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Evaluation of droplet velocity and size from nasal spray devices using phase Doppler anemometry (PDA)

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ABSTRACT

To determine aerosol deposition during the inhalation drug delivery, it is important to understand the combination of velocity and droplet size together. In this study, phase Doppler anemometry (PDA) was used to simultaneously characterize the aerosol velocity and droplet size distribution (DSD) of three nasal spray pumps filled with water. Thirteen sampling positions were located in the horizontal cross-sectional area of the nasal spray plumes at a distance of 3 cm from the pump orifice. The results showed droplet velocities near the center of the spray plume were higher and more consistent than those near the edge. The pumps examined showed significant differences in their aerosol velocity at the center of the spray plume, which suggest that this metric might be used as a discriminating parameter for in vitro testing of nasal sprays. Droplet size measurements performed using PDA were compared with results from laser light scattering measurements. The ability of PDA to provide simultaneous measurements of aerosol velocity and size makes it a powerful tool for the detailed investigation of nasal spray plume characteristics.

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1. Introduction

Inhalation drug products are usually characterized via measurement of shot weight, spray pattern, plume geometry, and droplet size distribution (DSD). These parameters are recommended in the FDA Draft Bioequivalence Guidance (U.S. FDA, 2003) and widely used by the pharmaceutical industry for assessment of equivalence between two nasal spray products.

Defining the sites of aerosol deposition is a universal difficulty which manufacturers of inhalation drug products have to overcome. According to the inertial impaction theory (Ranz and Wong, 1952), the combination of velocity and droplet size together determines aerosol deposition. As an example of the aerosol deposition problem, large aerodynamic diameter with high emitted velocity leads to a high oropharyngeal deposition (Dhand, 2005) for CFC-pMDI products. For nasal spray products, if spray velocity and droplet size are decreased, the nasal sprays will cover more area, be retained longer, and penetrate the nose better (Kimbell et al., 2007). The spray duration is also important for coordination of inhalation (Hochrainer et al., 2005).

Several techniques have been developed for measuring the spray velocity of inhalation drugs. Dhand et al. (1988) suggested a high-speed video recording method to analyze the aerosol velocity, and this technique has been adopted by others (Hochrainer et al., 2005). With this method, the velocity of the front edge of the aerosol cloud was used as first-order approximation of the droplet velocity. By photographing the developing aerosol cloud with a video camera at 100 frames per second, the length from the nozzle of the inhaler to the aerosol front on each frame was measured and assumed as a function of time. The time derivative of this function gave the aerosol velocity. They used this method to compare the aerosol velocities of several inhalers at the fixed length of 10 cm and showed that video recording is a convenient method for spray velocity measurement.

Particle image velocimetry (PIV), a technique which uses a high-speed non-invasive imaging system with a short pulsed laser light source, has also been used to obtain instantaneous velocity measurements for nasal sprays (Williams et al., 2007; Murphy et al., 2004). In a normal PIV setup, a pair of laser pulses (100 ns interval) impinges on the aerosol, and a fast CCD camera detects the scattered light and records the scattering signal as a pair of camera frames. The frames are next analyzed to obtain a velocity distribution. As an example, in Williams et al. (2007), PIV measurements were made for several nasal spray pumps containing water. Average aerosol velocities were found to vary between 8.4 and 12.8 m/s.

Phase Doppler anemometry (PDA) is a single point optical measuring technique which enables the velocity of droplets or particles conveyed by a fluid flow to be measured in a non-intrusive, real-time manner (Albrecht, 2003). In the PDA system as shown schematically in Fig. 1, two coherent laser beams are focused

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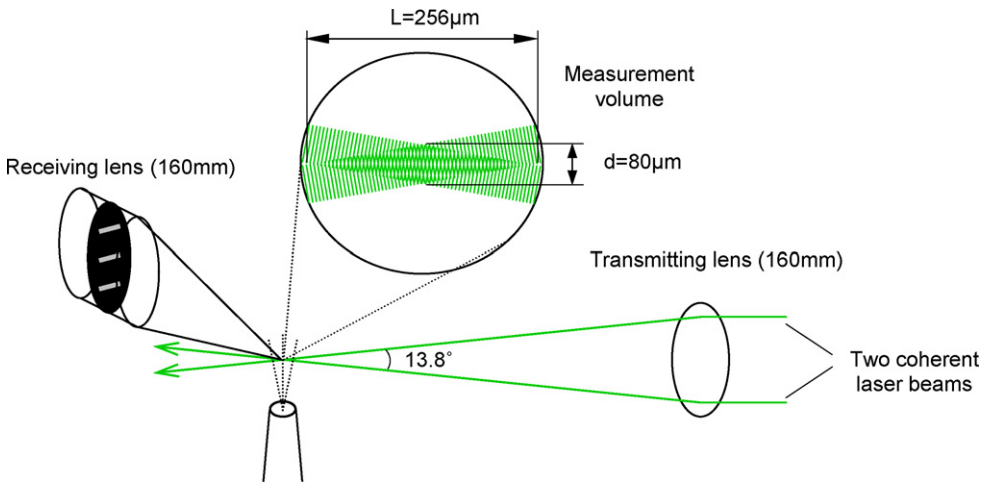

Fig. 1. Schematic of PDA system. The two coherent laser beams are focused by a 160 mm lens and intersect with a 13.8° angle to form a measuring volume of 80 μm in diameter and 256 μm in length.

by a 160 mm lens and intersect with a 13.8° angle to form a measuring volume of 80 μm in diameter and 256 μm in length. By analyzing the Doppler-equivalent frequency of the laser light scattered (intensity modulations within the crossed-beam probe volume) by the droplets within the flow, the droplet velocity can be determined. Droplet size is determined by measuring the phase difference between two Doppler bursts detected by two detectors at different angular positions. In this way, the PDA can simultaneously measure the size and velocity of individual droplets passing through the measurement volume. In this study, PDA is used to determine the spray velocity and droplet size distribution for several nasal spray pumps to develop an understanding of the droplet velocity distribution in nasal spray plumes.

2. Methods

Nasal spray pumps were actuated upward using a SprayVIEW NSx automated actuator (Proveris Scientific Corporation, Marlborough, MA). Proveris Viota software (Version 5.2.1) was used to control actuation of the NSx. The spray plume was translated through the crossing point of the laser beams by mounting the NSx atop a Jet MDT-77 cross-index stage (Jetform Company). The actuation system is shown in the insert of Fig. 2.

Two nasal spray pumps A and B (with curved and straight tubes, respectively) assembled with 20 ml bottles, and pump C assembled with a 10 ml bottle were filled with deionized water and tested in this study. All the nasal spray units were provided by Pfeiffer of America, Princeton, NJ and are claimed to deliver 100 μL per actuation, equivalent to 100 mg water per actuation.

For pumps A and B, actuation profiles were symmetric with a stroke length of 5.3 mm, velocity of 70 mm/s, acceleration of 2500 mm/s^2, and hold time of 200 ms. For pump C, the actuation profile was also symmetric with stroke length of 8.4 mm, velocity of 50 mm/s, acceleration of 4000 mm/s^2, and hold time of 100 ms. Stroke lengths used were the maximum stroke lengths as determined using the Proveris Viota software; other parameters were as

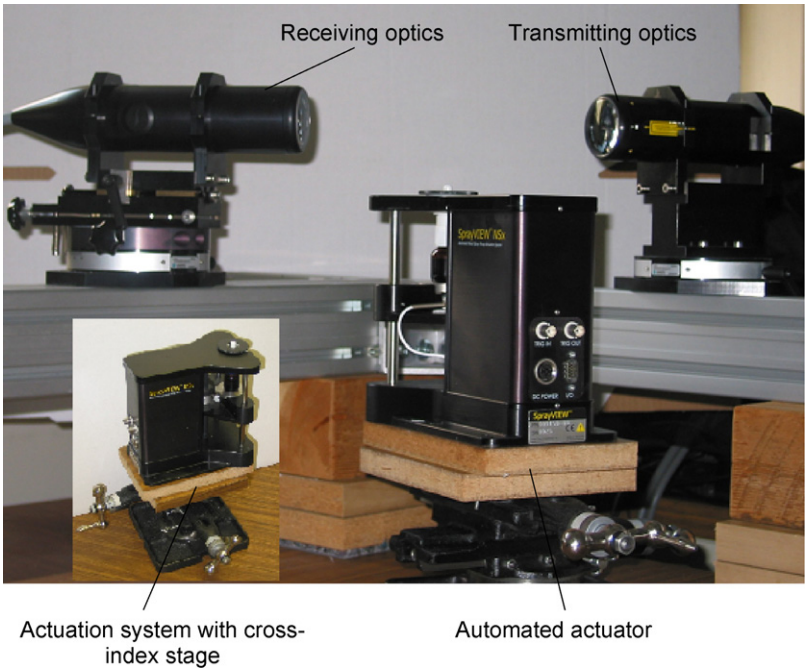

Fig. 2. The experimental setup for nasal spray velocity measurements, including transmitting optics, receiving optics, and the actuation system. The insert shows details of the actuation system with the cross-index stage.

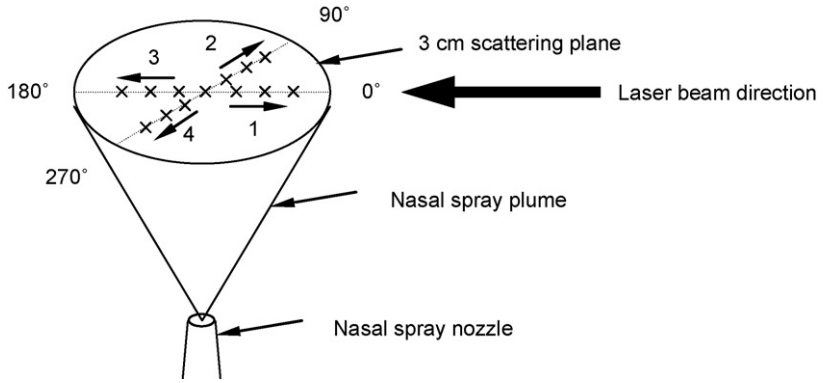

Fig. 3. Measurement points in the 3 cm scattering plane from the orifice. Thirteen sampling positions are marked: one at plume center position, and four each at 5, 10 and 15 mm from center on four sampling directions. The 1–4 sampling directions in the plume have 0°, 90°, 180°, and 270° with incoming laser beam direction, respectively.

used in previous work (Guo et al., 2008, 2009) and were adopted for the two types of nasal spray pumps, respectively.

A 1D PDA System (Dantec Dynamics, Skovlunde, Denmark) with FlowLite transmitting optics (f = 160 mm) and FiberPDA receiving probes (f = 160 mm) was used to measure the spray velocity throughout the nasal spray plumes. The BSA P60 Flow and Particle Processor of the PDA system were controlled by BSA Flow Software V.4 to monitor the PDA system during the measurements.

The experimental setup for nasal spray velocity measurements is shown in Fig. 2. The velocity and DSD of nasal sprays were measured at a vertical distance of 3 cm above the spray pump orifice. Measurements within the 3 cm plane of the spray plume were made at the 13 positions shown in Fig. 3 where the laser beams impinge upon the spray plume from the right. Sampling points were selected at 5 mm intervals along either axis as shown. Three repeated measurements were performed for each sampling point with 20 nasal spray actuations per measurement (typically, 1000–4000 droplets were counted for each measurement). Fig. 4 illustrates the index stage translations required to access points along the two axes.

For thick and/or dense plumes, the laser may not penetrate completely through the plume. The penetration will also depend upon the portion of the plume examined (*i.e.*, center vs. edge). This raises a concern that artifacts (such as those arising from double refraction, scattering, etc.) may be introduced which affect measurement results. The presence of artifacts will make it difficult to determine if measured velocity differences at the same radial distance but in different directions around the center are real, or artifactual.

To answer these questions and validate the velocity measurements, a "rotational" measurement strategy was designed and results compared with those from the translational method described above. Instead of moving the nasal spray pump in the manner shown in Fig. 4, the pump was offset from the laser crossing point by 10 mm and rotated clockwise through 90° intervals as shown in Fig. 5 where the angular designations refer to the original

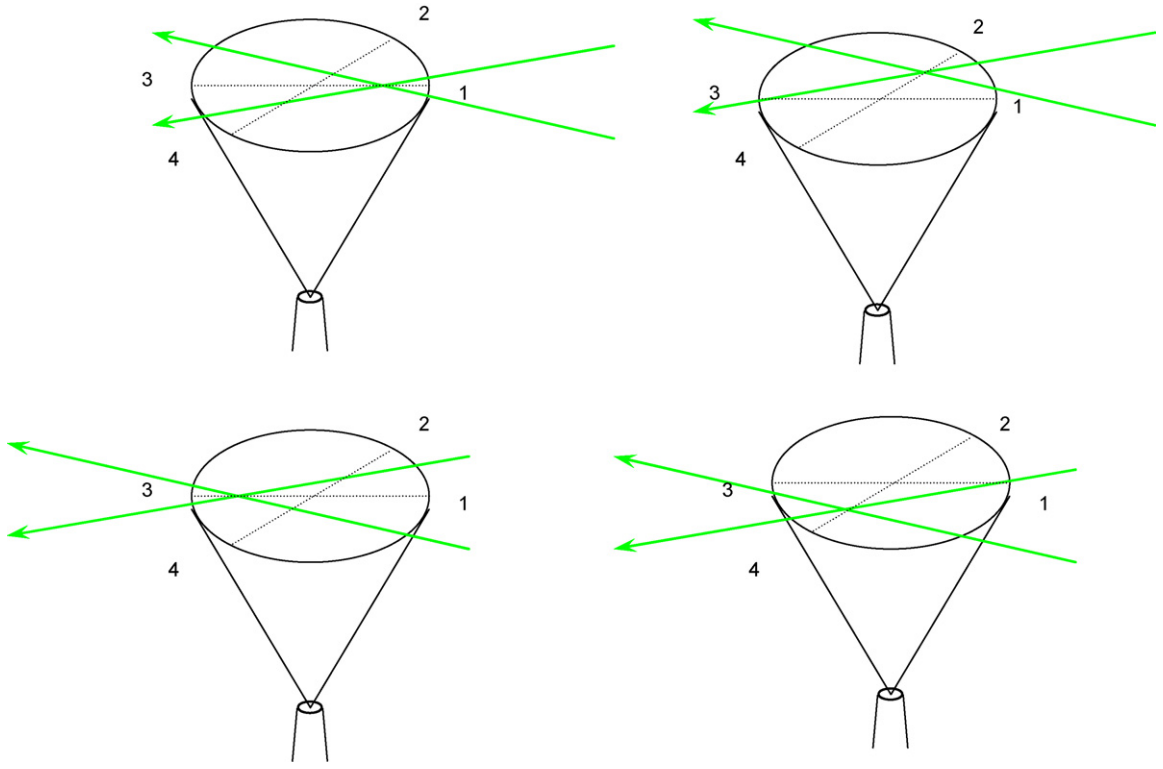

Fig. 4. Diagrams showing the arrangement for translational measurement method. Relative to point 1, the nasal spray pump was moved toward the laser and to the left relative to the laser axis for point 2, toward the laser for point 3 and toward and to the right for point 4.

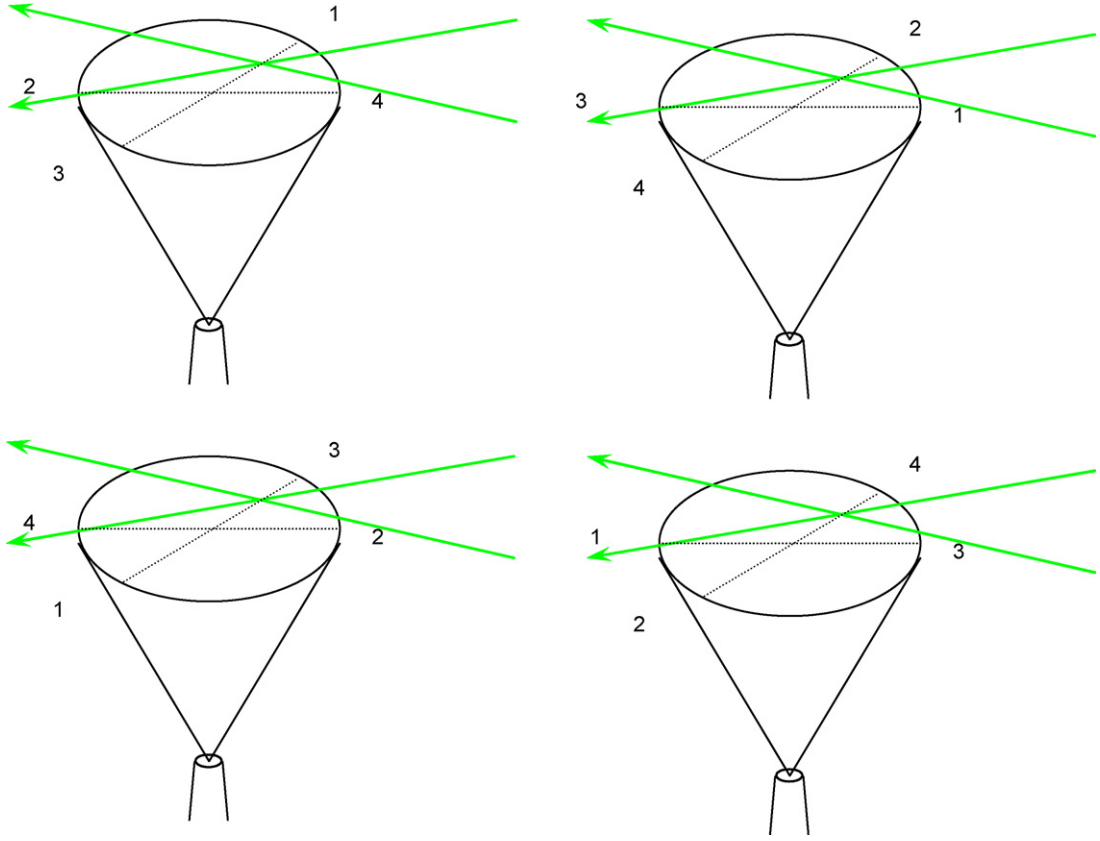

Fig. 5. Diagram showing the arrangement for rotational measurement method. The pump is offset from the laser crossing point by 10 mm and rotated clockwise through 90° intervals.

orientation. In this way, the laser crossing point will be at the same relative locations within the plume for the four different sampling spots at a fixed radical distance from the center and thus should experience similar flow field and light scattering conditions.

A Sympatec HELOS/BF (Sympatec GmbH., Clausthal-Zellerfeld, Germany) was also used to measure the droplet size distribution of the three samples and results were compared with those from PDA measurements. A lens with 100 mm focal length (R3) provided a measurement range of 0.9–175 μm. WINDOX 5 software was used for control of the instruments and evaluation of droplet size analysis data.

3. Results and discussions

3.1. Aerosol velocity

Table 1 and Fig. 6 show the velocity measurement results for aerosols generated by the three nasal spray pumps at 3 cm from the orifice. Measurements were made at four locations within the spray plume as illustrated in Fig. 4. Relative to point 1, the nasal spray pump was moved toward the laser and to the left relative to the laser axis for point 2, toward the laser for point 3 and toward and to the right for point 4.

The three tested nasal spray pumps showed different patterns of velocity distribution along the radial directions. At 3 cm from the orifice, the aerosol plumes generated by pumps A and B are distorted and not centered on the device. That is, the region of highest velocity droplets is observed to be 5–10 cm away from the physical center and the plume is not symmetric around the region of highest droplet velocity. The aerosol plume generated from pump C appears to be more centered with the largest velocity observed at the center point. The spray pattern area of the plume generated from pump C is much smaller than those from pumps A and B. The velocity drops quickly from the center to the edge, and insufficient aerosol is detected at 15 cm from the center to enable velocity measurement at those locations.

Due to the asymmetry of the spray plume and the turbulent nature of the spray, the velocity distribution within the nasal spray plume is complicated. The aerosols near the center of a spray plume showed smaller RSDs than those near the edge, which indicates

Table 1
Aerosol velocities of 3 nasal spray pumps measured by PDA in the cross-sectional area 3 cm from the orifice[a].

Sampling direction[b]	Center	5 mm	10 mm	15 mm
Aerosol velocities of pump A (m/s)				
1	10.8 (0.2)	12.2 (0.1)	12.1 (0.4)	12.2 (0.3)
2		12.1 (0.2)	12.1 (0.2)	10.8 (0.3)
3		10.6 (0.2)	9.8 (0.4)	8.6 (0.6)
4		7.3 (0.1)	8.1 (0.2)	7.4 (0.5)
Aerosol velocities of pump B (m/s)				
1	7.5 (0.2)	11.5 (0.1)	9.6 (0.3)	7.3 (0.5)
2		8.6 (0.2)	7.4 (0.2)	4.9 (0.5)
3		8.0 (0.2)	9.2 (0.4)	6.7 (0.1)
4		8.3 (0.1)	10.8 (0.2)	8.3 (0.5)
Aerosol velocities of pump C (m/s)				
1	11.3 (0.2)	6.1 (0.1)	1.8 (0.6)	NA
2		8.2 (0.3)	3.8 (0.7)	NA
3		6.8 (0.1)	3.7 (0.3)	NA
4		4.8 (0.3)	1.9 (0.2)	NA

[a] Numbers in brackets represent the standard deviation of all the measurements at the indicated measurement points.
[b] Per Fig. 3.

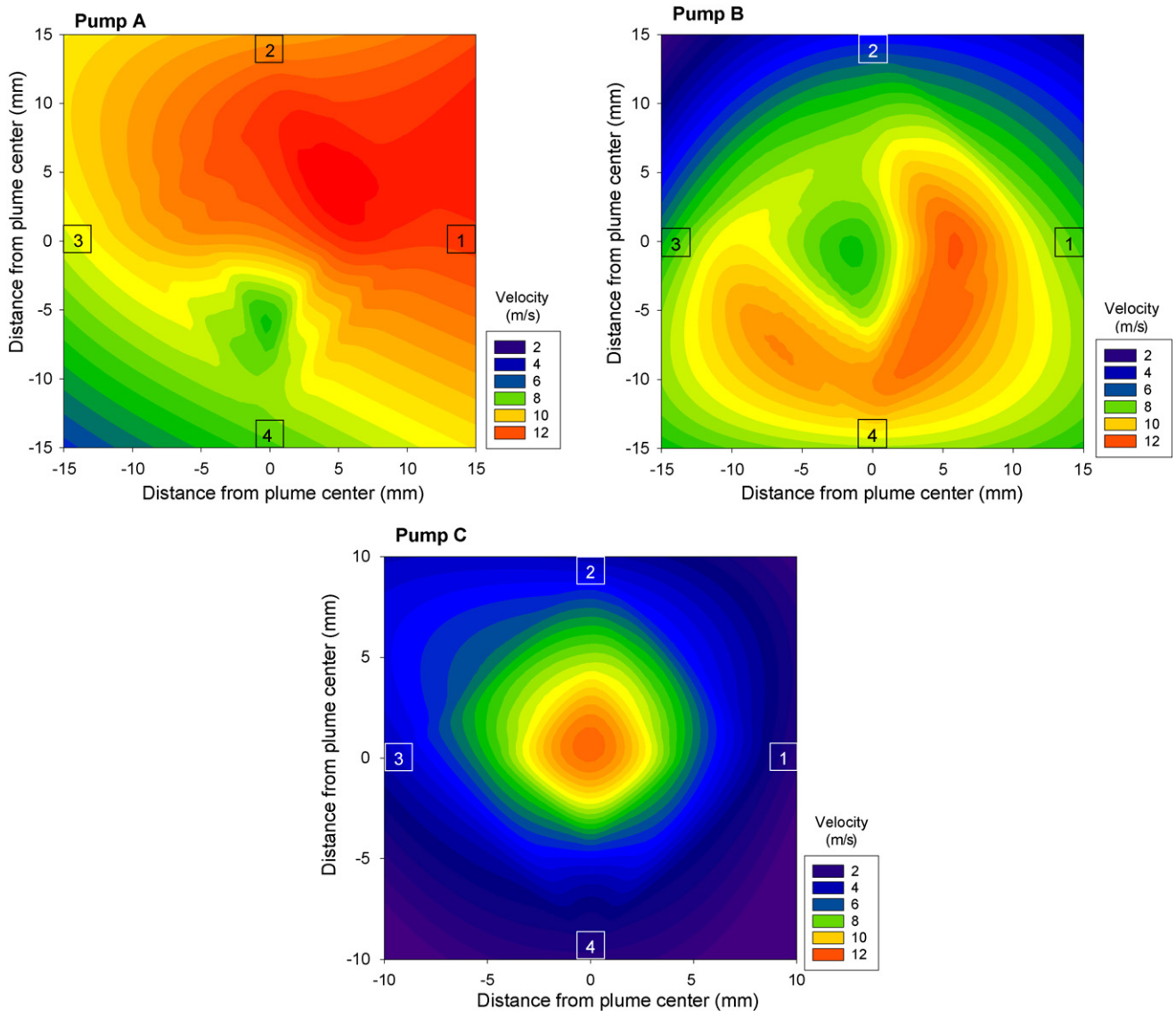

Fig. 6. The droplet velocity distribution in the nasal spray plumes of three nasal spray pumps. Locations per Fig. 4 are indicated by boxed numerals 1–4.

that the behavior of the aerosols near the center of a plume are relatively more consistent. For all three tested nasal spray pumps, significant differences are observed for the spray velocities at the same radial distance in different directions around the center. The velocity difference at the same radial distance can be as large as 40% between four different directions.

3.2. Velocity measurement validation

As indicated above, differences observed among the measurement points as illustrated by Fig. 4, may be due to double refraction, scattering, etc. To test this hypothesis, measurements were made as illustrated in Fig. 5 and the measured aerosol velocities were compared to those at 10 mm from the center using the "translational" positioning shown in Fig. 4. As shown in Table 2, the droplet velocities measured at the same sampling spots are not significantly different between the two measurement methods. This indicates that the depth into the nasal spray plume of the laser crossing point does not introduce measurement artifacts for the water samples examined here. Thus, the velocity differences observed along the four different axis directions represent true plume asymmetry with respect to the velocity distribution.

3.3. Droplet size distribution measurements

The PDA technique also provides measurement of aerosol droplet size. The PDA configuration used in this study allows measurement of droplets in the range 0–50.8 μm.

Droplet size measurements were performed at locations as illustrated in Fig. 3 at 3 cm from the nasal spray pump orifice, results

Table 2
The measurements of aerosol velocities at 10 mm sampling spots from the center using translational and rotational methods[a]. Application of the t-test indicates differences between results from the translational and rotational methods are not statistically significant at the 95% confidence level.

Aerosol velocities of pump A (m/s)		
Sampling direction[b]	Translational (Fig. 4)	Rotational (Fig. 5)
1	12.1 (0.4)	11.6 (0.2)
2	12.1 (0.2)	12.2 (0.1)
3	9.8 (0.4)	10.2 (0.2)
4	8.1 (0.2)	8.2 (0.2)

[a] Numbers in brackets represent the standard deviation of all the measurements at the indicated measurement points.
[b] Per Fig. 3.

Table 3
Droplet size distribution (represented by Dv50) of 3 nasal spray pumps measured by PDA and laser light scattering (LLS)[a]. Dv50 values indicated for PDA are the average of measurements in the four directions as shown in Fig. 3.

	Droplet size distribution—Dv50 (μm)				
	PDA sampling position				LLS
	Center	5 mm	10 mm	15 mm	Center
Pump A	34.8 (0.6)	34.3 (1.2)	36.0 (0.6)	38.7 (1.4)	33.4 (0.4)
Pump B	31.7 (2.1)	30.5 (1.7)	34.7 (3.8)	36.7 (1.9)	28.0 (0.1)
Pump C	41.9 (0.4)	40.3 (0.5)	38.6 (3.0)	NA	37.8 (0.9)

[a] Numbers in brackets represent the standard deviation of all the measurements at the indicated distance.

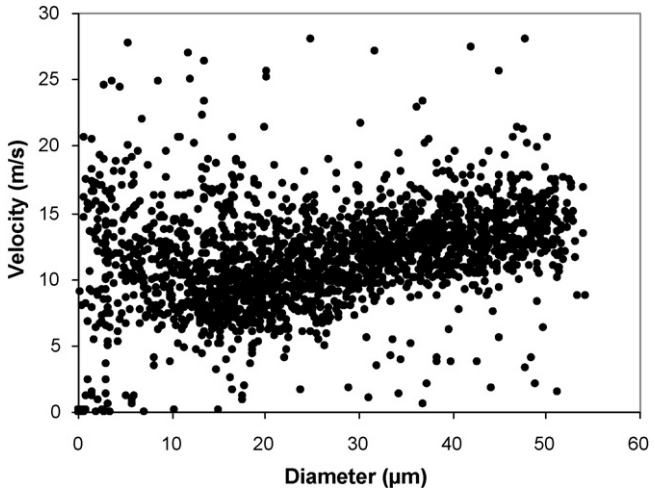

Fig. 7. Droplet velocity vs. diameter for pump A, measured by PDA.

are shown in Table 3. The Dv50 values from PDA are the average of measurements in four directions as shown in Fig. 3. For pump A and B, larger droplets are observed towards the edge of the plume; while for pump C, droplet size decreases from the center toward the edge.

The same nasal spray samples were also measured by the laser light scattering technique using the same actuation parameters. The laser light scattering results indicate a smaller droplet size than what was observed using PDA. Unlike PDA, a number-based measurement with a small measuring volume of 80 μm diameter, laser light scattering uses an ensemble method with a large measuring volume coming from its 18 mm diameter laser beam. While laser light scattering provides greater statistical confidence, it cannot provide detailed information regarding different locations within the plume.

3.4. Aerosol velocity vs. size

The ability of the PDA system to simultaneously measure both velocity and size of a single droplet allows us to link these two parameters and gain additional information regarding aerosol behavior than is available from other measurement techniques. Fig. 7 shows a scatter plot of size vs. velocity for 2000 droplets in a nasal spray plume produced by pump A. From the slight upward slope of the plot, it appears that, for this pump, droplets with larger size tend to have higher velocities. The other two pumps show the same trend. This finding is supported by other research (Takeuchi et al., 2004) which employed interferometric laser imaging technique (ILIDS) to measure droplet size and velocity in a spray. Along the spray central line, smaller droplets are decelerated rather quickly, whereas the inertia of the larger droplets is associated with a slower decrease of their axial velocity.

4. Conclusions

In this study, we demonstrated that nasal spray aerosol velocity can be successfully measured using a PDA system. For the three nasal spray pumps examined in this study, droplet velocities near the center of the spray plume were higher and more consistent than those near the edge. The pumps examined showed significant differences in their aerosol velocity at the center of the spray plume, which suggest that this metric might be used as a discriminating parameter for in vitro testing of nasal sprays. The PDA technique provides simultaneous measurements of aerosol velocity and size, thus making it a powerful tool for the detailed investigation of nasal spray plume characteristics.

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