INTERNAL FLOW AND SPRAY CHARACTERISTICS OF A PHARMACEUTICAL METERED DOSE INHALER USING THE KOS VORTEX NOZZLE

H.K. Versteeg*, G.K. Hargrave*, P.A. Genova°, R.C. Williams III°, D. Deaton°, P. Kakade°

*Wolfson School of Mechanical and Manufacturing Engineering, Loughborough University, Loughborough, Leics, LE11 3TU, UK.
°Kos Pharmaceuticals, Inc., 4020 Aerial Center Parkway, Morrisville, NC 27560, USA.

ABSTRACT

Pharmaceutical metered dose inhalers (MDIs) are drug delivery devices that are designed to produce self-propelled aerosols for inhalation therapies. The aerosols produced by conventional MDI actuators - based "two-orifice-and-sump" designs - have a good fraction of respirable drug particles, but high plume velocity. The latter causes high levels of unintended oropharyngeal drug deposition and, hence, reduced lung deposition. The Kos Vortex Nozzle Assembly® (VNA) is an innovative actuator concept, which utilises a combination of a vortex chamber and a diverging mouthpiece to reduce the plume velocity whilst increasing the respirable fraction. This paper reports the findings of an optical diagnostics study to investigate internal aerosol generation processes and spray characteristics for the Kos VNA®. High-speed video imaging was used to document the developing aerosol plume in the near-orifice region as well as the flow regime inside the vortex chamber of a transparent model of the Kos VNA®. We also report visualisations of external drug deposition, which represents an inefficiency of the drug delivery technology and can threaten drug dose repeatability. The paper demonstrates how this type of optical diagnostics study can be used to obtain detailed understanding of the processes governing primary atomisation and external drug deposition.

INTRODUCTION

The metered dose inhaler (MDI) is the most popular and widely prescribed delivery device for inhalation therapy. It produces a self-propelled aerosol with a high fraction of respirable drug particles (1-5μm). Moreover, it combines many advantages, such as low manufacturing cost, compactness and high patient and clinician preference. However, the device suffers from several well-known limitations [1], including (a) high oropharyngeal drug deposition caused by the high initial velocity of MDI aerosol plumes, and, (b) the cold-freon effect, which stops about 5% of patients from using MDIs and is partly attributable to the low spray temperatures and sudden impact of the plume on the throat wall. The Kos Vortex Nozzle Assembly® (VNA) is an innovative actuator concept developed to give reduced aerosol velocity, improved control over particle size and reduced drug deposition. The latter represents an inefficiency of the drug delivery technology that can also threaten dose uniformity. Figure 1 shows a sketch of the VNA.

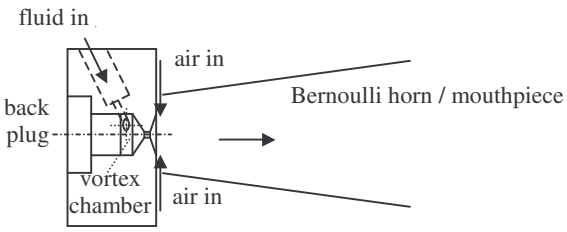


Figure 1: Concept sketch of Kos VNA®

Genova *et al* [2] provide details of the operating principles of the Kos VNA® along with a preferred geometry. Upon actuation of the device a metered drug dose is dispensed from a canister containing propellant/drug mixture. The mixture expands through a small orifice in the tangential inlet and enters at the periphery of the vortex chamber, setting up a swirling motion. The fluid leaves the vortex chamber through an axial exit orifice. The patient inhales through the mouthpiece, which is designed as a diverging passage to reduce the velocity of the spray as it mixes with ambient air.

This paper reports the findings of an experimental study using optical diagnostics to investigate the primary atomization mechanism of the Kos VNA®. High-speed video imaging was used to capture the processes leading to aerosol formation by and drug deposition within production VNA actuators. Moreover, transparent models produced by rapid prototyping were studied to visualize the internal flow regime. The paper demonstrates how optical diagnostics can be used to study the processes controlling the aerosol generation and drug deposition around the exit orifice.

EXPERIMENTAL METHOD

The main series of experiments was carried out with the imaging system is sketched in Figure 2. It comprised a copper-vapour laser as the illumination source in conjunction with a Kodak HS4540 high-speed digital camera, which has 256 x 128 pixel resolution. The laser provided a pulsed light source with imaging frequencies up to 9kHz. The camera was operated with a Nikon 115mm focal length microlens through a bellows arrangement to image at sufficiently high magnification. Fibre optic light delivery was used to provide front or backlighting. Near-orifice sprays of production VNA actuators were visualised, as well as near-orifice sprays and internal propellant flows for transparent models of the vortex chamber. The latter were produced by means of gravity moulding. MDI canisters with a 63 mm^3 valve were used to produce metered aerosols of an HFC134a propellant placebo and an HFC134a/active formulation. The diverging mouthpiece had to be removed to provide optical access for near-orifice imaging. The canisters were actuated manually.

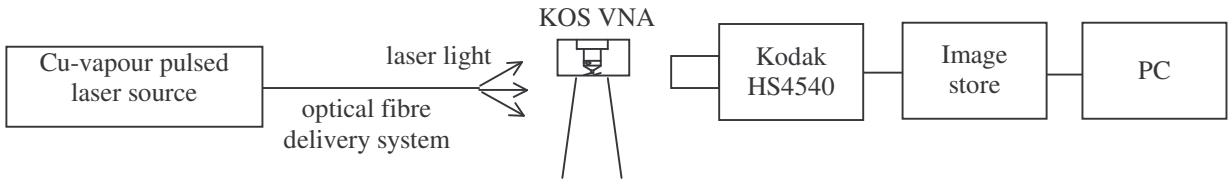


Figure 2: High speed imaging system

More detailed visualisations were obtained using a Kodak Ektapro ES1 camera with 2000x2000 pixel resolution in conjunction with a double-pulsed NdYAG PIV laser light source operated at 8Hz. For transient sprays with durations ranging from 0.2-0.5 seconds it is only possible to obtain 2-4 images per spray event at this modest acquisition rate. Nevertheless, if spray events are repeatable, the sequence of events can be obtained from images of a number of consecutive spray events with variations of the actuation timing relative to the trigger point of the imaging system. In our manually-actuated tests the timing variations occurred randomly, but analysis of a large number of high-resolution images along with high-speed video sequences allowed us to synthesise the most important aspects of a spray event.

RESULTS

Near-orifice spray characteristics

Figure 3 gives a selection of typical side-view images in the near-orifice region of the spray transient produced by actuation of a metered dose of placebo (i.e. propellant-only) with the production VNA. It should be noted that the spray was fired horizontally, but appears vertically downwards in the images. The visualisations used frontlighting to be able to observe the bulk of the spray as well as material on the periphery of the spray. After actuation of the MDI canister the following general development was observed. A gas-liquid propellant mixture initially starts to emerge as a lean, narrow plume. After about 10 ms the density and width of the spray both rapidly start to increase (Fig. 3a). The main phase of the actuation event involves a luminous, wide spray, which contains the bulk of the respirable particles. The process is quasi-steady and has a duration around 80 ms (Fig. 3b). The spray is most luminous at $t \approx 40$ ms and comprises large quantities of extremely fine droplets. When the propellant in the metering chamber starts to run out, the luminosity of the spray reduces and the spray narrows again (Fig. 3c). The spray largely consists of fine droplets, which emerge in pulses, the length of which decreases with time, whilst the duration of the period between pulses increases. Small quantities of somewhat larger droplets are also observed at the spray edges. Furthermore, very large droplets are occasionally emitted in short bursts with a duration around 2-4 ms (Fig. 3d). When the liquid has almost run out the spray becomes very narrow (jet-like) and lean and mainly consists of pulses of larger droplets (Fig. 3e).

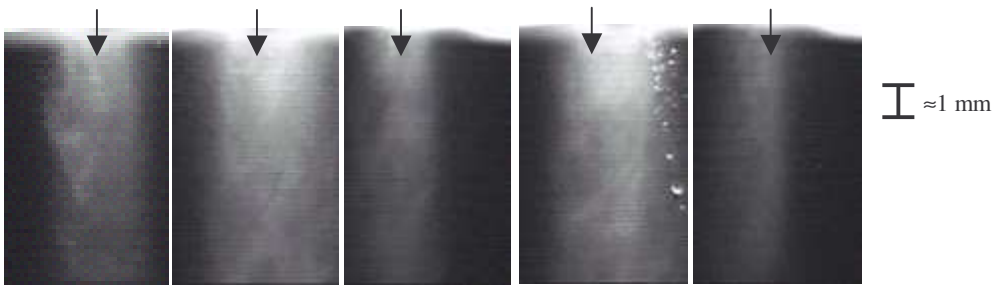
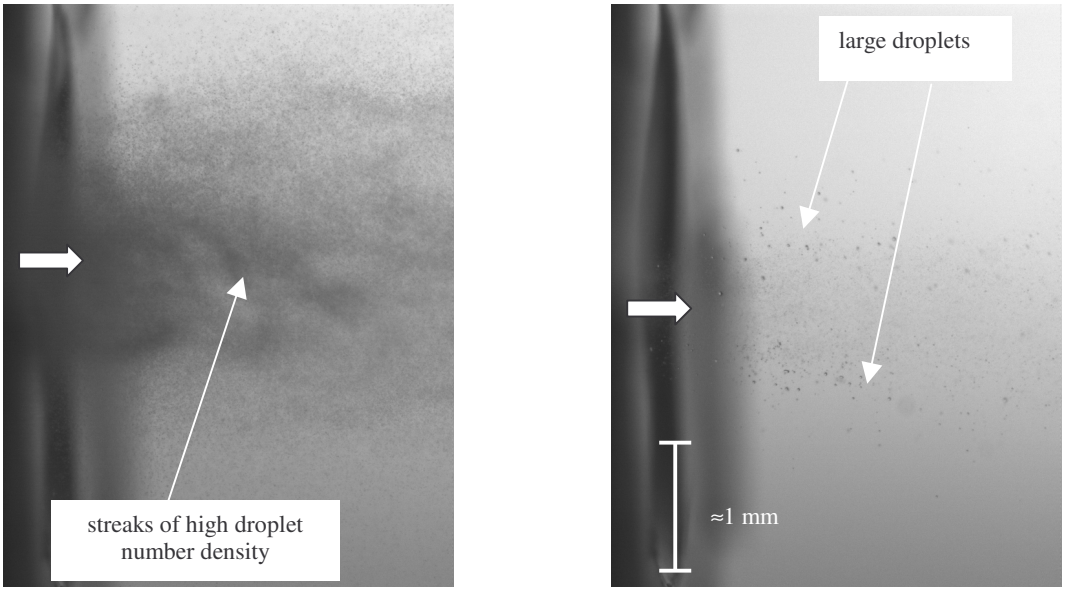


Figure 3: Visualisations of near-orifice spray



(a) main phase (b) final phase

Figure 4: High-resolution images of near-orifice spray

Figure 4 shows sample high-resolution images of the spray during the main and final phases of the actuation event revealing a considerable amount of structural detail that appears blurred in the high-speed video images. To the extent that valid drop size estimates are possible, images such as Fig. 4a indicate that liquid drops are extremely small during the main phase. All visible drops droplets in this near-orifice spray are smaller than 5µm and most appear to be around 2-3µm or smaller. Fig. 4b shows that, during the later stages of the spray event, the spray core still consists of very small droplets, but larger droplets with size around 10-20µm appear around the periphery of the spray.

Internal flow regime inside vortex chamber

In order to study the flow events inside the actuator responsible for pre-atomisation, we examine backlit images of HFC134a placebo flows inside a transparent model of the Kos VNA®. Light scattering due to the drug particles in HFC134a/active formulations made it impossible to visualise the internal flows for these mixtures. Figure 5 shows typical images of propellant flows inside the vortex chamber paired with corresponding ones of near-orifice aerosol plumes, which facilitates comparison with the external spray visualisation in Figure 3. The propellant flow through the tangential inlet appears dark grey in Figs. 5a-c indicating that this fluid initially enters the vortex chamber as a bubbly vapour-liquid mixture. The swirling motion executed by the mixture promotes separation of the phases. The vapour moves towards the central axis to join the air that originally fills the vortex chamber, whereas the liquid collects at the periphery. Shortly afterwards a narrow aerosol plume begins to emerge from the exit orifice. As the amount of liquid increases, the diameter of the gaseous core decreases and at the same time the aerosol plume becomes denser, more luminous and wider (Fig. 5b). The main (quasi-steady) phase of the spray event generated by the transparent nozzles is characterised by an internal flow regime, which is dominated by a liquid vortex with a small gaseous core. The core diameter is similar to that of the exit orifice (Fig. 5c) and was estimated to be around 80% of the orifice diameter when the external plume is most wide. To the extent that its surfaces allow observations, there is evidence that the vortex flow persists well into the exit orifice on the chamber-side and that flash evaporation takes place very close to the outlet side of the exit orifice. Flashing is instrumental in the production of very fine droplets that characterise the aerosols generated by all MDIs. As the metered dose of propellant runs out, the gaseous core diameter starts to increases again and the plume narrows, but the aerosol still largely consists of fine droplets (Fig. 5d). During the final phase of the spray event the vortex chamber is filled with vapour except for a thin liquid film on the chamber walls; the external spray is produced in short pulses with larger droplets. As before, these should be distinguished from the occasional brief pulses of very large droplets, which were also observed with the transparent models (Fig. 5f).

External flow in nozzle exit region

Figures 6a-e show visualisations in the exit orifice region of the spray of the HFC134a/active formulation. The viewing direction is just above the spray axis towards the orifice. The orifice is located at the apex of a conical nozzle exit (Fig. 6a). During the early part of the actuation event the only visible feature in this region is the widening spray plume (Fig. 6b). At the end of the main phase the cone angle starts to reduce and a faint ring of liquid becomes visible around the exit orifice (Fig. 6c). This ring has a maximum extent around $t \approx 65$-75 ms. In the course of the subsequent narrowing of the plume the edges of this liquid ring begin to dry out due to evaporation and drug deposits start to form (Fig 6d). This process continues throughout the final phase of the spray event and an elliptical region filled with drug deposits appears around the exit orifice (Figs 6e). The chosen mounting of the high-speed video camera shows the

images turned through 90 degrees in the clockwise direction. The inset shows the true orientation of the drug deposits for a horizontal actuation from a VNA. More detailed study indicated that the production of these droplets was concentrated in the same region where drug was deposited. Further visualisations in the exit region of a production VNA with placebo spray and slightly different illumination conditions and viewing direction revealed how bursts of large droplets are stripped away from the ring-shaped liquid accumulation at the rim of the nozzle exit cone by the meandering and pulsating spray plume (Fig. 6f). Thus, the formation of this liquid pool is responsible for drug deposition as well as the bursts of large droplets. Difficulty to observe this connection directly for the active formulation can be explained by the high reflectivity of the spray due to the presence of the drug particles.

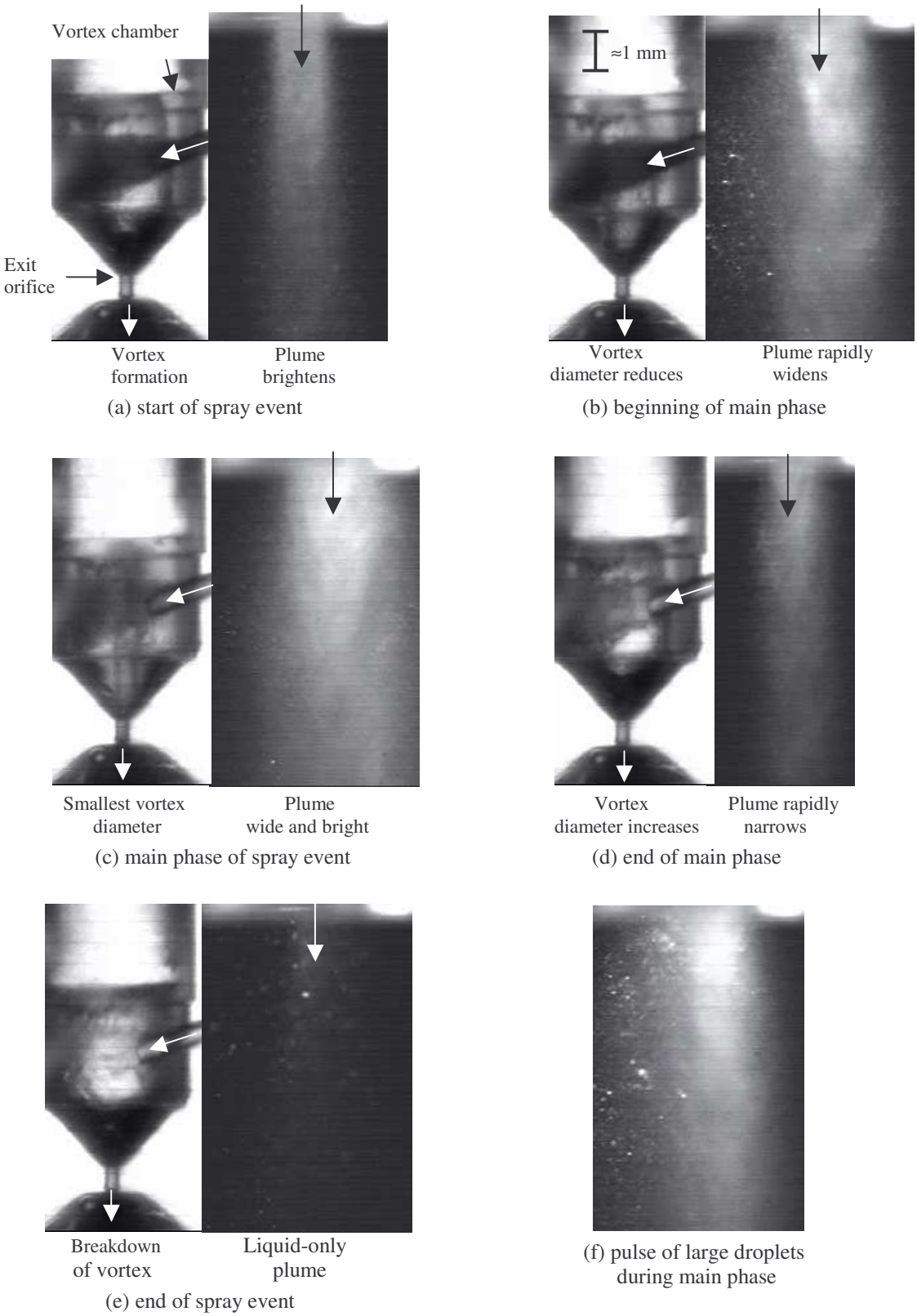


Figure 5: High-speed images of internal flow and near-orifice plume for transparent model of KOS VNA®

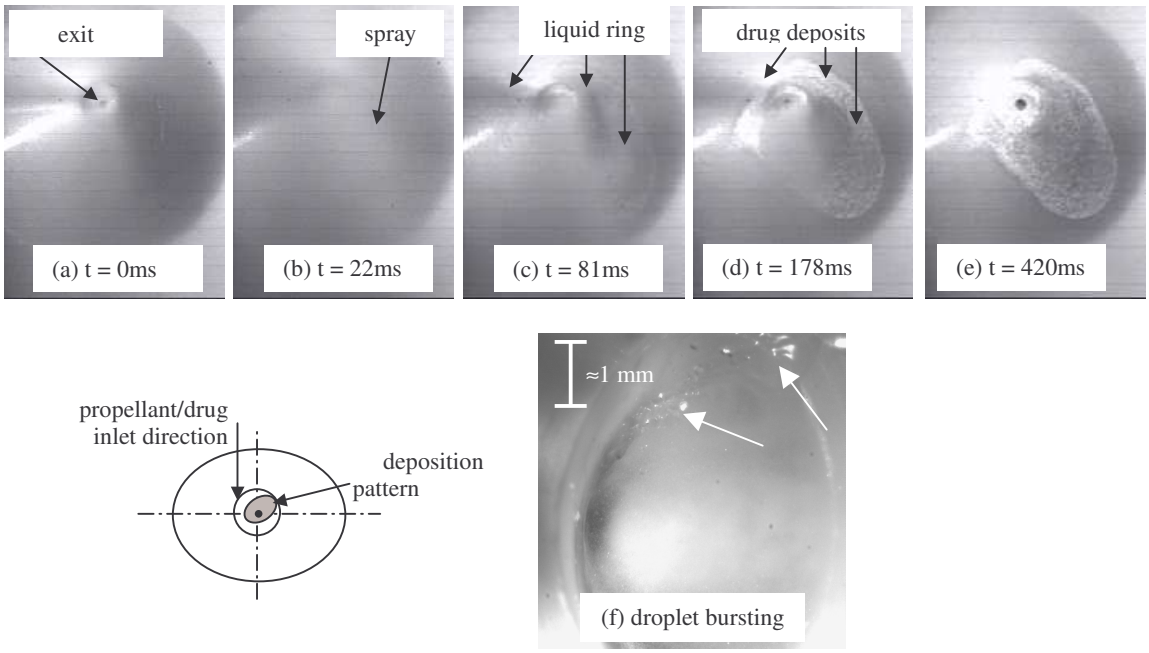


Figure 6: Visualisations of VNA nozzle exit region

DISCUSSION AND CONCLUSIONS

Table 1 provides a summary of in-house test data comparing the overall plume properties for two leading asthma formulations (Flovent® fluticasone propionate - CFC-based formulation - and Proventil® albuterol sulfate - HFA-based) when used in conjunction with their own (two-orifice-and-sump) actuator and with the Kos VNA®. The data shows that the vortex nozzle generates a longer plume duration and lower plume impact force than conventional actuators, suggesting a lower plume velocity. Moreover, the VNA also gives improved respirable fraction.

Table 1: Pharmaceutical performance comparison for two leading marketed asthma drug formulations

	Flovent®		*Proventil®*	
	Own actuator	*Kos VNA®*	*Own actuator*	*Kos VNA®*
Plume force (mN)	63	8	15	10
Plume duration (ms)	194	463	141	186
Respirable fraction (% ex-mouthpiece)	49	66	58	67
Fraction deposited in USP throat (% ex-mouthpiece)	40	11	30	22
Fraction deposited in device (% ex-valve)	8	20	16	22

Although the total duration of the spray event can be up to 3 times as long, the sequence of events is the broadly the same for a conventional (two-orifice-and-sump) actuator and the VNA. Table 2 gives a comparison of the timings of the main events during the metered spray transients of the two actuators.

Table 2: Comparison of spray event timings for conventional actuator and Kos VNA®

	Conventional actuator (ms) data from [3,4]	*Kos VNA® (ms)*
Initial pulse	0-10	0-10
Main phase of wide, fine, dense spray {max. density}	10-20 {15}	12-100 [40]
Narrow, fine, pulsating spray	45-100	130-330
Large liquid droplet spray from nozzle edge	100-150	330-450

Reporting the findings of a similar visualisation study on a model of a conventional MDI actuator, Versteeg and Hargrave [3] noted a frothy, non-homogeneous and chaotic flow regime in the actuator sump characterised by relatively high vapour fraction and a narrow external spray. The vapour content of the vortex chamber of the VNA is much lower during the main phase of the spray event and the flow appears quite stable. This suggests that the swirling flow structure may play a role in stabilising inlet conditions to the exit orifice.

It is interesting to note that the observed value of the minimum vapour core diameter (Fig. 5c) corresponds to a film thickness of 10% of the exit orifice diameter. Lefebvre [5] quotes the inviscid analysis due to Giffen and Masurzev, which links the cone angle, discharge coefficient and film thickness to the dimensions of a simplex pressure-swirl

atomiser. If the dimensions of the VNA are used this analysis yields a film thickness around 5% of the exit orifice diameter and a cone half-angle of 62 degrees. The discrepancy between the observed and theoretical value of the film thickness is attributable to inaccuracies in the measured value and/or viscous effects. The latter are known to cause an increase in the film thickness and decrease of the cone angle. Figure 7 shows an image of the vortex chamber and near-orifice region of a transparent model used with a pumped supply of water at an inlet pressure around 3 bar. This confirms that, if the device is used with a non-evaporating fluid, it acts as a typical pressure-swirl atomiser, producing a hollow-cone spray. Moreover, the visualisation highlights that the flow regime inside the vortex chamber is very similar for liquid-only and two-phase inflows.

Figure 7: High-speed image of near-orifice region of transparent model of Kos VNA® with water showing formation and partial break-up of hollow-cone liquid sheet

Unfortunately, obscuration of the orifice exit plane prevent us from making meaningful estimates of the cone angle in the immediate vicinity of the exit orifice to assist in the further validation of the film thickness estimate. However, we can make some further progress by examining the drop size estimates. The driving force causing propellant mixture to flow from the metering chamber in the canister into the vortex chamber is propellant expansion in the metering chamber, valve stem and across the orifice in the tangential inlet. The expansion can be considered as adiabatic so the two-phase mixture entering the vortex chamber will become progressively colder as the spray event progresses. Initially, the temperature of the mixture will be highest and the swirling flow and high liquid content will inhibit further propellant expansion in the vortex chamber. The fluid will enter the exit orifice with superheat and subsequent rapid depressurisation through the exit orifice promotes flash boiling at the nozzle exit. During this phase of the spray event the drop size was found to be around 2-3μm and the spray undergoes rapid lateral expansion in the nozzle exit region, which confirms that vigorous flash boiling must be occurring. During the later stages of the spray event the superheat of the liquid is insufficient to support rapid evaporation. Lefebvre [5] states that the final drop size should be of the order of the film thickness for a non-evaporating fluid. It appears that part or all of the annular liquid film remains intact, which explains the appearance of droplets of size around 10-20μm at the edges of the spray.

In summary, the following aspects of the processes governing primary atomisation and external drug deposition for the Kos VNA® can be inferred from the results of our visualisation study:

- The internal flow regime is closely related to the pressure-swirl atomiser: swirling liquid flow with gaseous core.
- A thin annular liquid film exists inside the exit orifice. Very close to the nozzle exit the propellant undergoes flash boiling and the liquid film disintegrates into a very fine droplet spray with all droplets < 5μm.
- Cooling of the expanding mixture inhibits flash boiling during the later parts of the spray event. The annular liquid film now remains intact causing the formation of larger droplets with size around 10-20μm at the spray edge.
- The incoming flow is a two-phase mixture of liquid and gaseous propellant. The phase separation in the vortex chamber must cause a nett outflow of propellant vapour via the core during large parts of the spray event.
- Bursts of very large droplets and external drug deposition are both associated with the ejection of quantities of unevaporated liquid in the nozzle exit region during the main phase of the spray event. Further work is currently in progress to determine the underlying causes of this phenomenon and to develop geometric nozzle designs to prevent droplet bursting and external drug deposition.

REFERENCES

1. Ganderton D., General factors influencing drug delivery to the lung, *Respiratory Medicine*, vol. 91 (Suppl. A), pp. 13-16, 1997.
2. Genova P.A., Williams III R.C., Jewett, W., Low spray force, low retention atomization system, US Patent 6,418,925, 2002.
3. Versteeg HK and Hargrave GK, Near-orifice spray and valve flow regime of a pharmaceutical pressurised metered dose inhaler, *Proc. 18th Ann. Conf. Liquid Atomization and Spray Systems ILASS-Europe 2002*, Paper 27, pp. 171-176, 2002.
4. Wigley G., Versteeg H.K. and Hodson D., Near-orifice PDA measurements and atomisation mechanism of a pharmaceutical pressurised metered dose inhaler, *Proc. 18th Ann. Conf. Liquid Atomization and Spray Systems ILASS-Europe 2002*, Paper 27, pp. 165-170, 2002.
5. Lefebvre A.H., *Atomization and sprays*, Taylor & Francis, 1989.