Seeing is Believing: Using Optical Diagnostics to Investigate MDI Sprays and DPI Fluidization

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SUMMARY

Inhaler device modifications directly influence aerosol generation mechanisms, so the development of inhalation products could be advanced effectively if the relevant processes can be studied *in situ*. However, the ability to visualize, in real time, atomization in a metered dose inhaler (MDI) or fluidization in a dry powder inhaler (DPI) remains challenging. This article reviews high-speed imaging, fluorescence imaging, particle image velocimetry (PIV) and phase-doppler anemometry (PDA) and demonstrates how these techniques can be used to characterize aerosol clouds whilst they are being generated and reveal the nature of aerosol production processes as they unfold inside inhaler devices. The different optical diagnostics generate complementary data including aerosol droplet size, velocity and overall aerosol/spray attributes. Understanding the details of transient events during

metering of a drug dose into the inhaled airflow at the appropriate temporal and spatial resolution creates opportunities for targeted interventions to solve problems e.g. excessive device deposition. Moreover, the images generated by optical techniques represent a readily accessible form of information which supports multi-disciplinary collaboration, so, when using optical diagnostics, we can legitimately claim that “Seeing is Believing”.

INTRODUCTION

The key parameters that determine the aerodynamic performance of an inhalation product are the aerosol particle size and the particle size distribution. Cascade impaction is the preferred measurement approach, because it is API specific and measures the entire cloud, but the technique is labor intensive, complicated to use and, therefore, prone to operator errors [1]. Moreover, the particle size distribution measured using a cascade impactor represents the end of a dynamic transport process that may itself induce specific changes.

Without adequate knowledge of the processes responsible for primary aerosol generation and drug deposition and without deeper understanding of aerosol behaviour during transport, device design is unlikely to proceed in an optimal way. In this paper, we review the application of high-speed imaging, fluorescence imaging, particle image velocimetry (PIV) and phase-doppler anemometry (PDA) to characterize inhalation devices. These optical techniques are used to study MDI sprays and DPI aerosols and the processes leading to device drug deposition and identify opportunities for the wider application of these research techniques to device development.

High-speed Imaging and Digital Image Analysis

Imaging systems such as Envision Pharma (Oxford Lasers, Shirley, MA, USA) and ISI5000 (InnovaSystems, Mooretown, NJ, USA) are widely utilized in the pharmaceutical industry to characterize spray patterns and plume geometry of MDIs and nasal sprays. Laser sheet illumination, perpendicular to the spray centreline, is used for spray pattern analysis in quality control testing recommended by FDA guidelines [2]. Geometric properties of the cross-section of the developing aerosol cloud, such as diameter, centroid and ellipticity, are found by means of digital image analysis. Laser sheet illumination along the spray centreline can image the plume geometry, which is recommended by the FDA, during product development [2]. This optical arrangement enables the characterization of spray cone angle, plume width and spray direction relative to the orifice centreline. The SprayVIEW® (Proveris Scientific, Marlborough, MA, USA) patternation system has been used to investigate the effect of MDI geometry on spray patterns in conjunction with laser diffraction for particle sizing [3]. Spray patterns and particle size were both found to be sensitive to actuator orifice diameter, length and sump depth, providing evidence that spray pattern analysis can be useful during product development.

Imaging of inhaler devices and their aerosol plumes is beneficial, because it provides large amounts of visual information in a very accessible form. To capture sufficient detail, imaging systems must be able to freeze the motion of micron-size small particles that move at high speeds, which is achieved using high-power Nd:YAG or Cu-vapor lasers producing 10-20 ns pulses at frequencies up to 20 kHz as the light source. A planar sheet is formed from a pencil beam of laser light using a cylindrical lens, which can be directly used for light sheet illumination or to pump light into a dye cell to generate a uniform source of backlighting. High-speed digital

cameras, such as the 1 Mpixel Fastcam SA (Photron, San Diego, CA, USA), are synchronized to the laser pulse frequency to capture the flow images. The camera is equipped with suitable macro-lenses to magnify regions of interest where newly formed aerosols emerge from a device mouthpiece or liquid atomization / powder fluidization takes place.

The flow and spray generation mechanism inside a transparent model of a novel MDI actuator with a vortex nozzle (Kos Pharmaceuticals, Morrisville, NC, USA) was imaged using a Kodak HS4540 digital high-speed camera and Cu-vapor pulsed laser illumination [4]. Large droplet production and high drug deposition for the standard vortex nozzle assembly (VNA) were found to be associated with the formation of a liquid pool on the surfaces of the nozzle exit cone during the spray event. Subsequent evaporation of the propellant left a large drug residue (Figure 1). This observation led to design changes including the removal of the exit cone, which virtually eliminated drug deposition in the nozzle exit region of the optimized vortex nozzle [4].

High-resolution, high-speed imaging has also been used to study the fluidization of lactose placebo formulations and aerosol plumes just outside the mouthpiece of Nexthaler® DPI (Chiesi Farmaceutici, Parma, Italy) [5]. The operation of the dose protector in the device was revealed, as well as details of the transient powder fluidization process. Analysis of the digital images of the aerosol near the mouthpiece gave precise information relating to the timings of key fluidization events after the start of inhalation. The main fluidization event was found to be subdivided into two stages: (i) a short, dense initial pulse of 15-25 ms duration with the large bulk of the particle dose released and (ii) a second, slightly overlapping pulse of 50+ ms duration with particles that were released more slowly by the device.

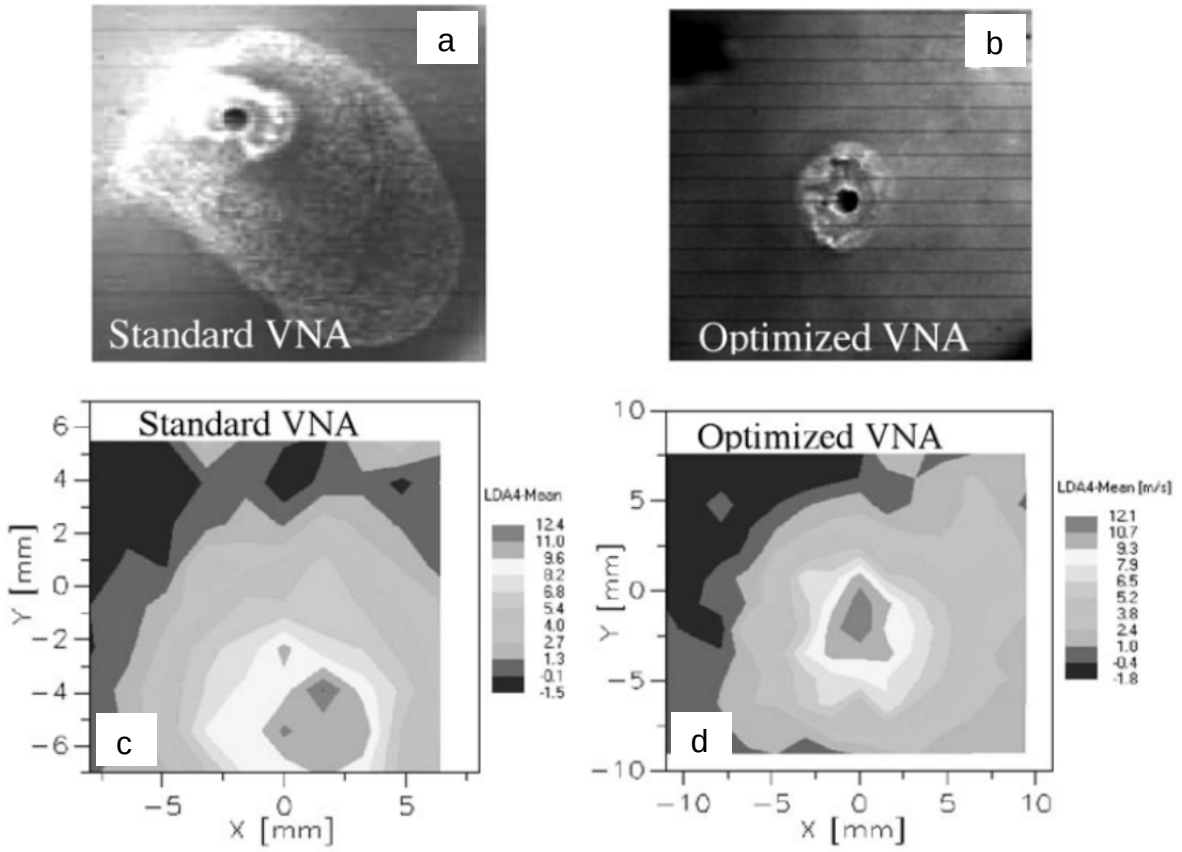


Figure 1: Images of nozzle exit region (a-b) and contour maps of whole-actuation-averaged velocity at the mouthpiece exit (c-d) of standard vortex nozzle assembly (VNA) and optimized VNA. Reproduced with permission from [4]

While digital image analysis can provide detailed and quantitative understanding of the powder dose release characteristics of DPIs, a major drawback of scattered light imaging is that the bulk of the powder formulation is carrier material not API. A new imaging technique has recently been proposed to study the release of fines based on fluorescence imaging [6]. The method employs a model API system consisting of fluorescent microspheres (Cospheric, Santa Barbara, CA, USA) manufactured from a proprietary polymer with a diameter range of 1-5 µm (D_{50} = 2 µm). The microspheres have a peak fluorescent emission of 607 nm under excitation by laser light with a wavelength of 527 nm. They are blended with

proprietary lactose carrier before loading into the Nexthaler DPI. Figure 2 illustrates the aerosol plume in the vicinity of the device mouthpiece utilizing a two-camera system (Photron, San Diego, CA, USA) for simultaneous imaging of scattered light and fluorescent emission. One of the cameras is equipped with a short pass filter (λ < 607 nm) to image scattered light representing all the powder and the other camera equipped with a long-pass optical filter (with λ > 527 nm) to record fluorescent emission from model API microspheres only. Comparison of the images highlights differences between the distribution of the microspheres and the powder. Detailed analysis of the fluorescent images showed that the bulk of the microspheres are released during the short initial peak along with the bulk of the powder dose.

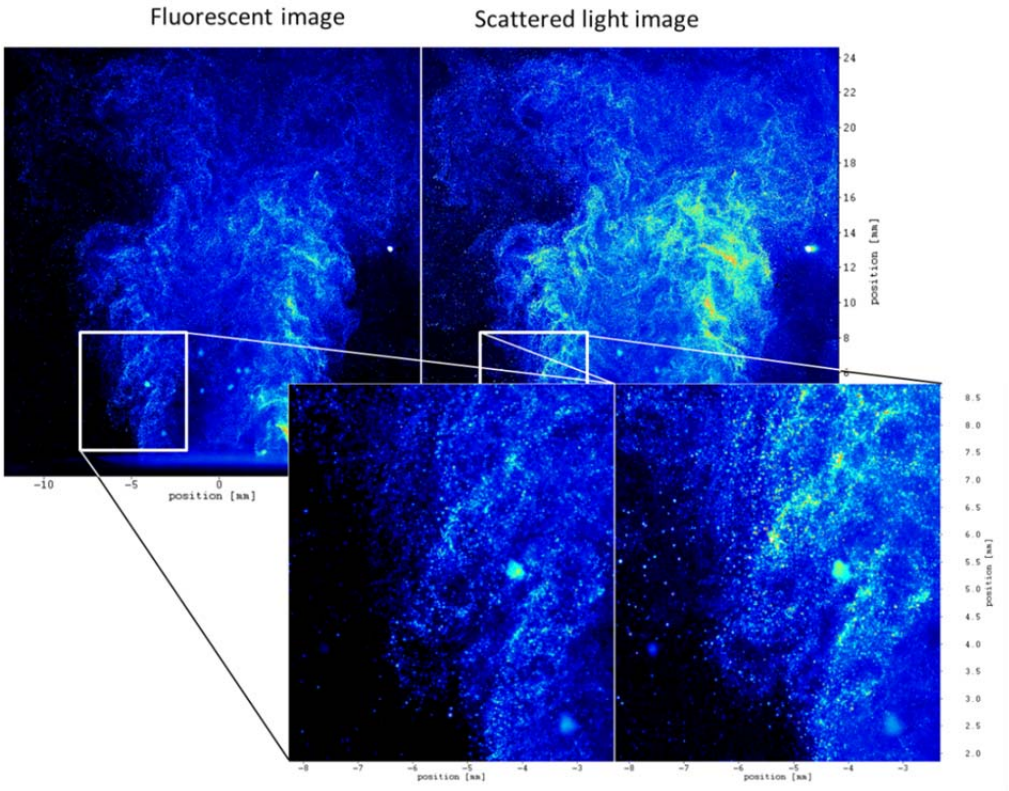


Figure 2: Sample images of laser-induced fluorescence and scattered light comparing the distribution of microspheres and the carrier powder

Particle Image Velocimetry (PIV)

Spray patternation has been used to estimate the velocity of the expanding aerosol by tracking the front of MDI sprays [7] and Respimat® soft-mist inhaler [8], respectively. Spray front tracking provides useful indications of the velocity of transient spray events, but the spray front is not representative of the spray as a whole. Two- and three-dimensional velocity vector fields can be measured using high-speed imaging in conjunction with a digital image analysis technique called particle image velocimetry (PIV). Briefly, a laser sheet illuminates a fluid region of interest. In 2D PIV, double-pulsed lasers are synchronized with the shutter opening of one digital camera perpendicular to the laser sheet to record pairs of images of moving particles in the laser sheet at a known time separation [9]. After recording, the image pairs are analyzed off-line to determine the velocity field. Each image pair is subdivided into analysis sub-regions (e.g. 32x32 pixels). Groups of particles that move with the flow will be located at slightly different positions in the two images. PIV image processing algorithms seek the highest correlation between pairs of sub-region images to identify the most probable displacement of groups of particles. This displacement divided by time interval between the laser pulses gives the x- and y-components of the in-plane velocity vector describing the average particle motion within the chosen sub region. The analysis is repeated over the entire image to build up a spatially resolved two-dimensional velocity vector map (Figure 3).

Stereoscopic systems use two cameras recording at 45^{o} angles to the laser sheet to make it possible to reconstruct all three components of the velocity vector of spray particles in the plane of the laser sheet [9]. All these systems are commercially available (e.g. Dantec Dynamics, Skovlunde, Denmark; LaVision,

Göttingen, Germany; TSI, Shoreview, MN, USA), including tomographic PIV or thick-sheet PIV for full 3D (whole-volume) velocity vector mapping.

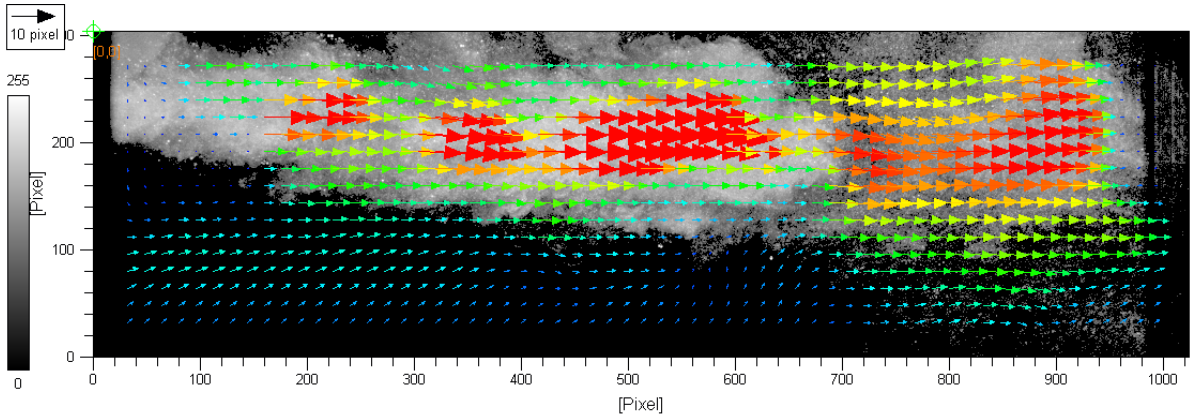


Figure 3: Typical PIV velocity vector map of flow induced by a MDI spray event showing pulsatile behaviour and entrainment of ambient air by the spray plume

The plume characteristics of a HFA budesonide solution MDI were compared with those from a CFC budesonide suspension MDI using PIV measurements via a USP throat, using windows for optical access [10]. The observed flow fields were correlated with deposition patterns in the USP throat, which were found to be concentrated in the horizontal section of the USP throat rather than high velocity particles impacting at the back. This implies particle dispersion by turbulent flow followed by deposition. A comprehensive study of the spray and flow induced by firing commercial salbutamol sulphate / HFA 134a MDIs using PIV velocity maps outside the mouthpiece [11] revealed the complex temporal and spatial structure of the spray flow. Velocity distributions were shown to have a Gaussian radial distribution with decaying centreline velocity and widening spray with distance due to friction between the spray plume and the surrounding air. Substantial variations of the spray cone angle were observed, which were correlated with variations of the spray direction relative to the spray orifice centreline.

Phase-Doppler Anemometry (PDA)

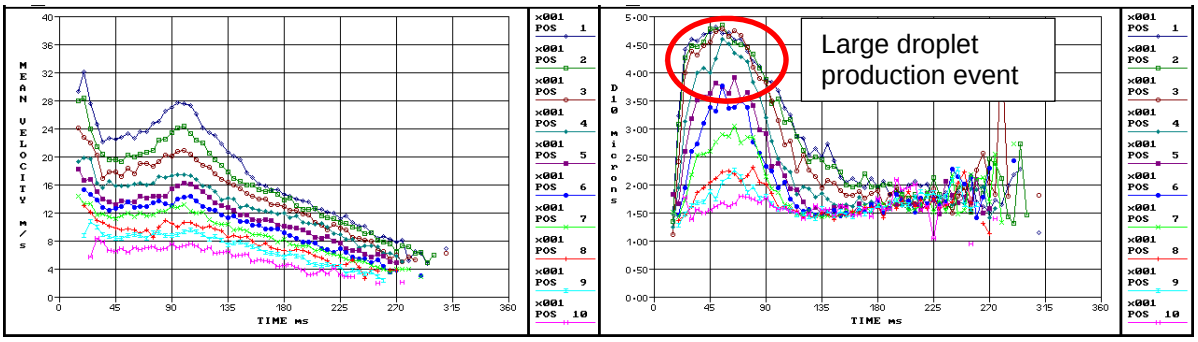
Phase-Doppler Anemometry is an optical technique for simultaneous measurement of particle velocity and size, at a point. A laser beam is divided into two by a beam splitter and the beams focused and crossed to form a small probe volume (typically 100 μm diameter). Light scattered by particles travelling through the probe volume is modulated by a Doppler frequency f_D that is proportional to the velocity component U of the particle in the plane of the crossing laser beams and perpendicular to their bisector. The scattered light is collected by means of photomultiplier tubes. It can also be shown that the phase difference $\phi_{1\text{-}2}$ between scattered light signals travelling along slightly different paths to two or more separate detectors is proportional to the size d of the scattering particle [12]. Different signal processing methods are available to compute the particle velocity and size for a given optical arrangement.

The earliest comprehensive study of MDI aerosols using PDA surveyed the spray velocity and droplet size distributions of MDIs with placebos and commercial CFC and HFA formulations [13]. PDA was used to determine “whole-actuation-averaged” values of velocity (see Figure 1) and droplet size outside the mouthpiece of pMDI sprays produced by a standard vortex nozzle and an optimized design [4, 14]. The experiments showed that the optimized vortex nozzle produced reduced particle deposition in the device and USP throat without changing the average spray plume velocity.

A Dantec 1D-PDA system (Dantec Dynamics, Skovlunde, Denmark) was used to determine the axial velocity and droplet size for nine MDI products including CFC and HFA formulations [15]. The work confirmed the ability of the instrument to

discriminate velocity differences between individual products, but droplet size comparisons produced inconclusive.

A two-component PDA system using an argon-ion laser with strong emission lines at green and blue wavelengths 532 nm and 379 nm, respectively has been described [16]. Two beam pairs are intersected in perpendicular planes at the same measurement point to allow simultaneous measurement of two velocity components and droplet size by equipping photomultipliers with suitable optical filters. Figure 4 illustrates PDA surveys of a HFA227 placebo aerosol. Temporal distributions of droplet velocity and number mean droplet size D_{10} of a HFA227 placebo aerosol are shown at 10 radial sampling points across the actuator mouthpiece. These were analyzed in time bins with a width of 5 ms to reveal details of the temporal behavior. The D_{10} value varied considerably as a function of time and radial position. A discrete event that is responsible for the production of many large droplets in distinct local areas is evident during the first 100 ms of the spray event.



(a) Mean droplet velocity (b) Number mean drop size D_{10}

Figure 4: Results of PDA survey of HFA227 placebo spray across mouthpiece exit of a prototype actuator

Measurements were also undertaken in the near-orifice region at an axial distance of 2.6 mm from the spray orifice of a modified actuator equipped with windows for optical access [16]. The radial velocity component was also obtained,

which revealed considerable variations of the spray direction with time. It was found that considerable care must be taken to make measurements at a sufficient number of locations to ensure that a representative sample of the MDI aerosol plume is obtained. Recently, the droplet size and velocity distributions of HFA134-ethanol placebo sprays generated from a Bespak actuator were examined using a new systematic test protocol [17]. The sprays velocities with 0, 10 and 20% w/w of ethanol were found to be similar (26.5±1.5 m/s) during the main phase of the spray event when 95% of the measured droplet mass was emitted by the MDI [18]. The number mean droplet size (3.3±0.5 μm) was found to increase with ethanol content, whereas the Sauter mean diameter was much higher for pure HFA134 (16.9 μm) than for the formulations containing ethanol (6.1 and 7.6 μm for 10 and 20% w/w ethanol, respectively). High-speed imaging in transparent models showed significant differences of the flow regime in the actuator sump. Again, optical diagnostics were able to highlight the probable causes of subtle differences of the droplet size for formulations, with and without ethanol. The findings suggested that the state of the flow at the spray orifice entrance, which is governed by gravity, viscous and surface tension effects, might play a role in controlling MDI spray droplet size distributions.

Discussion and Conclusions

Cascade impaction measurements of aerodynamic particle size distributions of pharmaceutical aerosols take place at a distance from the source of the aerosol, which does not provide insight into the underlying processes. Without this fundamental understanding, device design for new products generally involves the adaptation of existing platforms by means of trials guided by past experience. Device

modifications directly influence aerosol generation, so the study of aerosol production at source is likely to be more beneficial to guide device development. Different optical diagnostics have been shown to generate complementary, and mutually reinforcing, information. For example, PIV and PDA data provide information relating to aerosol droplet size and velocity, which both affect unwanted drug deposition. PIV yields whole-field time-resolved velocity information at modest spatial resolution. PDA, on the other hand, generates the temporal behavior of particle size and velocity simultaneously on a point-by-point basis. Droplets and particles smaller than (say) 5-10 μm are usually below the diffraction limit of a typical imaging setup, so these appear blurred in imagery. Phase-doppler anemometry, however, is highly suited to the measurement of such small particles. Larger particles and droplets can be imaged individually and their shape can be determined if the magnification is sufficient and the pixel grid of the digital camera has high resolution. Such large particles are often undesirable for inhalation therapy and a good visual indication can be a first step towards understanding the processes that produce them. Having identified and localized these problematic contributions to the final particle size distribution - there may be opportunities for design improvements targeted at their elimination. It is difficult to imagine how such insight could be obtained using performance characterization with impactor measurements only. Finally, optical techniques generate quantitative data as well as still images and videos. In our work, we have found that the joint interpretation of visualization material is a very fruitful activity in multi-disciplinary collaborations. By using optical diagnostics we can legitimately claim “Seeing is Believing”.

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