Internal Flow and Near-Orifice Spray Visualisations of a Model Pharmaceutical Pressurised Metered Dose Inhaler

H.K. Versteeg*, G.K. Hargrave and M. Kirby

Wolfson School of Mechanical and Manufacturing Engineering, Loughborough University, Loughborough, LE11 3TU, UK

Email: H.K.Versteeg@lboro.ac.uk

Abstract. The pressurised Metered Dose Inhaler (pMDI) has become the most prescribed drug delivery system for treating the respiratory diseases. However, the spray generation mechanism of these devices has not been extensively researched and there is very little information regarding the two-phase fluid dynamics associated with pre-atomisation inside the valve stem. The aim of the work presented in this paper is to provide high-quality, time-resolved imaging of the internal flow structures of pMDIs in an attempt to link the characteristics of the internal flow to external spray atomization processes. Visualisations of the aerosols in the near-orifice region findings from previous studies of commercial pMDIs and showed the following characteristics: (i) start-up transient, (ii) fully developed spray with slow spray density variations and (iii) rapid spray density pulsations with large droplet production. The results clearly highlighted the potential of optical diagnostics in the development of improved accounts of the state of the flow inside a pMDI valve and its relationship with drop formation.

1. Introduction

In a pharmaceutical pressurised metered dose inhaler (pMDI) a mixture of propellant, excipients and the active component is dispensed as suspension or solution by means of a two-orifice system. The effectiveness of such a system in producing finely atomised sprays has been known since the start of the 20th century. The principle has been used in pharmaceutical applications since Riker Laboratories developed the first metered dose inhaler (MDI) in the late 1950’s. Subsequently, the pressurized Metered Dose Inhaler (MDI) has become the most prescribed drug delivery system for treating the respiratory diseases. The compactness, ease of use and low cost of these devices and reasonable effectiveness in treating lung diseases has ensured high preference amongst patients as well as clinicians. However, MDIs have some well-known limitations, the most important being their low drug delivery efficiency (just between 5 – 20%). The conventional MDIs are known to produce aerosol with excessively high velocities and a substantial fraction of large droplets, which causes high oropharyngeal deposition. Poor coordination between MDI actuation and inhalation by many patients compounds the problem. Apart from reducing the dose available for delivering to the lungs, this unintended deposition in the oropharynx often causes oral thrush and in about 5% patients, cough and bronchospasm.
In spite of its therapeutic significance the spray generation mechanism of the MDI has not been extensively researched. External spray characteristics in the far-field \((x/D_{250}) \geq 50\) were documented in three studies by (i) Fletcher (1975) using dual exposure high-speed microphotography, (ii) Clark (1991) with an aerodynamic particle sizer and (iii) Dunbar (1996) by means of Phase Doppler Anemometry (PDA). The results of this work on external sprays combined with temperature and pressure measurements by Fletcher (1975) and Clark (1991) suggest the following qualitative description of the processes inside an MDI actuator:

- At the start of an actuation event an accurately known amount of mixture is contained in the metering chamber of the MDI. As the actuator is depressed flash boiling of the propellant takes place in the metering chamber and a two-phase mixture starts to flow from the metering chamber through the valve orifice into the valve stem/expansion chamber.
- Air, which initially fills the valve stem/expansion chamber, is entrained by the incoming propellant two-phase mixture vapour or pushed out through the spray orifice. The pressure in the valve stem/expansion chamber is lower than the metering chamber, but higher than atmospheric, so two-phase mixture is expelled through the spray orifice.
- Here the final droplet aerosol is produced before it enters the ambient atmosphere. Liquid ligaments embedded in the propellant vapour are torn apart by flow forces and small droplets are formed.
- The droplets move away from the actuator orifice and entrain surrounding air. Heat supplied by this entrained air causes further evaporation of droplets.
- Discharge continues until the pressure in the metering chamber and valve stem is equal to atmospheric.

Due to the absence of suitable instrumentation much of the above picture of the two-phase fluid dynamics associated with pre-atomisation inside the valve stem and the subsequent external spray formation is, of course, only on circumstantial evidence. Fletcher (1975) and Dunbar (1996) both presented small selections of high-speed photographs, but it is difficult to obtain a clear picture of flow conditions.

Versteeg and Hargrave (2002) were the first to report a flow visualisation study of the transient flow and primary atomisation process of a pharmaceutical MDI highlighting its complexities. Visualisations of the aerosols in the near-orifice region of a commercial pharmaceutical MDI confirmed the spray characteristics: (i) start-up transient, (ii) fully developed spray with slow spray density variations with a characteristic time scale around 100ms related to changes of pressure and vapour mass fraction of the two-phase mixture inside the actuator valve and expansion chamber and (iii) rapid spray density pulsations with large droplet production and considerable spray cone angle variations with characteristic time scale around 2ms. The concentration of larger droplets around the top and bottom edges of the spray strongly suggests that an annular liquid flow is present inside the spray orifice.

In addition to this study on a commercial actuator a partially transparent rectangular model MDI was studied. External spray characteristics showed similar spray characteristics to those of the commercial MDI. Imaging of the propellant flow inside the expansion chamber of the rectangular model revealed the existence of an annular flow regime with a vapour core and an unsteady wall film consisting of foamy liquid. Simultaneous visualisations of the internal flow and the near-orifice spray showed links between the flow regime in the expansion chamber and the nature of the external spray. The internal flow regime was found to involve large variations of vapour mass fraction in the actuator orifice with obvious consequences for spray formation processes at the exit of this orifice. Pulsations and density waves that are found in the external spray of a MDI appear to be closely related to unsteadiness of the foamy wall film in the expansion chamber due to liquid inertia effects.

These results clearly highlighted the potential of optical diagnostics in the development of improved accounts of the state of the flow inside a pMDI valve and its relationship with drop formation. However, the flow imaging took place at comparatively low resolution, so the spray
forming mechanisms could not be studied in detail. Moreover, the model geometry was rectangular and the effects of geometry on the internal flow and spray generation are unknown. The aim of this paper is to report the findings of a follow-up study with an improved transparent model with a more realistic, cylindrical expansion chamber and spray orifice.

2. Experimental Procedure

The model of the pMDI was manufactured from polycarbonate and was highly polished to achieve a good optical finish. The improved geometry eliminated some of the sealing problems that were experienced at the seat of cylindrical valve stem on the rectangular expansion chamber. Near-orifice sprays due to actuation of HFC227 placebo from commercial MDI canisters were imaged using laser-based high-speed visualisation to reveal the near-orifice sprays and internal propellant flows. The system comprised a copper-vapour laser as the illumination source in conjunction with a Kodak HS4540 high-speed digital camera for image recording. The laser provided a pulsed light source with a frequency of 9kHz. Fibre-optic light delivery was used to provide front and backlighting. The camera provided 256 x 128 pixel resolution images and was operated with a Nikon 115mm focal length microlens through a bellows arrangement to image the expansion chamber and near-orifice region. The canister was actuated manually.

3. Results

Figure 1 shows sample images of the near orifice spray. Metered dose inhalers produce highly transient sprays as a consequence of time variations of the pressure and liquid mass fraction in the valve stem and expansion chamber upstream from the actuator orifice. During the first 1-2ms of the spray event some liquid enters the valve stem where the pressure is atmospheric. Thus, the liquid is superheated and flash evaporation takes place. This produces a vapour-only spray. During the next 5-10ms, a vapour-liquid spray with rapidly increasing density is formed. This constitutes the fully developed phase of the spray event (duration approximately 60-70ms). The bulk of the spray is a dense mass containing very fine droplets, but much larger droplets are formed at the edges of the spray.

![Figure 1: Visualisations of near-orifice spray](image-url)
Figure 2 presents further near orifice spray images where the production of large droplets can be visualized. These are particularly seen issuing from the lower edge of the nozzle, apparently caused by the liquid film forming around the exit nozzle and moving, due to gravity, to the lower edges of the orifice. In the high-speed videos of the spray, pulsations of the spray density in the near-orifice region are clearly observed. Each pulsation causes a large fluctuation of the instantaneous spray cone angle. The visualisations show that the dense phase of these pulsations involves a pattern of two to four density waves. Dense spray and lean spray episodes are found to alternate with a frequency around 500-1000Hz. This process is accompanied by the ejection of pulses of large droplets. During the latter half of the spray event (final 60-70ms) the propellant runs out. This causes the spray density to reduce, but the proportion of larger droplets increases. These visualisations reveal that the near-orifice spray formation process of a pharmaceutical pMDI is quite complex. These findings correspond closely to our own previous visualisations and those reported by other investigators.
Figure 3 shows sample images of the internal flow inside the expansion chamber of the model actuator. Our results show that the propellant flow regime in the expansion chamber is strongly non-homogeneous with some flash boiling and bubble formation. The primary spray formation process mainly involves flashing near the spray orifice exit. Moreover, evidence of the postulated annular flow regime in the spray orifice can be found.

In order to further clarify the structure of the flows in the final exit nozzle, the imaging system was configured to provide high magnification visualization of this region. The results are given in figure 4, which presents a sequence of four images extracted from a high-speed video recording. In each of the images there appears to be swirl present in the exit flow. This is particularly noticeable in figure 4a and 4b, where a spiral formation of alternate dark and light bands can be seen. It is also evident that as
the flow progresses down the exit nozzle that the liquid moves to the exit wall forming an annular liquid flow. This is evidenced by the dark liquid layers appearing on the wall and may be a result of the swirl nature of the flow. The presence of a swirl flow may also explain the wave-like nature of the flow seen in the exit spray (figures 1a and 1b).

4. Conclusions

Imaging of the propellant flow inside the expansion chamber of the rectangular model revealed the existence of an annular flow regime with a vapour core and an unsteady wall film consisting of foamy liquid. Simultaneous visualisations of the internal flow and the near-orifice spray once again showed the same links between the flow regime in the expansion chamber and the nature of the external spray as were observed during our earlier study (Versteeg & Hargrave, 2002). The small droplet size in near-orifice aerosols suggests that flash boiling plays a key part in spray generation except during the final phase of an actuation event. Concentrations of larger droplets around the top and bottom edges of the spray at these later stages strongly suggests that an annular liquid flow is present inside the spray orifice. Our visualisation study has confirmed the non-homogeneous flow regime in the expansion chamber with some flash boiling and bubble formation. The primary spray formation process mainly involves flashing near the spray orifice exit. Moreover, clear evidence of the postulated annular flow regime in the spray orifice has been found.

Our results highlight the potential of optical diagnostics in the development of improved accounts of the state of the flow inside an MDI and its relationship with external aerosol formation. Knowledge of the pre-atomisation mechanisms in two-orifice systems is crucial for improved control of the external spray characteristics and improved drug delivery efficiency of pharmaceutical MDIs.

Figure 4. Visualisation of the flow in the 0.8 mm exit nozzle.
5. References

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