A Study of Factors Affecting Nucleation and Bubble Growth in Pressurised Metered Dose Inhalers

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Summary

Various hypotheses have been introduced to explain disintegration of the continuous liquid phase into individual droplets leading to spray formation in pressurised metered dose inhalers (pMDIs). In a practicable system, the liquid formulation to be discharged from the pressurised container needs to be nucleated to ensure spray generation. Nucleation can be described as the generation of a nucleus of the vapour phase within the bulk liquid. As a stable nucleus is formed, it grows significantly and then detaches from its nucleation site to move upwards in the liquid phase. In our research, the effects of various parameters on the nucleation of HFA227 was analysed with the aim of gaining a better understanding of bubble formation and the nucleation process in HFA propellants, including the surface geometrical properties, actuator orifice size and the mass flow rate through the orifice. Other important factors influencing the nucleation process that were considered comprised the viscosity and surface tension of the formulation, thermodynamic state variables including temperature, pressure and degree of superheat. The results highlighted the effect of surface imperfections on the rate of nucleation and bubble growth. A comparison of two different orifice sizes was made and a significant change in the shape and motion of the bubbles was observed. An intense nucleation was also observed at higher mass flow rate of HFA227 through the valve. It is anticipated that recognising the factors affecting nucleation and bubble growth of HFA227 may lead to potential routes of influencing the medical aerosol generation mechanism inside the pMDI and control the fine particle size distribution.

Introduction

The function of the pMDIs is highly dependent on the coordination of patient inhalation and device actuation. Correct synchronizing of the breathing and firing the inhaler leads to a better drug deposition in the lungs. However, even with good inhalation technique, only 10-20% of the emitted dose reaches the biological target with most of the dose being trapped in the mouth and oropharynx [1]. High oropharyngeal deposition, which is due to the large particle size distribution and spray high velocity, may lead to the systemic and localized side effects. To some extent, recent developments in HFA pMDIs have addressed poor lung deposition and high oropharyngeal deposition. Despite the significant importance of pMDIs in treating respiratory diseases, there is a poor understanding of the inhaler internal flow characteristics and spray formation mechanism. The present research is a study of aerosol formation in pressurised metered dose inhalers. Its major aim is to improve understanding of the thermo-fluid dynamic processes leading to droplet generation to predict the characteristics of the aerosol cloud and eventually control the fine particle size distribution.

The process of disintegration of the liquid formulation within the inhaler into the discrete droplets leading to spray formation is termed atomization. There are many hypotheses developed to explain atomization process. According to Wiener [2] disintegration of the continuous liquid phase into the individual droplets happens due to flash evaporation. Finlay [3] also suggested that there are numerous vapour bubbles and cavities trapped on the internal surface of the pMDI components. Flash evaporation or cavitation is likely to be the main mechanisms dominating atomization in pMDIs. According to Polanco et al [4] flash evaporation of pressurised liquid formulation is critically reliant on the nucleation and existence of nucleation sites. Nucleation can be described as the onset of a phase transition through which the system is temporarily brought into a thermodynamic unstable condition from its initial sub-cooled state and becomes superheated. In the superheated liquid state, a nucleus can overcome the nucleation energy barrier and is free to grow. In a pMDI, the superheated condition is achieved by an isothermal pressure drop and results in the appearance of vapour bubbles in the low-pressure regions. These vapour bubbles grow rapidly to a comparatively large size. The faster pressure drop results in higher degree of superheat for liquid formulation, and the more intense vaporisation. The nucleation process is categorised into two types: homogeneous nucleation and heterogeneous nucleation.

Superheat is crucial for the generation of vapour phase to overcome the cohesive strength of the continuous liquid phase and tear it up. Homogeneous nucleation occurs entirely within the bulk liquid without the presence of vapour nuclei and normally requires high degrees of superheat. The heterogeneous nucleation initiates from pre-existing vapour nuclei in the bulk liquid or when the superheated liquid is in contact with a gas phase or a solid phase (e.g. container walls, valve components or suspended drug particles). Relatively low degrees of superheat are sufficient for heterogeneous nucleation, so the probability of heterogeneous nucleation is much higher than that of homogeneous nucleation [5]. Newly formed vapour bubbles in a pMDI actuator grow to form small bubbles, which detach from the bulk liquid as the flashing jet is moving downstream from the spray orifice. Among the important parameters governing the liquid disintegration process are the number and size of the bubbles at the spray orifice. Bubble growth rate has been extensively researched in the past studies and it has been concluded

that the growth process is generally controlled by the liquid inertia, surface tension, and the pressure difference between the ambient and inside of the bubble [6]. This paper reports the findings of a visualisation study to investigate nucleation and bubble growth in HFA placebo formulations used in pMDI applications.

Experimental Method

The major aim of this research is the microscale analysis of the nucleation process and bubble growth taking place within a pressurised container filled with mixtures of liquefied pharmaceutical propellants. To fulfil this goal a test rig, which is shown in Figure 1, has been designed and manufactured. The experimental procedure involved imaging the bubble formation and growth within the propellant mixture along with measuring the changes in pressure and temperature of the mixture during the nucleation and bubble growth processes.

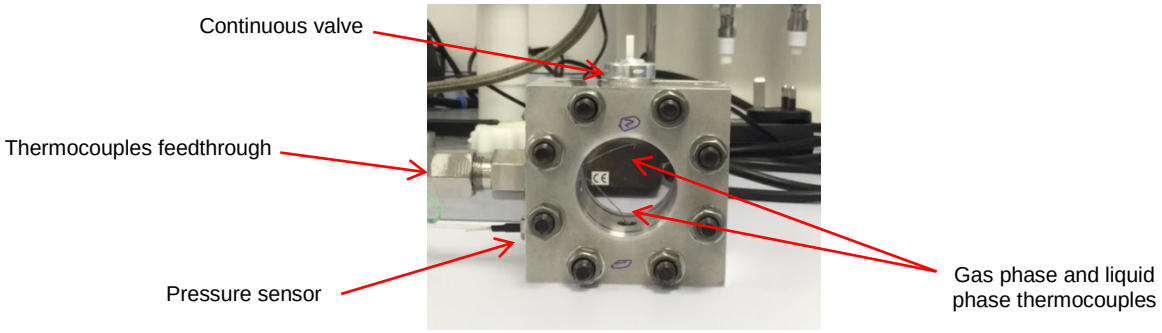

Figure 1 - Experimental setup

The test rig is made from aluminium with two large circular openings that receive two windows made from transparent PET (polyethylene terephthalate) to allow clear imaging. The test apparatus with a volume of about 44 mL is relatively large in size compared to a typical metering chamber (25 to 100 µL in volume), but this choice facilitates a fundamental study of vapour nucleation. Small openings are made in the aluminium enclosure for plugs receiving pressure sensors, thermocouples, and the continuous flow valve. The filling was performed through the continuous valve. Discharge of the pressurised formulation was accomplished by two methods: (i) through the continuous flow valve for small mass flow rates and (ii) by opening one of the plugs to achieve larger flow rates. A high speed video camera connected to a computer was used to record the nucleation and growth of vapour bubbles while propellant was discharging into the atmosphere (Figure 2). The captured videos were analysed by means of a Matlab® program and parameters, such as the bubble diameter, bubble growth rate along with the changes in the bubble shapes and dynamics, were calculated. In addition, a second computer equipped with data logging software was utilised in order to monitor the changes in the temperature and pressure during each actuation.

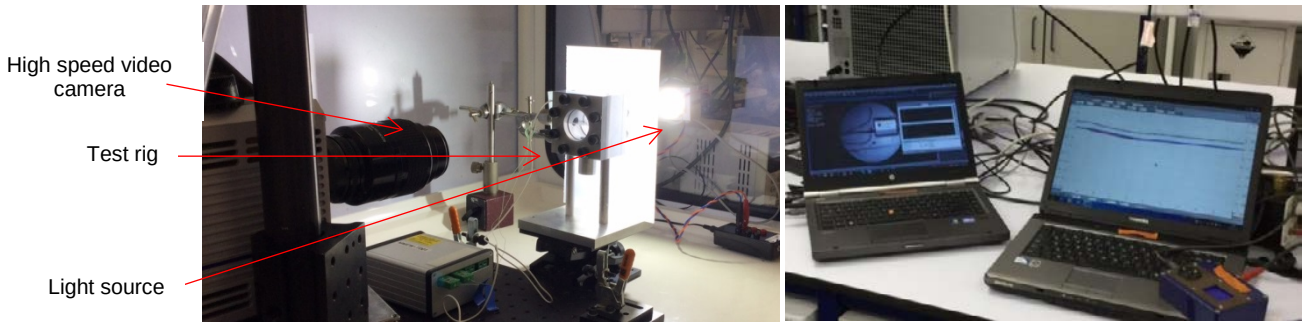

Figure 2 - Experimental layout

Results

Initial Observations

The videos captured during the initial experiments showed bubbles originating from the bottom and the sidewall where the pMDI valve and the pressure tapping were located, as shown in Figure 3. It is likely that defects and crevices on the container internal surface led to air being trapped at these surface imperfections during the filling process, and resulted in bubble nucleation originating from pre-existing gas cavities and vapour nuclei trapped at these locations. When the bulk liquid is in contact with a solid phase or a gas phase the interfacial energy is lower, which reduces the minimum energy required for the initiation of nucleation, the so-called nucleation free energy barrier [7]. Videos taken when propellant discharged through the pressure-tapping plug showed intense nucleation. This was due to the fact that a larger propellant flow rate discharged from the container, the pressure

drop between the container and ambient was much smaller[8]. This resulted in an increase in the degree of superheat; hence, the conditions were more favourable for bubble nucleation and consequently the number of nucleation sites increased, resulting in intense nucleation.

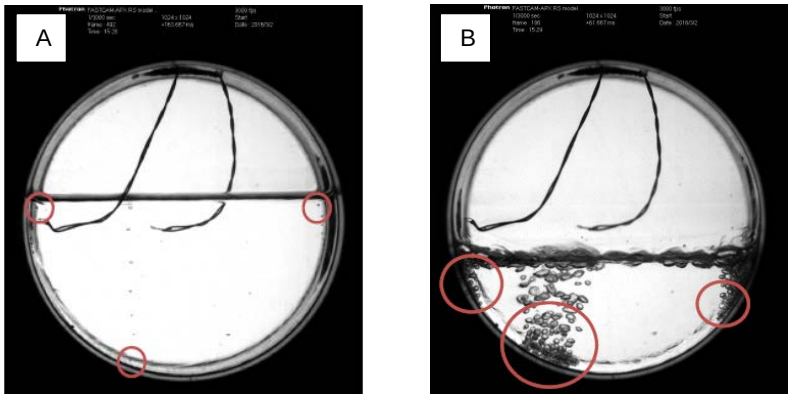

Figure 3 – (A) Initial observation of nucleation and (B) Nucleation during propellant discharge

Bubble Shape Observations

Experiments using actuators with different orifice sizes showed an interesting change in the shape and motion of the bubbles. Videos captured during experiments with smaller actuator orifice showed bubbles moving in a vertical line. In this case, as can be seen in Figure 4(A), bubbles remained relatively spherical. However, bubbles produced while the propellant was discharging through the larger actuator orifice, deviated from spherical as they were travelling in a zigzag manner in the liquid phase (Figure 4(B)).

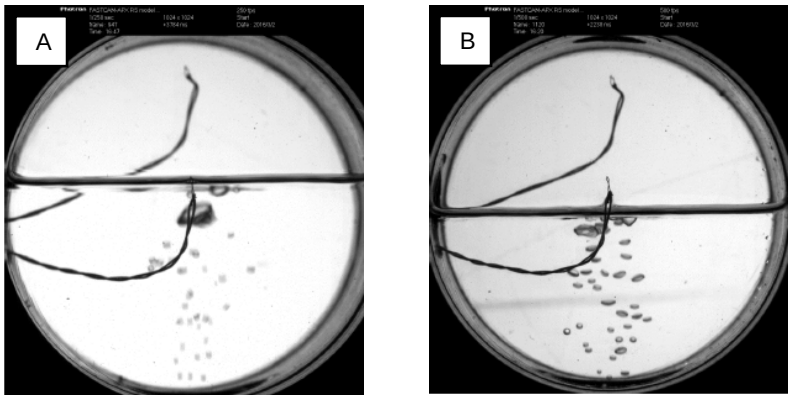

Figure 4 – (A) Nucleation using smaller actuator orifice and (B) Nucleation using larger actuator orifice

Bubble growth rate and rise velocity

The changes in the diameter of a specific bubble, the clearest bubble in the captured videos, along with the fluctuations in its rise velocity, were calculated. A sequence of images was analysed by following a bubble while it was rising in the liquid phase until it coalesced with the liquid-vapour interface and eventually entered the vapour phase. These results were plotted against time in Figure 5. They showed an increase of approximately 0.21mm for the bubble diameter while it was moving upwards in the liquid phase. As can be seen in the figure, the bubble diameter grew gradually up until 3.3 seconds and then it started to oscillate. The same trend can be seen in terms of the bubble rise velocity. It was relatively constant until 3.3 seconds, and then it quickly dropped and started to oscillate. The reason was that after 3.3 seconds the vapour bubble reached the liquid-vapour interface and before entering the vapour phase it rebounded back into the liquid phase a few times. As the vapour bubble approached the liquid-vapour interface the following forces were acting on the bubble determining its size and trajectory: (i) the downward force due to the surface tension in the thin layer of liquid between the bubble and the interface, (ii) the bubble buoyancy force, (iii) inertia of the accelerating liquid (including added mass) and (iv) the bubble internal pressure. The combination of these forces resulted in oscillations in the bubble diameter and bubble rise velocity; until the vapour bubble overcame the pressure build up made by liquid layer, and coalesced with the interface [9].

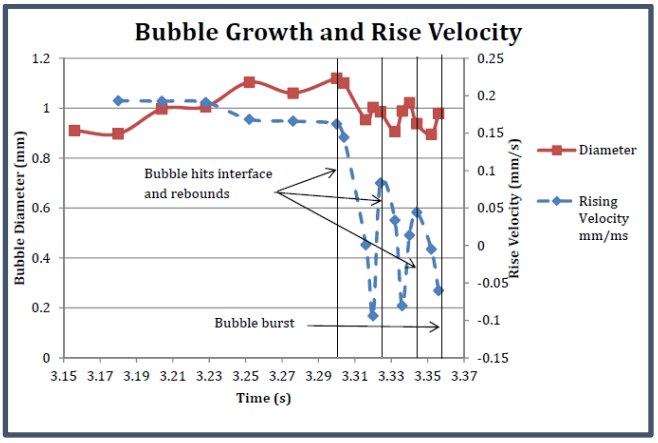

Figure 5 - Bubble growth rate and rise velocity

Discussion and Conclusions

Bubble nucleation and growth in pharmaceutical propellants is dominated by device macro- and micro-geometry (i.e., metering chamber volume, expansion chamber geometry, orifice dimensions and geometrical properties of the internal surface), physicochemical properties of the fluid (viz. nature of the liquid formulation, liquid surface tension, liquid density, gas density and liquid viscosity), and operating parameters, such as the propellant flow rate and degree of superheat at the beginning of the process. These parameters generally govern the bubble size at the discharge orifice by controlling the mode of bubble formation, bubble frequency, and also bubble detachment [10]. In this work a procedure for the study of these factors affecting nucleation and bubble growth was developed and demonstrated. The results suggested that vapour nucleated from pre-existing gas cavities due to surface imperfections. It was shown that different mass flow rates through actuators with different orifice sizes affect bubble shapes and dynamics. In particular, intense nucleation at high mass flow rates was observed. Furthermore, the changes in the diameter and displacement of bubbles while they were travelling up through the liquid were studied. Once bubbles reached the liquid-gas interface, they were found to bounce back into the liquid phase a few times before they burst through the interface. As a result, an oscillation was observed in terms of bubble growth rate and bubble rise velocity. The results showed that nucleation process and bubble growth can be affected by changes in the surface geometrical properties and mass flow rate through the valve. Increasing the number of heterogeneous nucleation sites inside the experimental setup gives rise to a significant increase in the rate of nucleation and bubble growth. Further work will also seek to investigate the role played by surface roughness in nucleation as well as the effects of scale and volume/surface area ratio. These results may ultimately lead to routes of influencing spray generation mechanism inside the pMDI with potential contributions to the design and development of next-generation inhaler devices meeting the patient's requirements more effectively.

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