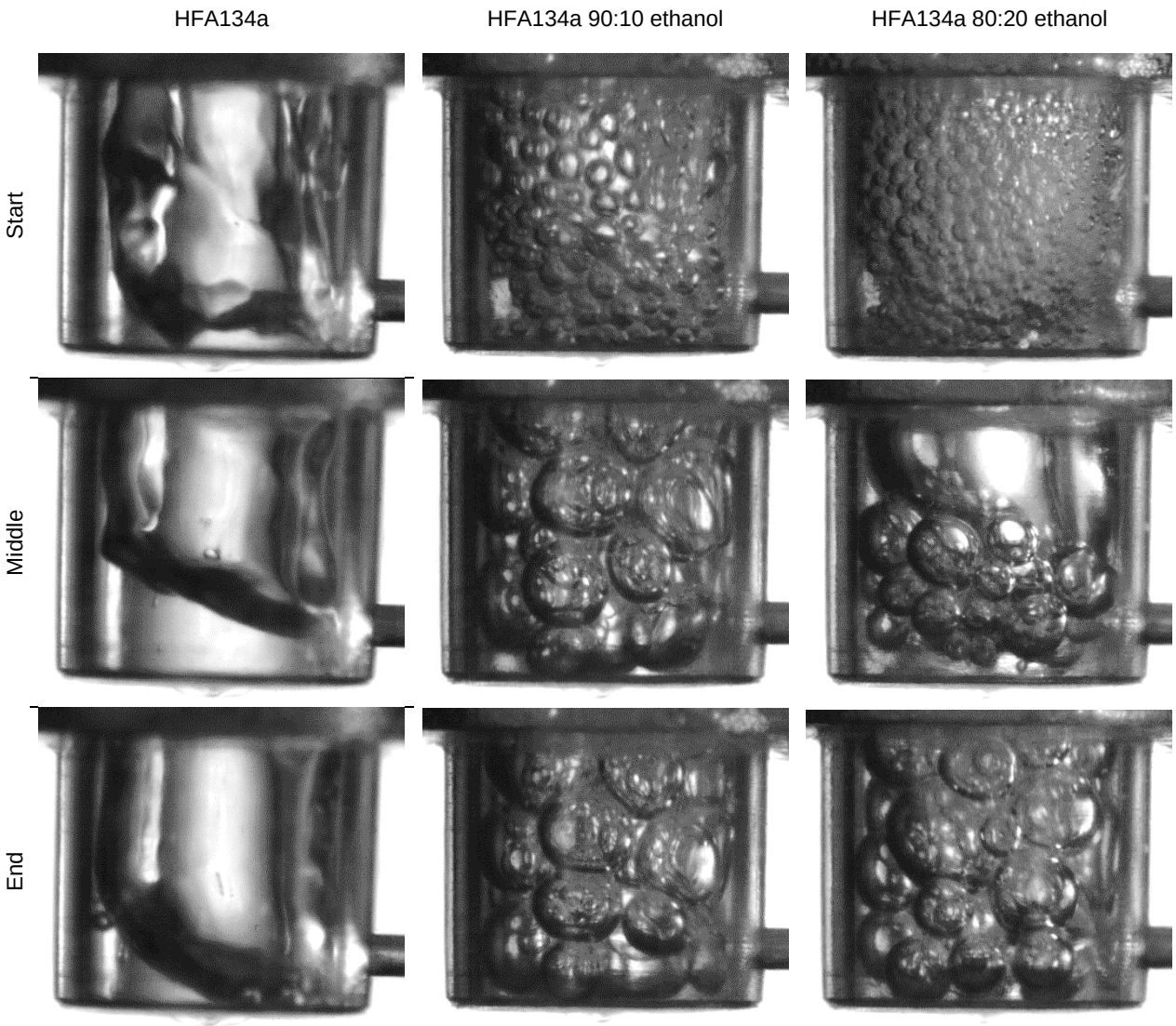

Figure 4 – Expansion chamber internal flow images. Formulations left to right; HFA134a, HFA134a 90:10 ethanol and HFA134a 80:20 ethanol. Event duration top to bottom; start middle and end of actuation event.

Discussion

The number mean droplet diameter of each formulation displays a steep increase as the actuation initiates. Following a peak the diameter trend steadily decreases until the end of the main portion of the spray event. As the actuation terminates the trend of droplet diameter varies with formulation. The plume velocity of each formulation exhibits a sharp initial reduction during the first phase of the spray event. The second spray phase commences at the first velocity minimum, with velocity generally increasing until the end of that phase. During the final phase the velocity once again decreases until the metered dose is depleted and the event concludes. The three phases of the spray event seen here show good agreement with those proposed by Versteeg and Hargrave[10] and are qualitatively indicated by the green, purple and orange arrows in Figure 1 to Figure 3. An inverse relationship of temporal plume velocity and temporal droplet diameter can clearly be seen which agrees with the observations made by Clark[11].

During the second spray phase the HFA134a and HFA134a 90:10 ethanol formulation number mean diameter trends are smaller (by up to 1.5 µm, decreasing over the phase) than the diameter trend of the HFA134a 80:20 ethanol formulation. This is also reflected in Sauter mean diameter values of HFA134a 80:20 ethanol formulation larger than those of the HFA134a 90:10 ethanol formulation by around 1 to 2 µm. These data show a direct relationship that increasing the concentration of ethanol increases the droplet diameter.

The velocity magnitude and trend remained broadly equal for all three formulations, particularly in the first and second phases, indicating that the concentration of ethanol had no significant effect on overall velocity. This observation is contrary to that of previous works in this area and suggests that other physical properties (e.g. surface tension and/or viscosity) play more significant roles in governing the drop size than previously acknowledged.

Internal flow images of the expansion chamber during each of the three phases, presented in Figure 4, show a marked difference in flow structure in the expansion chamber between formulations containing and not containing ethanol. HFA134a propellant forms a central vapour core which feeds vapour and liquid into the spray orifice (seen in the bottom right of each image). The formulations containing ethanol exhibit a bubbly flow, with initial bubble size inversely proportional to increasing ethanol content. A constant flow of vapour bubbles to the spray orifice is maintained throughout the course of the spray event. In each case the vapour core and vapour bubbles grow in size during the course of the event.

The Sauter mean diameter of pure HFA134a shows significantly larger fluctuations and larger magnitude than the formulations containing ethanol, throughout the whole event. This indicates that ethanol acts to stabilise the spray plume and smooth the droplet diameter trend. The presence of ethanol also seems to bring a more immediate end to the spray event with a sharper decrease in velocity and reduction in droplet diameter during the final spray phase when compared to the HFA134a formulation which is generally more erratic.

Large Sauter mean diameter values indicate the presence of a small number of large droplets in the spray plume which have a more heavily weighted effect on this metric compared with the number mean diameter. An increased number of large droplets as seen with the HFA134a formulation will inevitably lead to an increase in the amount of oropharyngeal deposition due to inertial impaction. The larger droplets will contain a proportionally significant amount of the active pharmaceutical ingredient, by mass, of the metered dose.

Conclusion

We present for the first time temporal trends of droplet velocity and diameter of HFA134a/ethanol formulations emitted by a commercial actuator captured using PDA. These trends have been discussed alongside internal images of the flow structures within the expansion chamber. A significant difference in the internal flow structure was observed between formulations containing and not containing ethanol.

An inverse relationship between plume velocity and droplet size as proposed by Clark[11] was found to be generally applicable as a description of each formulation on a temporal basis. However, the aerosol velocity was found to be almost independent of ethanol concentration in the formulation whilst the diameter showed a strong correlation.

This work indicates that careful consideration of the effect of increasing ethanol concentration on resultant droplet size should be made when designing formulations. The initial findings suggest that the velocity and droplet size of the spray plume are governed by parameters other than just the vapour pressure of the formulation. It is suggested that other physical properties (e.g. surface tension and/or viscosity) play more significant roles in governing the drop size than previously acknowledged.

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