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Research Article

Assessment of the Influence Factors on Nasal Spray Droplet Velocity Using Phase-Doppler Anemometry (PDA)

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Abstract. Droplet velocity is an important parameter that can be used to characterize nasal spray products. In this study, a phase-Doppler anemometry (PDA) system was used to measure the droplet velocities of nasal sprays. A survey of seven commercial nasal spray products showed a range of droplet velocities from 6.7 to 19.2 m/s, all significantly different from each other. A three-level, four-factor Box–Behnken design of experiments (DOE) methodology were applied to investigate the influences of actuation parameters and formulation properties on nasal spray droplet velocity using a set of placebo formulations. The DOE study shows that all four input factors (stroke length, actuation velocity, concentration of the gelling agent, and concentration of the surfactant) have significant influence on droplet velocity. An optimized quadratic model generated from the DOE results describes the inherent relationships between the input factors and droplet velocity thus providing a better understanding of the input factor influences. Overall, PDA provides a new *in vitro* characterization method for the evaluation of inhalation drugs through assessment of spray velocity and may assist in product development to meet drug delivery equivalency requirements.

KEY WORDS: design of experiments; droplet velocity; nasal spray; phase-Doppler anemometry.

INTRODUCTION

Inhalation drug products can be characterized via measurements such as shot weight, spray pattern, plume geometry, and droplet size distribution (DSD). These parameters are recommended by the FDA (1–3) and have been used by the pharmaceutical industry for assessment of equivalence between two nasal spray products. In addition to the abovementioned parameters, which describe the dosage amount, spray plume shape and droplet size, the impaction force, and droplet velocity, which describe how strong or soft a spray plume is and are directly felt by patients, are also useful information for characterizing nasal spray products. Both impaction force and velocity could be used as a discriminative parameter for *in vitro* testing of nasal spray products (4–6).

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 (7). With this technique, droplet velocity can be determined by analyzing the Doppler-equivalent frequency shift of the laser light scattered by the droplets within the flow. The scattering is manifest by intensity modulations within the crossed-beam probe volume, and droplet size is determined simultaneously by measuring the phase difference between two Doppler bursts detected by two detectors at different angular positions. PDA has traditionally been applied to the study of unconfined atomizer sprays and thus far has not been widely used for the assessment of medical inhaler aerosols.

In a recent study, droplet velocities of nasal sprays were measured using PDA (6). The 2-D nasal spray droplet velocity profiles showed that droplet velocities near the center of the spray plume were normally higher and more consistent than those near the edge. Different nasal spray pumps filled with water 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 spray products.

The drug delivery performance of a nasal spray product is greatly influenced by both the formulation properties and the device capabilities (8–10). In previous studies, design of experiments (DOE) methodology was used to elucidate interactions between four factors (actuation stroke length, actuation velocity, concentration of gelling agent, and concentration of surfactant) with respect to their influences on nasal spray shot weight, DSD, spray pattern, plume geometry, and impaction force (5,11). The measured responses were fit to a polynomial model, and an analysis of the polynomial coefficients and their standard errors were used to identify the statistically significant factors and interaction terms for each model.

In this paper, a three-level, four-factor Box–Behnken DOE methodology was applied to investigate the influences of actuation parameters and formulation properties on nasal

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spray droplet velocity using a set of placebo formulations. In addition, seven commercial nasal spray products were surveyed by PDA and the relation between droplet size and velocity was investigated.

METHODS

A 1-D PDA System (Dantec Dynamics, Skovlunde, Denmark) with FlowLite transmitter optics (f=160 mm) and FiberPDA receiving probes (f=160 mm) was used to measure the droplet velocities of nasal spray plumes. The PDA system and data acquisition were controlled by a BSA P60 Flow and Particle Processor operating with BSA Flow Software V.4 (Dantec Dynamics, Skovlunde, Denmark).

The instrumental settings and optical alignment of the PDA system were optimized for nasal spray products, and were validated using a method published in an early paper (6), to insure accurate velocity measurements for spray plumes within the density, size, and velocity range of nasal spray products. The same PDA configuration was used to measure both the placebo samples and commercial nasal spray products described in this paper. The droplet velocities were measured at a distance of 3 cm directly above the nasal spray pump orifice, with 20 actuations per measurement and three replicates per sample. Typically, for each measurement, 1,000–4,000 droplets were recorded, and the mean droplet velocity was reported. The PDA system is shown schematically in Fig. 1.

Nasal sprays were actuated upward using a SprayVIEW NSx automated actuator (Proveris Scientific Corporation, Marlborough, MA), controlled by Proveris Viota software (Version 5.2.1). Actuation stroke lengths for the commercial products were determined using the auto characterization function with the force of contact set at 0.3 kg and force at end of stroke set at 6 kg. Actuation profiles for all the surveyed products were symmetric using an actuation velocity of 50 mm/s, actuation acceleration of 4,000 mm/s^2, and hold time of 100 ms. An exhaust pump was mounted 10 cm above the nasal spray tip to prevent droplet fall back.

The viscosity and surface tension values of the nasal spray formulations were measured by a Fisher Scientific Cannon–Fenske viscometer (size 150), and Fisher Scientific Surface Tensiomat (model 20), respectively.

A three-level, four-factor Box–Behnken DOE design was applied to investigate the influence of four input factors on droplet velocity of nasal sprays using placebo solutions. JMP software (Version 5.1.1, SAS Institute, Cary, NC, USA) was used to generate the DOE matrix and analyze the response surface models. The experimental design allowed us to study quadratic interactions between pairs of the four factors—actuation stroke length, actuation velocity, concentration of gelling agent, and concentration of surfactant—each at three different levels, for a total of 27 experiments.

A Pfeiffer 0.10-mL nasal spray pump and 20-mL bottle (Pfeiffer of America, Princeton, NJ) filled with 18-mL placebo formulations was used in the DOE study. The diameter of the nasal spray pump orifice is 0.3 mm, and the maximum stroke length of the pump is 5.3 mm. Carboxymethylcellulose Sodium (CMC, Avicel RC-591, FMC, Newark, DE) was used to control solution viscosity in the nasal spray formulations. Tween80 (Fisher Scientific, Fair Lawn, NJ) was used to adjust the surface tension.

In addition, the droplet velocity was measured for seven commercial nasal spray products using PDA.

RESULTS AND DISCUSSIONS

Influence of Actuation Parameters and Formulation Properties on Nasal Spray Velocity

A three-level, four-factor Box–Behnken design was used for this study. Four factors, actuation stroke length (3.5, 4.4, 5.3 mm), actuation velocity (30, 50, 70 mm/s), concentration of CMC (0%, 1%, 2%), and concentration of Tween-80 (0%, 2.5%, 5%) were investigated for their influences on the droplet velocity of nasal spray at a distance of 3 cm. Of the four factors, stroke length and actuation velocity are related to the actuation performance of the nasal spray pump; the concentration of CMC and Tween-80 are the dominant factors which influence the formulation viscosity and surface tension, respectively. Selection of the range of these factors was based on previous studies (8,9).

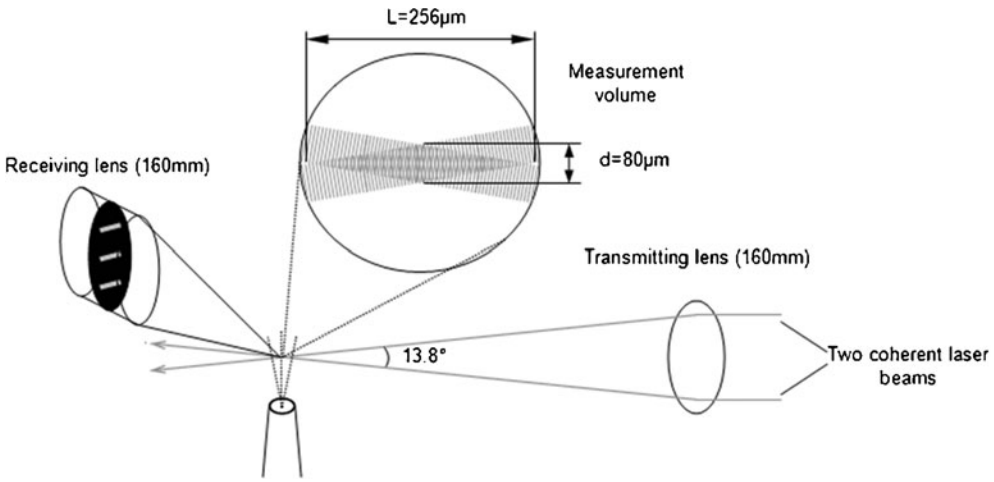

Fig. 1. Schematic of PDA system. The two coherent laser beams are focused by a 160-mm lens and intersect with a 13.8° angle to form a measuring volume of 80 μm in diameter and 256 μm in length

A nonlinear quadratic model of nasal spray droplet velocity generated by regression of the experimental factor values on the measured response is expressed as follows:

$$R = b_0 + b_1S + b_2V + b_3C + b_4T + b_5SV + b_6SC + b_7VC + b_8ST + b_9VT + b_{10}CT + b_{11}S^2 + b_{12}V^2 + b_{13}C^2 + b_{14}T^2 \quad (1)$$

Where R is the response, S, V, C, and T are scaled factors of stroke length, velocity, concentration of CMC and Tween80, and are defined as

$$S = \frac{2 \cdot (\text{StrokeLength} - 4.4)}{(5.3 - 3.5)} \quad (2)$$

$$V = \frac{2 \cdot (\text{Velocity} - 50)}{(70 - 30)} \quad (3)$$

$$C = \frac{2 \cdot (\text{CMC\_concentration} - 1\%)}{(2\% - 0\%)} \quad (4)$$

$$T = \frac{2 \cdot (\text{Tween80\_concentration} - 2.5\%)}{(5\% - 0\%)} \quad (5)$$

and the b_i are scaled estimates of the regression coefficients (the coefficients corresponding to scaled factor values). A positive sign for b_i indicates a constructive effect, whereas a negative sign represents a destructive effect. The magnitudes of coefficients of the scaled factors reflect the importance of those factors to the droplet velocity.

Table I shows the DOE input parameter and results table for the three-level, four-factor Box–Behnken design. Nine placebo formulations which varied with respect to viscosity and surface tension were prepared as aqueous solutions by adjusting the concentrations of CMC and Tween-80. A total of 27 experiments using the factor values described in Table I were performed, and responses were measured for each experiment. The coded design patterns shown in Table I symbolize the scaled factor values (high (+), middle (0), and low (−)) used in each run, in the order of stroke length, actuation velocity, concentration of CMC and Tween80, respectively. The measured droplet velocities (response) are also tabulated in Table I.

The regression coefficients and statistical hypothesis test results of the quadratic DOE model (Eq. 1) are presented in Table II. The DOE results showed that all four input factors had statistically significant influence on droplet velocity. From the effect tests and scale estimates we see that the V, C, T, V^2, C^2, VC, and T^2 terms all had a significant influence on droplet velocity ($p<0.01$), while the S term made a relatively small contribution ($p=0.0312$).

The negative signs of T and T^2 terms indicate that increasing formulation surface tension will lead to smaller droplet velocities, *i.e.*, a softer plume.

For the S, V, and C factors, the scaled estimates of the first-order terms and their interaction terms have positive signs, while the signs of their second-order terms are negative. Since the scaled factor values are in the range of −1 to 1, the first-order terms will have more influence than the second-order terms in most cases. Thus, increasing actuation velocity and/or formulation viscosity will lead to larger droplet velocities, *i.e.*, a stronger plume.

By eliminating all insignificant terms from Eq. (1) ($p>0.05$), an optimized impaction force model (shown in Eq. 3 and Table III) was recalculated using JMP software.

$$R = 15.55 + 0.64S + 2.6V + 1.45C - 0.96T + 2.22VC - 1.99V^2 - 1.97C^2 - 1.1T^2 \quad (3)$$

Figure 2 shows a plot of actual *versus* predicted impaction force from the simplified quadratic model. The simplified model shows good fit with a correlation coefficient (R^2) of 0.91.

The DOE study helps to identify the source of variability in nasal spray product performance, thus giving us a better understanding of how to control the variability. For example, spray plumes with higher droplet velocities may be obtained by increasing the formulation viscosity, reducing formulation surface tension, and/or selecting a pump with desired actuation performance. Moreover, the quadratic models developed from the DOE study quantitatively describe the inherent relationships between the formulation/actuation factors and the droplet velocity, which will assist in product design to achieve desired droplet velocity.

Droplet Velocity Survey of Commercial Nasal Spray Products

Our previous study showed that by measuring droplet velocities near the center of the spray plume where the results were higher and more consistent than those near the edge, PDA could provide adequate discrimination for *in vitro* testing of nasal sprays.(6)

Seven commercially available nasal spray products were surveyed in this paper. For each product, three units from the same lot were tested. The seven products all use somewhat different nasal spray pumps as well as different formulations. The droplet velocities of the seven nasal spray products were measured by the PDA using the optimized configuration for nasal spray products. The results are summarized in Table IV.

The droplet velocities of the surveyed samples ranged from 6.7 to 19.2 m/s, with a relative standard deviation (RSD) less than 5% for three repeated measurements. T test results shows that the droplet velocity differences between the seven products were statistically significant ($p<0.05$), except for that between NasalCrom and Nasarel. This result demonstrates that droplet velocity is a discriminative parameter for *in vitro* testing of nasal spray products.

Results from the abovementioned DOE study suggest that a formulation with higher viscosity will lead to larger droplet velocities, while a formulation with higher surface

Table I. Design of Experiments Table Shows the Coded Design Patterns, Designed Values of the Four Factors (Stroke Length, Actuation Velocity, Concentration of CMC and Tween80)

Experiment number	Pattern	Stroke length (mm)	Velocity (mm/s)	CMC (%)	Tween 80 (%)	Droplet velocity			Droplet size (μm)		
						Mean (m/s)	SD (m/s)	RSD (%)	D10	D30	Dv50
1	00−−	4.4	50	0	0	10.54	0.21	2.0	23.3	27.3	35.8
2	0−0−	4.4	30	1	0	11.34	0.31	2.7	24.8	29.8	40.5
3	−00−	3.5	50	1	0	14.88	0.18	1.2	23.1	27.9	38.9
4	+00−	5.3	50	1	0	16.34	0.46	2.8	23.0	28.0	35.0
5	0+0−	4.4	70	1	0	16.16	0.22	1.4	22.4	27.1	36.9
6	00+−	4.4	50	2	0	15.26	0.12	0.8	24.6	29.3	39.1
7	0−−0	4.4	30	0	2.5	11.24	0.38	3.4	22.6	26.9	36.4
8	−0−0	3.5	50	0	2.5	11.29	0.02	0.2	20.0	24.5	34.5
9	+0−0	5.3	50	0	2.5	11.28	0.13	1.2	18.7	23.1	33.6
10	0+−0	4.4	70	0	2.5	11.03	0.09	0.9	19.9	24.6	35.5
11	−−00	3.5	30	1	2.5	9.06	0.14	1.5	24.2	28.7	38.3
12	+−00	5.3	30	1	2.5	10.06	0.13	1.3	23.6	29.4	42.1
13	0000	4.4	50	1	2.5	15.62	0.11	0.7	21.8	26.1	35.8
14	0000	4.4	50	1	2.5	15.91	0.20	1.2	22.1	26.4	35.8
15	0000	4.4	50	1	2.5	16.82	0.12	0.7	22.5	26.8	35.8
16	−+00	3.5	70	1	2.5	15.83	0.12	0.8	21.4	25.8	35.3
17	++00	5.3	70	1	2.5	16.82	0.21	1.2	19.6	23.8	33.9
18	0−+0	4.4	30	2	2.5	8.91	0.17	1.9	25.1	30.7	41.9
19	−0+0	3.5	50	2	2.5	14.05	0.13	0.9	24.3	28.8	38.3
20	+0+0	5.3	50	2	2.5	16.07	0.15	1.0	23.7	28.1	37.6
21	0++0	4.4	70	2	2.5	17.56	0.09	0.5	22.5	26.8	36.2
22	00−+	4.4	50	0	5	11.20	0.37	3.3	19.2	23.7	34.1
23	0−0+	4.4	30	1	5	8.98	0.32	3.6	24.2	28.8	38.6
24	−00+	3.5	50	1	5	12.52	0.23	1.8	23.8	28.3	38.3
25	+00+	5.3	50	1	5	14.77	0.23	1.6	22.6	27.0	36.5
26	0+0+	4.4	70	1	5	13.42	0.68	5.1	23.0	27.3	36.7
27	00++	4.4	50	2	5	12.14	0.43	3.6	25.1	29.5	38.4

PDA measurements were taken at 3 cm above the nasal spray pump nozzle tip
The arithmetic mean, standard deviation (SD), and relative standard deviation (RSD) for each the droplet velocity experiment were listed in the table
The arithmetic mean diameter (D10), volume mean diameter (D30), and volume median diameter (Dv50) from each PDA experiment were also provided

Table II. The Regression Coefficients and Statistical Hypothesis Test Results of the Droplet Velocity DOE Model

Term	Estimate	Standard error	Prob>|t|
Intercept	16.12	0.53	**<0.0001**
S	0.64	0.26	**0.0312**
V	2.60	0.26	**<0.0001**
C	1.45	0.26	**0.0001**
T	−0.96	0.26	**0.0034**
S*V	0.00	0.46	0.9957
S*C	0.51	0.46	0.2877
V*C	2.22	0.46	**0.0004**
S*T	0.20	0.46	0.6727
V*T	−0.10	0.46	0.8385
C*T	−0.95	0.46	0.0605
S*S	−0.64	0.40	0.1340
V*V	−2.21	0.40	**0.0001**
C*C	−2.19	0.40	**0.0001**
T*T	−1.31	0.40	**0.0061**

Terms with significant influence are marked in bold

tension will lead to smaller droplet velocities. However, the droplet velocity measurement results of the seven commercial products showed there was no direct relationship observed between the droplet velocities and formulation viscosity and/or surface tension. The reason for this disagreement is that the seven commercial nasal spray products all use different nasal spray pumps which are customized based on their own product design to meet their specified delivery performances. For a highly viscous

Table III. Optimized DOE Models for Nasal Spray Characteristic Recalculated by Eliminating all Insignificant Terms ($p>0.05$)

Term	Estimate	Standard error	Prob>|t|
Intercept	15.55	0.42	<0.0001
S	0.64	0.28	0.0340
V	2.60	0.28	<0.0001
C	1.45	0.28	<0.0001
T	−0.96	0.28	0.0031
V*C	2.22	0.48	0.0002
V*V	−1.99	0.40	<0.0001
C*C	−1.97	0.40	<0.0001
T*T	−1.10	0.40	0.0124

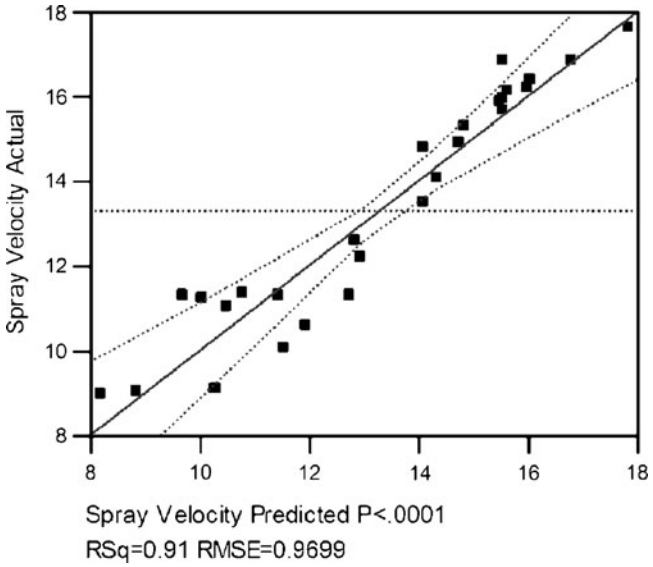

Fig. 2. The correlation between the predicted spray velocity results and the actual results from PDA measurements using optimized DOE model. The *horizontal broken line* shows the mean velocity, the *solid line* is the line of fit, and the *two broken curve lines* describe the 95% confident region relative to the line of fit. *RSq:* R^2, correlation coefficient; *RMSE*: root mean square error

formulation, such as Nasonex, a special type of pump is required for proper operation.

Nasal spray products are a combination of device and formulation. The formulation physical properties (viscosity and surface tension) alone cannot determine the droplet velocity of a nasal spray product. On the other hand, similar droplet velocity can be produced for formulations with large difference in viscosity and surface tension, for example Nasarel and Nasonex, by choosing different pump types.

Since the commercial nasal spray products tested using pumps that were different from the one used in our DOE study, it is impropriate to use the DOE model to predict the droplet velocities of the tested samples.

Droplet Size Measurements by PDA

PDA is an extension of Laser Doppler anemometry and can determine not only the Doppler shift frequency of light refracted by a droplet within the flow (hence its velocity) but the phase shift can also be utilized to derive the diameter of the scattering droplet. The droplet size, reported as the arithmetic mean diameter (D10), obtained from the same PDA measurements in the abovementioned DOE study were listed in Table I. The volume mean diameter (D30) and volume median diameter (Dv50), calculated from the arithmetic mean diameter, are also provided in Table I. The D10, D30, and Dv50 results were subjected to the DOE modeling analysis, but none of the input factors showed statistically significant influence on droplet diameters.

In one of our earlier studies, the influence on droplet size were examined by laser light scattering (LLS) technique using the same lot of nasal spray pumps, the same placebo formulation compositions, and same DOE experiment design (11). The Dv50 obtained from LLS were significantly different with the ones obtained from PDA. The Dv50 results from PDA were in a tight range of 33 to 42 μm, while the Dv50 results from LLS could be much larger, especially for the experiments with lower actuation velocity and higher formulation viscosities. The DOE modeling results for Dv50 from LLS confirmed differences from those obtained from PDA, with significant influences from actuation velocity and concentration of gelling agent being observed.

The difference in the droplet size DOE results arises from fundamental differences in the measurement technique used.

First, PDA and LLS have different measurement volumes. For PDA, the measurement zone is the crossing point of the two laser beams, with a small measuring volume of 80-micron diameter; while for the LLS, an 18 mm diameter laser beam is used, with the measuring depth varying from 9 to 43 mm, depending on the plume width of a nasal spray actuation (11).

The difference in measurement volume leads to a difference in sample volume and sample location. For the experiment setup used in this paper, the PDA was targeting to droplets passing through the crossing point of the two laser beam near the center of the plume; while the LLS examined a large 18 mm diameter cylindrical region which penetrates the nasal plume and includes a large part

Table IV. Product Characterization of Several Commercially Available Nasal Spray Products Used for PDA Testing

Nasal spray products	Manufacturer and location	Droplet velocity			Viscosity (cp)	Surface tension (dynes/cm)
		Mean (m/s)	SD (m/s)	RSD		
BeconaseAQ	Glaxo Wellcome Inc., Research Triangle Park, NC	16.0	0.2	1.0%	1.0	72.6
DDAVP	Rhone-Poulenc Rorer Pharmaceuticals Inc., Fort Washington, PA	6.7	0.3	4.5%	0.9	29.9
Flonase	Allen & Hanburys, Division of Glaxo Inc., Research Triangle Park, NC	19.2	0.3	1.8%	11.2	45.0
NasalCrom	Pharmacia Consumer Healthcare, Peapack, NJ	12.5	0.1	0.8%	1.2	47.6
Nasalide	Dura Pharmaceuticals, San Diego, CA	13.9	0.4	2.6%	8.8	49.9
Nasarel	IVAX Laboratories, Inc., Miami, FL	12.6	0.0	0.4%	3.3	30.6
Nasonex	Schering Corporation, Kenilworth, NJ	12.8	0.0	0.3%	>100	42.2

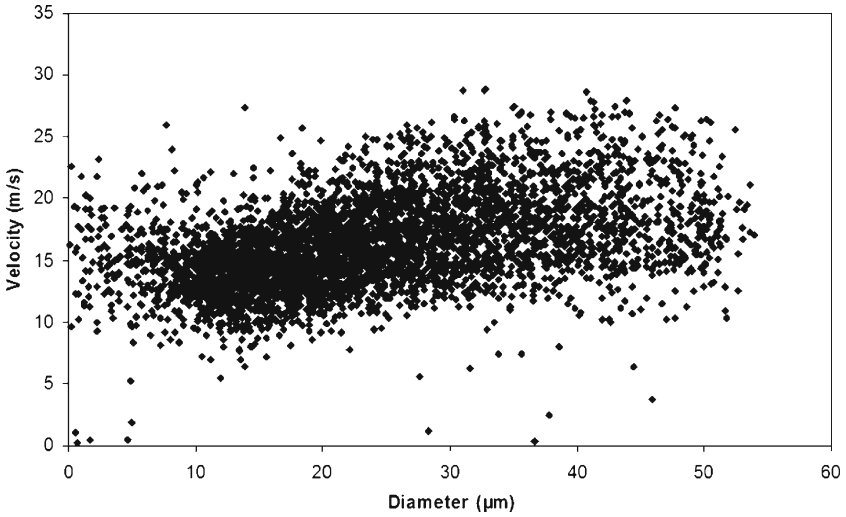

Fig. 3. Scatter plot of droplet size *vs.* velocity in a nasal spray plume produced by BeconaseAQ

of the plume edge. As shown in an early study (6), larger droplets were observed toward the edge of the plume. For experiments using low actuation velocity with high-viscosity formulations, droplets large enough to be identified visually occurred at the edge of the plume. Therefore, the PDA method, which targets at a small measurement volume near the center of the plume, will miss the droplets at other locations in the plume, especially those larger droplets which occur near the edge of the plume.

Last but not least, PDA is a number-based technique which measures individual droplets and provides number-weighted droplet size distribution, while LLS provides volume-weighted droplet size distribution. The nature of the technique determines that PDA will bias toward the droplets of larger populations. Since large droplets are weighted much heavier than small droplets in a volume/mass-weighted distribution, LLS results will bias toward large droplets. The PDA droplet distribution curves (number of droplets *vs.* droplet diameter) for the 27 DOE experiments all showed a single peak around 20–30 μm. For the experiments with lower actuation velocity and higher formulation viscosity, more noticeable tails toward large droplet size were observed. In addition, since PDA may not catch all droplets passing through the measurement volume, the low population of large droplets is more likely to be missed than the high-populated droplets in the range of 10–40 μm. For inhalation drugs where the mass in a certain size range matters, the volume/mass-weighted size is more relevant, which makes LLS a more popular method than PDA in droplet/particle size analysis.

In summary, as a number-based technique, PDA is sufficient for velocity analysis, but its number-based nature and limitation in measurement volume determines that PDA is not a suitable droplet/particle size analysis tool for inhalation drugs. However, PDA's capability to simultaneously measure the size and velocity of individual droplets could provide a chance for a close look at the droplet status in a plume.

Figure 3 shows a scatter plot of droplet size *vs.* velocity in a nasal spray plume produced by BeconaseAQ. The velocity data points are widely spread, and there is no direct relationship between the droplet size and velocity observed. However, a slight upward trend could be identified in the scatter plot, which indicates that large droplets tend to have higher velocity. Similar results were also observed in the other six commercial products. The trend can be explained by considering that 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 (12).

CONCLUSION

Phase-Doppler anemometry has been used to characterize the droplet velocity profiles of nasal spray drugs. This technique exhibits good repeatability as evidenced by a low RSD for repeated measurements. The PDA technique can also facilitate the characterization of the droplets delivered by nasal spray products.

The DOE study demonstrates that all four input parameters studied (stroke length, actuation velocity, concentration of gelling agent and surfactant) have significant influence ($p<0.05$) on droplet velocity of a nasal spray. An optimized quadratic model generated from the DOE results describes the inherent relationships between the factors and droplet velocity. This gives us a better understanding on how to optimize the device and formulation parameters to achieve the desired droplet velocity for this device. The response surfaces developed from the DOE model may assist drug product sponsors in product development to meet drug delivery equivalence requirements.

PDA shows its limitation as a number-based droplet/particle size analysis technique when compared with results from a previous nasal spray droplet size DOE study using LLS (11). Considering the purpose of the droplet/particle size analysis in inhalation drugs, a number-based technique such as PDA is not the suitable solution. A mass/volume-based technique, such as LLS, the Anderson cascade impactor, *etc.*, would be a better choice.

A survey of seven commercial nasal spray products shows that the droplet velocities of these products differ significantly from each other over a range of 6.7–19.2 m/s,

indicating that droplet velocity can be used as a discriminating parameter for *in vitro* testing for nasal spray products. The capability of PDA to detect droplet velocity and size simultaneously provides us with an insight into the correlation between the two variables. The observation that droplets with larger size tend to have higher velocities may assist in controlling the drug delivery performance in commercial nasal spray products.

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REFERENCES

1. U.S. Food and Drug Administration. Draft guidance for industry: metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products. 1998.
2. U.S. Food and Drug Administration. Guidance for industry: nasal spray and inhalation solution, suspension, and spray drug products—chemistry, manufacturing, and controls documentation. 2002.
3. U.S. Food and Drug Administration. Draft guidance for industry: bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action. 2003.
4. Guo C, Doub WH. Development of a novel technology to measure impaction force of nasal sprays and metered dose inhalers using the texture analyser. In: Byron PR, Peart J, Suman JD, Farr SJ, Dalby RN, editors. Respiratory drug delivery. River Grove: Davis Healthcare International Publishing; 2006. p. 621–4.
5. Guo C, Ye W, Kauffman JF, Doub WH. Evaluation of impaction force of nasal sprays and metered-dose inhalers using the texture analyser. J Pharm Sci. 2009;98(8):2799–806.
6. Liu X, Doub WH, Guo C. Evaluation of droplet velocity and size from nasal spray devices using phase Doppler anemometry (PDA). Int J Pharm. 2010;388(1–2):82–7.
7. Albrecht H-E, Damaschke N, Borys M, Tropea C. Laser Doppler and phase Doppler measurement techniques. In: Merzkirch, Wolfgang, Rockwell, Donald, Tropea, Cameron, editors. Experimental fluid mechanics, ed. New York: Springer-Verlag Berlin Heidelberg; 2003. p. 738.
8. Dayal P, Shaik M, Singh M. Evaluation of different parameters that affect droplet-size distribution from nasal sprays using the Malvern Spraytec. J Pharm Sci. 2004;93:1725–42.
9. Guo C, Doub WH. The influence of actuation parameters on *in vitro* testing of nasal spray products. J Pharm Sci. 2006;95:2029–40.
10. Dayal P, Pillay V, Babu, JR, Singh, M. Box-Behnken experimental design in the development of a nasal drug delivery system of model drug hydroxyurea: characterization of viscosity, *in vitro* drug release, droplet size, and dynamic surface tension. AAPS PharmSciTech. 2005; 6(4):Article 72.
11. Guo C, Stine KJ, Kauffman JF, Doub WH. Assessment of the influence factors on *in vitro* testing of nasal sprays using Box-Behnken experimental design. Eur J Pharm Sci. 2008;35 (12):417–26.
12. Takeuchi G, Kawaguchi T, Hishida K, Maeda M, Sommerfeld, M. Spatial distributions of droplet size and velocity in air heated spray measured by interferometric laser imaging technique. 12th International Symposium on Applications of Laser Techniques to Fluid Mechanics, ed., Lisbon, Portugal. 2004.