

Laser imaging for the implementation of BABE guidelines for the characterization of the physical properties of Nasal Sprays

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ABSTRACT

The United States Food & Drug Administration (FDA) recommends the measurement of the physical properties of Nasal Sprays [1]. The guidelines on how these should be measured are set out in the revised guidelines for nasal devices published in April 2003. These revised guidelines placed significantly stronger emphasis on automated measurements and on the use of laser-sheet based measurement.

Among other parameters the guidance calls for the measurement of Spray Pattern and Plume Geometry [1,2] and suggests that these can be done using laser illumination and digital cameras. Measurement of spray pattern and plume geometry are achieved using a laser lightsheet and taking a series of digital images, which are stored and key dimensions measured.

The switch to automated analysis of non-invasive laser-sheet images provides self-evident benefits in measurement speed, ease and objectivity, but it introduces some interesting challenges. For example, a human operator can easily judge the longest and shortest chords within a spray pattern, but an algorithmic definition of this is more difficult. Also, since the original records become computer based files, 21 CFR Part 11 compliance is required. We describe how we have overcome these challenges to develop a single tool for the characterization of both Nasal spray and MDI properties.

LASER IMAGING TECHNIQUE

The FDA's, BABE guidelines now place significantly stronger emphasis on the automatic measurement of spray pattern and plume geometry. The use of a non-invasive laser imaging systems are seen to eliminate problems which have been associated with conventional physical methods, such as TLC plates, Filter paper & collection buckets[3]. These techniques involve either single or multiple actuations of a spray device. The collection device is then analysed and a spray distribution obtained. Although physical methods measure mass distribution directly, they are limited in the following way;

- The process is time consuming
- The collection device may interfere with the airflow and therefore influence the result
- The resolution pattern is limited by the physical analysis

Non-invasive imaging system employs a light-sheet to slice through the spray plume and a high speed digital camera to capture a high-speed movie of the spray cloud as it passes through the illuminated sheet. Fig 1(a) & 1(b) show the lightsheet orientation to obtain information on both plume geometry & spray pattern. The advantage of taking a high-speed movie is that the intensity in each image can be calculated to determine spray pattern size & shape, plume geometry angle and orientation. In addition blur free images produced by the short laser pulse duration (1.0 μ s) allows detailed flow field vector analysis.

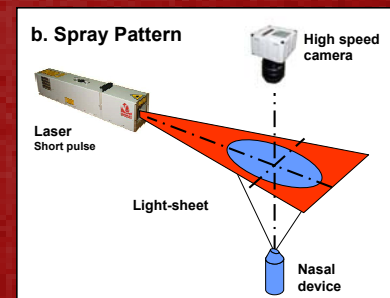
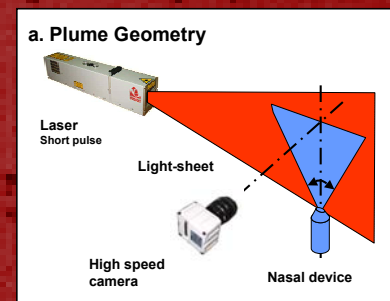


Fig 1. Schematic geometry of lightsheet orientation for (a.) Plume geometry (b.) spray pattern

SPRAY PATTERN ANALYSIS

The spray pattern analysis is used to provide information on the cross section of the spray (Fig.1b) To obtain this information the Oxford Lasers EnVision system was used. A sequence of images was captured at 500Hz and EnVision software used to analysis the image sequence. The analysis procedure combines the sequence of images to produce a single image (Fig. 2). User defined peak intensity identifies the extent of the pattern. Advanced fitting routine [4] is used to report the properties of the pattern. Figure 3 shows the pattern and ellipse fitted, results show goodness of fit 89%, angle of inclination 148° , major axis 35.22 mm and minor axis 30.39mm.

Fig 2. Image from time averaged sequence acquisition 500fps

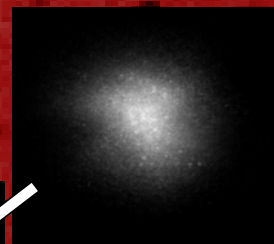
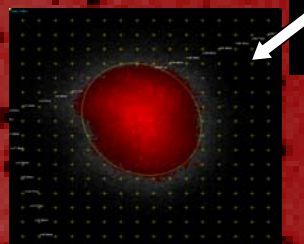


Fig 3. Composite image of best ellipse fitted to the 20% contour

PLUME GEOMETRY ANALYSIS



Fig 4. Snap shot image of plume geometry data acquisition 500 fps

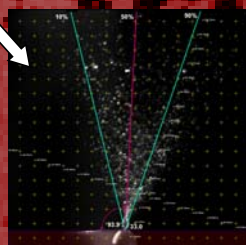


Fig 5. Plume geometry analysis of single image plume geometry 33.0°

The plume geometry provides information on the longitudinal section of the spray (Fig. 1a) when in the fully developed phase of the actuation. In the same way as spray pattern a sequence of images was captured for the actuation and image for the defined time delay (snap shot) identified for analysis(Fig 4). The extent of the plume geometry was determined using EnVision software[4]. The analysis determines the plume geometry based on defined limits of the integrated intensity in the image. Fig 5 shows the result of the analysis, plume geometry 33° and plume orientation 93.9° .

DISCUSSION

High speed non-invasive imaging system provides information necessary to characterise the spray from a nasal device as requested by the FDA. The results generated are electronically based and contained in a single file comprising of calibration information, analysis, system setting and acquired images. To protect this information this file can be electronically signed to provide compliance with the FDA's 21 CFR Pt11. The results show a plume geometry of 33° and spray pattern of, major axis 35.22mm and minor axis 30.39mm.

By using short laser pulsed system, image quality is improved and the range of information that can be obtained extended, to include information on event duration and flow field velocity information. Figure 6 shows the average velocity vector magnitude and direction during one actuation of the device. The velocity ranges from 0.56 to 11.13 m/s. The modular design of the system allow easy reconfiguration system, for use on pMDI and DPI devices.

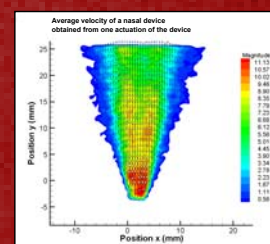


Fig 6. Velocity profile of plume from Nasal device, captured at 1000Hz. (Colour indicates velocity – red is faster, blue is slowest)

CONCLUSION

Non-invasive laser image systems are becoming established as a alternative to physical methods, providing detailed information on the spray characteristics to conform with FDA. A electronic files containing the results can be electronically signed.

References

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- [4] Envision: Patternate software v0.9. Oxford Lasers, Oxon, UK, 2002.