Evaluation of Plume Geometry and Spray Pattern from a Dry Powder Devices using FDA Guidance

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Summary

General plume characterisation first became a regulatory requirement in 1998[1], with the introduction of the CMC draft guidance on pMDIs and DPI devices. The document outlined the basic data requirement for spray pattern and plume geometry measurement for pMDI devices. The requirements are designed to monitor consistency and quality of a device when actuated. In 2003 guidance for Nasal products on BABE (Bioavailability and Bioequivalence)[2] provided details on data required and the distances where pattern information is obtained. In 2013, draft guidance on pMDIs[3] start to implement the same requirements as those laid down in the Nasal guidance in 2003[2]. At present there is no requirement for the measurement on plume geometry and spray pattern for DPI devices, because of the complexity of imaging the powder flow from DPI devices. The poster outlines the techniques used for the evaluation and implementation of FDA guidance on DPI devices. A vacuum pump operating at 50l/min extracts powder from the DPI device through Oxford Lasers OL test chamber. FDA guidances[1,2], provides details on plume geometry and spray pattern, image collection and evaluation. The Spray patterns were collected at 2 distances 3cm and 6cm from the exit of the device. The results show the Plume geometry varies between 15 & 17 Degrees across 3 replicates with mean event duration of 82ms. The spray pattern ovality results at 3cm show 12.7% variation & 6cm results show 6.1% variation. The poster clearly shows that FDA guidance can be applied to DPI devices.

Introduction

Plume characterisation is not confined to the medical device sector. In the automotive sector; characterisation of fuel spray has been a standard technique for many years. Information on the pattern and geometry are important parameters in the assessment of the fuel injection process. In 1992 Nishida[4] used Oxford Lasers imaging system to look at plume geometry and spray pattern from a fuel injector. In the medical device sector, the last two decades produced a significant number of papers and workshops on spray characterisation. These techniques are used to assess device actuation quality and consistency. As a result the Food and Drug Administration (FDA) released the first draft, CMC Guidance in 1998[1]. The draft guidance focused on pMDI & Dry Powder devices and introduced the need for Spray Pattern and Plume geometry details as part of regulatory submissions for pMDI devices. The guidance[1] did not place the same requirements for shape characterisation for DPI devices because of complexity in implementation. In 2003[2], guidance on Bioavailability and Bioequivalence studies (BABE) for Nasal Aerosols and Nasal Sprays was released. The document introduced additional details on data requirements for spray pattern and plume geometry measurements. The guidance defined when the plume geometry details are captured and identifies the distance where the spray patterns are collected. In 2013[3], draft guidance on Albuterol Sulphate starts to bring inline the pMDI requirements with Nasal guidance[2] and provides greater clarity on the data requirement for pMDI testing and acceptance.

In 2012, publication by Shur et al[5] in conjunction with $FDA_{(USA)}$ examined capsule based DPI devices, the research article examined the effect of device design on the In Vitro performance and comparability, but spray pattern and plume geometry were not looked at. For DPI devices, there are only a small number of papers / posters available which report shape characterisation information[6]. The measurement of shape characterisation on DPI devices are seen as difficult to complete because of the difficulties imaging the powder flow from the device.

The following poster considers how FDA guidance on spray pattern and plume geometry could be applied to DPI devices in a consistent manner with a defined protocol. The poster outlines how characterisation information on the spray pattern and plume geometry are captured. Using EnVision patternate software, spray pattern and plume geometry were determined at two positions, over multiple actuations from a DPI reservoir device.

Methodology;

The evaluation was completed on a reservoir dry powder device, *"Easyhaler®"* from Orion Pharma. The *"Easyhaler®"* device delivered 8mg dose of *"SV003 Lactose"* supplied from DFE pharma. The Easyhaler® device was operated in accordance with manufacturer guidelines. For all configurations a minimum of 3 replicates were obtained for each configuration.

The *EnVision* QS system (Figure 1), was configured with the OL DPI test chamber. Figure 2 shows the typical configuration for (a.) plume geometry and (b.) spray pattern for DPI devices.

The OL test chamber allows a camera and pulsed laser to capture high quality blur-free images of the lactose as it is evacuated from the device, through the test chamber. A vacuum pump connected through a solenoid valve was operated at 50l/min to extract the powder from the *Easyhaler®* device. The Fire*FLY* laser, generates a laser light-sheet using integrated light-sheet optics, the optics control the divergence of the light from the laser to generate a fine light-sheet of 1mm in thickness. The orientation of the light-sheet is determined based on the type of information required. For *plume geometry*, the light-sheet dissects the plume along the centre line, and is parallel to the flow of the lactose existing the device (figure 2a). For *spray pattern* the light-sheet dissects the plume at a specified distance of 3cm and 6cm from the exit of the device and perpendicular to the flow of the lactose existing the device (figure 2b).

A high-speed camera operating at 500Hz, captures images of the lactose *SV003* particles moving through the light-sheet. The captured images are processed by the EnVision application software, to provide detailed data on the plume geometry, spray pattern at 3cm and 6cm from the device & event duration.

The imaging and data analyses was carried out with reference to FDA guidance documents[2 & 3].

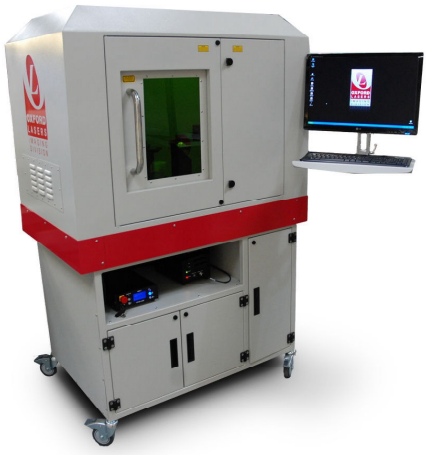

Figure 1. EnVision QS, with DPI configuration System

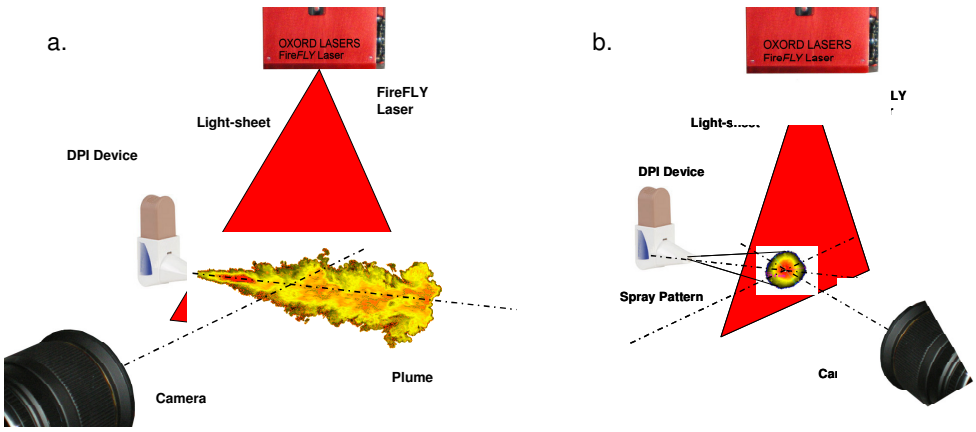

Figure 2. Hardware configuration for (a.) Plume Geometry, (b.) Spray Pattern

Results and Discussion

Results show consistent data across the 3 replicates. For plume geometry, results in Table 1 show, 8.9 % variation in the data for the plume angle, from 15.05 degrees to 17.52 degrees. At 6cm the mean width from the device was 2.15cm. The mean plume length was 16.1cm. The event duration varies from 74ms up to 98ms a variation of 16%. Figure 3 shows plume geometry details from the DPI device.

Table 1 Plume Geometry data for 3 event from a single device

No.	Plume Angle (^{O})	Plume Width at 6 cm	Length (cm)	Duration time (ms)
1	17.52	2.09	16.87	98.00
2	15.05	2.45	16.39	74.00
3	15.08	1.90	15.08	76.00
MEAN	15.89	2.15	16.11	82.67
STDEV	1.42	0.28	0.92	13.32
% RSD	8.93	12.93	5.73	16.11

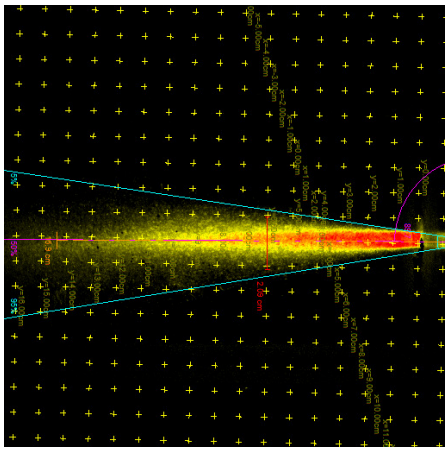

Figure 3 Image of Plume Geometry from DPI device

The spray pattern results shown in Table 2 provide details on Dmin, Dmax, Area & ovality ratio. Comparisons of the ovality ratio show a 12% variation at 3cm, at 6cm the variation is reduced to 6%. The area results show variation of 10.03% and 9.29% at 3cm and 6cm respectively. The data show at 6cm the pattern is more consistent than at 3cm. Figure 4, shows sample images of the spray pattern at 3cm and 6cm.

Table 2 Spray Pattern results for 3 repetitions @ 3 & 6cm from the DPI device

Rep	Spray Pattern at 3cm				Spray Pattern at 6cm			
	Area (cm^2)	Dmax (cm)	Dmin (cm)	Ovality Ratio	Area (cm^2)	Dmax (cm)	Dmin (cm)	Ovality Ratio
1	0.90	1.47	0.80	1.84	1.33	1.76	1.03	1.71
2	0.87	1.50	0.80	1.87	1.34	1.70	1.12	1.51
3	1.05	1.43	0.97	1.48	1.13	1.60	0.97	1.65
MEAN	0.94	1.46	0.85	1.73	1.27	1.68	1.04	1.62
STDEV	0.09	0.04	0.10	0.22	0.12	0.08	0.08	0.10
% RSD	10.03	2.57	11.18	12.72	9.29	4.71	7.34	6.17

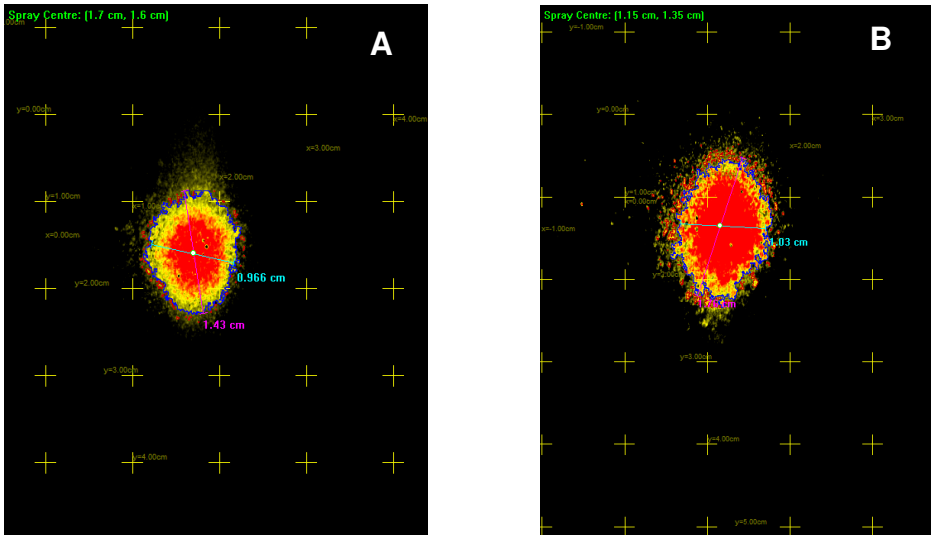

Figure 4 Image of Spray Pattern from DPI device at 2 positions, (A) 3cm, (B.) 6cm

Conclusion

Draft guidance developed by the FDA for pMDI and Nasal devices for the characterisation of spray pattern and plume geometry has been applied successfully to a dry powder device. Using OL EnVision system with DPI test chamber, the system captured high quality image of the spray pattern and plume geometry.

References

1. Guidance for Industry: **Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation**. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) October 1998 CMC

2. Guidance for Industry: **Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action**. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Biopharmaceutics April 2003

3. Draft **Guidance on Albuterol Sulfate**, Recommended Apr 2013, Revised Jun 2013 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

4. Masahiko Nishida, et al; **Observation of High Pressure Fuel Sprays with Laser Light Sheet Method**, SAE Technical Paper Series 920459, 1992

5. J. Shur, S. Lee, W. Adams, R. Lionberger, J. Tibbatts, & R. Price; **Effect of Device Design on the In Vitro Performance and Comparability for Capsule-Based Dry Powder Inhalers**, Research Article, AAPS Published online 22 June 2012

6. Shur, J., Murphy, S.D., Price, R. **Visualisation of Powder Fluidisation and Particle Entrainment from Dry Powder Inhalers.** Drug Delivery to the Lungs 21 P126 - 129