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RESEARCH PAPER

Effect of Formulation- and Administration-Related Variables on Deposition Pattern of Nasal Spray Pumps Evaluated Using a Nasal Cast

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ABSTRACT

Purpose To systematically evaluate the effect of formulation- and administration-related variables on nasal spray deposition using a nasal cast.

Methods Deposition pattern was assessed by uniformly coating a transparent nose model with Sar-Gel®, which changes from white to purple on contact with water. Sprays were subsequently discharged into the cast, which was then digitally photographed. Images were quantified using Adobe® Photoshop. The effects of formulation viscosity (which influences droplet size), simulated administration techniques (head orientation, spray administration angle, spray nozzle insertion depth), spray pump design and metering volume on nasal deposition pattern were investigated.

Results There was a significant decrease in the deposition area associated with sprays of increasing viscosity. This appeared to be mediated by an increase in droplet size and a narrowing of the spray plume. Administration techniques and nasal spray pump design also had a significant effect on the deposition pattern.

Conclusions This simple color-based method provides quantitative estimates of the effects that different formulation and administration variables may have on the nasal deposition area, and provides a rational basis on which manufacturers of nasal sprays can base their patient instructions or post approval changes when it is impractical to optimize these using a clinical study.

KEY WORDS deposition pattern · droplet size · formulation · nasal spray · spray pump design · viscosity

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INTRODUCTION

Given its large surface area, a permeable and vascularized mucosa, avoidance of first-pass metabolism and rapid onset of therapeutic action, there is significant interest in nasal administration for both local and systemic drug delivery (1,2). However, relatively little research addresses the factors that influence drug distribution in the nasal cavity because it is somewhat inaccessible, and delivery of aerosols into the nasal cavity is a complex process that depends on many parameters. These include parameters associated with the device used to generate the spray, the formulation which the device atomizes, the way a patient handles the device during generation and inhalation of the spray, and the obvious anatomical complexity of the nose. Optimization of drug delivery to the nasal cavity requires consideration of all the factors listed above, all of which are interrelated (3,4). For example, volumetric nasal spray pump devices and formulations interact to influence the spray plume shape and droplet size, whose characteristics are believed to have a profound effect on the resulting intranasal distribution of droplets (5). The delivered dose and the sprayed droplet size distribution are usually regarded as the key parameters which define a nasal delivery system. Aerosol droplets with a mass median aerodynamic diameter greater than 10 μm deposit ostensibly in the nasal cavity, while droplets (and perhaps isolated primary drug particles if the formulation contains undissolved drug) smaller than this reduce naso-

pharyngeal capture and increase the possibility of pulmonary deposition. In a scintigraphic study, Harris *et al.* investigated the effects of changing droplet sizes using solutions with varying viscosities and showed that larger droplets deposited primarily in the anterior portion of the nose (6). Similarly, Cheng *et al.* used anatomical data obtained from magnetic resonance imaging to conclude that narrow plume angles and small droplet sizes provided the greatest deposition beyond the nasal valve region (7). Foo *et al.*, using a fluorescent marker, demonstrated that administration angle was a critical factor in the efficient delivery of nasal spray and concluded that maximal deposition was observed at an administration angle of 30° above horizontal (8). Additional patient technique-dependent variables, including the spray tip insertion depth, were also investigated by Kimbell *et al.* using computational fluid dynamics (9). While formulation and administration techniques have been shown to influence nasal deposition pattern, these studies did not look at a wide range of values associated with each variable.

Therefore, the purpose of this study was to systematically investigate the effect of a wide range of formulation parameters, simulated administration techniques (head position, spray administration angle, spray nozzle insertion depth) and spray pump designs on nasal deposition patterns. The use of a fast and inexpensive color-based method (10) in combination with a simplified nasal cast (as opposed to spraying into unobstructed air) allows many variations of each parameter to be screened in such a way that physiological and anatomical influences are reflected in the results. Since it is unlikely that developers of nasal spray products will be able to justify such exhaustive testing in patients and volunteers, this approach represents a way for product developers to show they thoroughly understand the factors that influence the quality of their drug products, and can subsequently define and set boundaries for safety and efficacy-related critical quality attributes. This opens the way to using the precepts of FDA's Quality by Design initiative to justify product changes without the necessity of clinical studies to support each change (11,12).

MATERIALS AND METHODS

Sar-Gel® (Sartomer Company Inc.), a commercially available water-level-indicating paste which changes from white to purple on contact with water was used to visualize deposition of aqueous droplets within an anatomically correct, transparent, silicone human nose model (Koken Co., Ltd.). Three commercially available nasal sprays were evaluated: Ayr Saline Nasal Gel No-Drip Sinus Spray (B.F. Ascher & Co., Inc), Afrin No Drip Original 12 h Pump Mist (Schering-Plough Healthcare Products, Inc.), and Zicam No-Drip Liquid Nasal Gel Non-Drowsy Seasonal Allergy Relief (Zicam LLC). A variety of different nasal-pump designs were kindly provided by Aptar Pharma (listed in Fig. 12). All the images were captured using a digital camera (Canon PowerShot SD100 6.1MP Digital ELPH Camera w/3× Optical Zoom) and were quantified using Adobe Photoshop (CS3 Version). Spray pattern and plume geometry was measured using Aerosol Drug Spray Analyzer (ADSA) (Innova Systems, Inc.).

Assessment of Deposition Pattern

Deposition pattern was assessed by uniformly coating the inner surface of the nose model with Sar-Gel followed by discharge of nasal sprays (which are largely comprised of water) into the nose model at a 45° angle to the horizontal and at a nostril insertion depth of 5 mm. The head position was upright (perpendicular or 90° to the horizontal). Before and after spray images were captured using a digital camera under standardized photographic conditions, and the region of color change was quantified using Adobe Photoshop. For quantification using Photoshop, the image size was first adjusted to 20×20 cm with a resolution of 100 pixels per cm. The 2,000×2,000 pixels image contrast was then adjusted so that only the purple area was selected, using *Hue Saturation*. The *Magic Wand* tool was used to identify the purple color indicating nasal spray deposition after the *Tolerance* level was adjusted. The *Similar* command was then used to automatically select the entire purple region whose projected area in pixels could be automatically obtained using the *Histogram* tool. Dividing the pixel area by resolution gives the projected spray area in cm^2. In order to overcome variations in the image size and the deposition area that result from use of different camera-to-nose model distances, a 1 cm^2 purple square was incorporated which served as an area standard and was imaged simultaneously with deposition pattern in all nose model photographs. The variations in starting image size could then be corrected using the known area of the reference square. The procedure and associated validation tests were described in detail by Kundoor *et al.* (10).

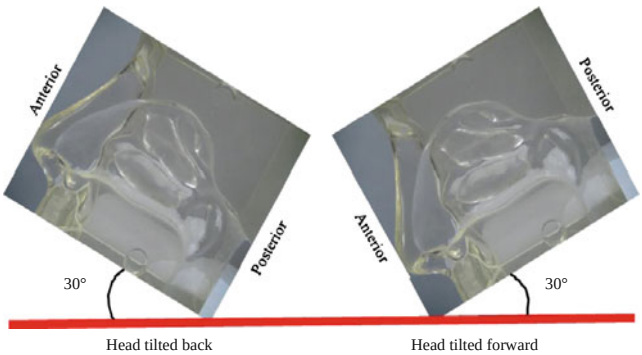

Fig. 1 Different head positions for administering nasal sprays.

Table I Droplet Size Distributions of Formulations at Different Actuation Distances

			Ayr	Afrin	Zicam
Droplet Size	3 cm	Dv_{10} (μm)	32.45 ± 2.47	48.08 ± 2.88	144.57 ± 7.98
		Dv_{50} (μm)	53.11 ± 3.09	72.51 ± 2.72	207.09 ± 5.38
		Dv_{90} (μm)	98.57 ± 1.86	138.7 ± 1.45	240.70 ± 4.86
	6 cm	Dv_{10} (μm)	22.17 ± 1.68	29.12 ± 2.22	86.36 ± 6.47
		Dv_{50} (μm)	51.76 ± 1.91	61.5 ± 1.01	138.46 ± 6.30
		Dv_{90} (μm)	98.93 ± 0.69	129.32 ± 1.95	223.71 ± 7.50

Effect of Formulation Variables on Deposition Pattern

Droplet Size Distribution Measurement

Droplet-size analysis of nasal aerosols was conducted by laser diffraction using a Malvern Spraytec® (Malvern Instruments Ltd., Malvern, UK) with RT Sizer software equipped with a 300 mm range lens, which has a droplet-size range of 5.8–564 μm. Before each experiment, each nasal spray was actuated five times into waste to prime the device, followed by one test actuation. The nasal spray device tip was aligned vertically at a distance of 3 and 6 cm below the center of the laser beam. The pump was positioned in such a manner that the laser beam intersected the center of the expanding spray cone. All actuations were fired upward, and a vacuum was applied above the laser line at a distance of 20 cm from the tip of the nasal spray to avoid fall-back of droplets. All the sprays were manually actuated, and data were reported as volume diameter defined by 10%, 50% (volume median), and 90% of the cumulative volume undersize (Dv_{10}, Dv_{50}, and Dv_{90}, respectively). Three repeated measurements were made for each pump, and three units of each type of pump were tested.

Viscosity Studies

The viscosity of the three commercially available formulations, Ayr, Afrin and Zicam, was studied using a cone and plate Brookfield rheometer (Brookfield Engineering Laboratories, Middleboro, MA) with spindle 40. Three measurements per formulation were carried out at a temperature of 25°C ± 0.1°C. Viscosity measurements of test formulations were made by pipetting 0.5 ml of formulation onto the plate of rheometer and allowing it to rest for 5 min. Increasing shear rates from 1 RPM to 10 RPM were applied to the formulation to yield measurements between 10 and 100% of maximum rheometer torque.

Spray Pattern Measurement

The pumps were actuated by an automated actuation station (InnovaSystems, Inc.) with actuation parameters specified by Doughty *et al.* (13) (compression velocity of 33 mm/s, velocity hold time of 323 ms and release velocity of 45.5 mm/s). Before each experiment, each nasal spray was actuated five times to waste to prime the device, followed by one test actuation. Spray pattern measurements were made at a distance of 3 and 6 cm below the laser beam, and the nasal sprays were sprayed perpendicular to the laser light. In all cases, images were captured at 500 frames/sec, and data were reported as D_{max} and D_{min} (corresponding to the maximum and minimum diameter of the elliptical image, respectively). The ratio of D_{max} and D_{min} (ovality ratio) was also calculated. All actuations were fired upward, and a vacuum was applied above the laser line at a distance of 20 cm from the tip of the nasal spray to avoid fall-back of droplets. Three units of each pump were tested. Each unit was tested in triplicate.

Plume Geometry Measurement

The pumps were fired by an automated actuation station using the settings described for spray pattern measurement. All actuations were fired upward, and a vacuum was

Table II Viscosities of Formulations Under Different Rates of Shear

Rotation speed (rpm)	Viscosity (cP)		
	Ayr	Afrin	Zicam
1	734.89 ± 63.71	1042.04 ± 73.72	1564.69 ± 116.09
2	408.72 ± 50.45	598.95 ± 67.85	1126.92 ± 74.58
3	317.93 ± 45.86	463.25 ± 57.89	901.70 ± 59.9
5	223.67 ± 30.28	382.59 ± 77.92	634.70 ± 13.41
10	112.49 ± 21.39	284.05 ± 76.28	No reading

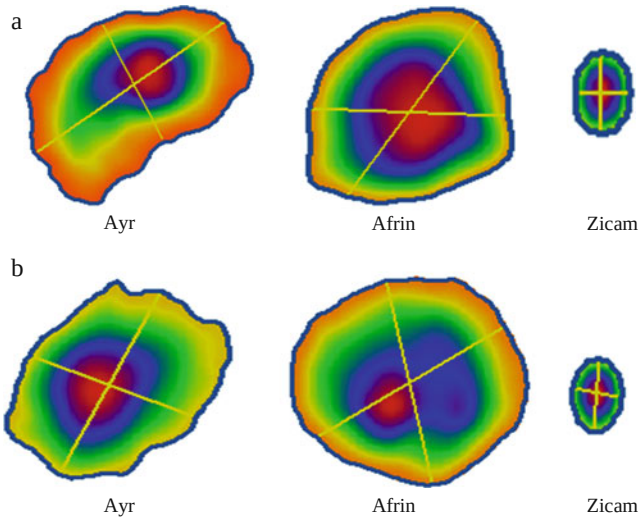

Fig. 2 (**a**) Spray pattern images of nasal spray pumps at a distance of 3 cm from the laser beam. (**b**) Spray pattern images of nasal spray pumps at a distance of 6 cm from the laser beam.

applied above the laser line at a distance of 20 cm from the tip of the nasal spray to avoid fall-back of droplets. Plume geometry images were taken along the centerline of the device parallel to the laser beam. In all cases, images were captured at 500 frames/sec, and maximum width of the plume and plume angle were reported. Three units of each pump were tested. Each unit was tested in triplicate.

Effect of Administration-Related Variables on Deposition Pattern

Head Position

We studied the intranasal distribution of Afrin nasal spray when administered at two different head positions (Fig. 1), both assumed to be used by patients since they are shown on the approved labeling of nasal spray products sold in the United States. Nasal package inserts of Flonase (GlaxoSmithKline) suggest to tilt head slightly forward, whereas Nasacort (Rhone-Poulenc Rorer) suggests to tilt head back slightly when spraying (14). The two head positions were defined as *head tilted back* (anterior end of the nose model was tilted 30° from horizontal) and *head tilted forward* (posterior end of the nose model was tilted 30° from horizontal). Afrin nasal spray was manually actuated into the nose model at a spray angle of 30° to the plane of the head and at a nostril insertion depth of 5 mm in both positions ($n=5$).

Table III Spray Pattern Data Comparing Different Nasal Sprays at 3 cm from the Laser Beam

Parameter	3 cm		
	Ayr	Afrin	Zicam
D_{max} (cm)	2.52 ± 0.04	1.8 ± 0.23	0.54 ± 0.05
D_{min} (cm)	1.58 ± 0.1	1.4 ± 0.15	0.38 ± 0.04
Ovality ratio	2.42 ± 0.1	1.27 ± 0.04	1.55 ± 0.16

Table IV Spray Pattern Data Comparing Different Nasal Sprays at 6 cm from the Laser Beam

Parameter	6 cm		
	Ayr	Afrin	Zicam
D_{max} (cm)	3.74 ± 0.27	2.28 ± 0.16	0.58 ± 0.04
D_{min} (cm)	2.18 ± 0.08	1.94 ± 0.25	0.38 ± 0.04
Ovality ratio	1.7 ± 0.12	1.18 ± 0.08	1.48 ± 0.05

Spray Administration Angle

Afrin nasal spray was discharged into the Sar-Gel-coated nose model at an angle of 0, 15, 30, 45, 60, 75 and 90° to the horizontal with the head in upright position and at a tip insertion depth of 5 mm ($n=5$).

Nasal Spray Insertion Depth

Deposition pattern was assessed as described previously, when the Afrin nasal spray tip was inserted 0, 2.5, 5, 10 and 15 mm into the nostril at an administration angle of 45° to the horizontal and head in upright position ($n=5$).

Effect of Nasal Spray Pump Design on Deposition Pattern

A variety of different nasal spray pump designs listed in Fig. 12 were evaluated. Six ml of water was filled into

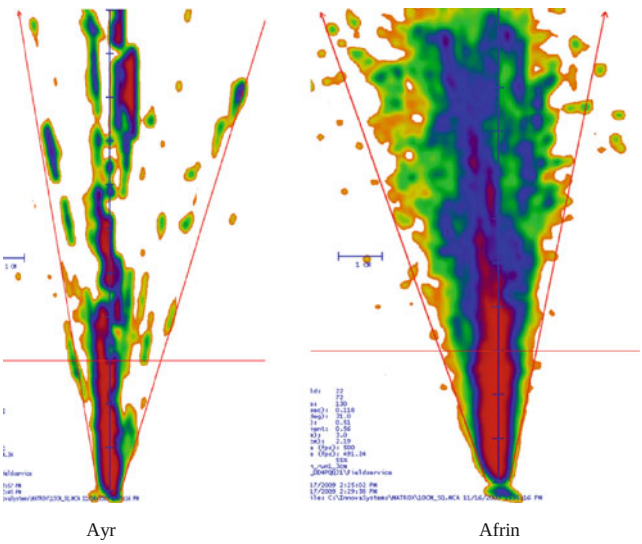

Fig. 3 Plume geometry images of different nasal spray pumps.

Table V Plume Geometry Data Comparing Different Nasal Spray Pumps

Nasal spray	Plume width (cm)	Plume angle (°)
Ayr	2.89 ± 0.22	38.8 ± 3.63
Afrin	1.99 ± 0.21	26.08 ± 2.64

each of the nasal spray pump, and the deposition pattern was assessed at a 5 mm insertion depth with the spray angle of 45° to the horizontal and head in upright position ($n=5$).

Statistical Analysis

All data are presented as mean ± standard deviation (SD). A Kruskal-Wallis one-way analysis of variance test was used to identify significant differences in deposition pattern between nasal sprays with different formulation properties. The same test was also used to determine significant differences between spray nozzle designs, nasal spray insertion depths and administration angles. A Mann-Whitney rank test (two-tail) was used to determine significant differences between two different head positions. P values less than 0.05 were considered to represent significant differences.

RESULTS

Effect of Formulation Variables on Deposition Pattern

Droplet Size Distribution

Table I indicates that the droplet size distribution of nasal products varies as a function of distance from the spray pump nozzle regardless of the type of formulation. In general, the droplet size data showed a decrease in the Dv_{50} values with increasing distance between the nozzle and measurement zone of the laser. Similar trends were also observed for Dv_{90} and Dv_{10} values.

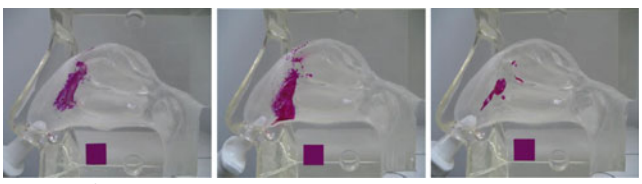

Fig. 4 Deposition patterns of Afrin, Ayr and Zicam (Insertion depth = 5 mm; Spray angle = 45°).

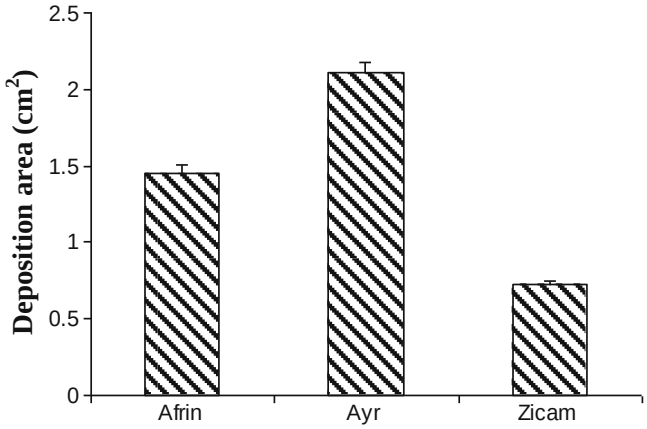

Fig. 5 Projected deposition areas of Afrin, Ayr, and Zicam. All values are expressed as mean ± standard deviation of the mean ($n=5$).

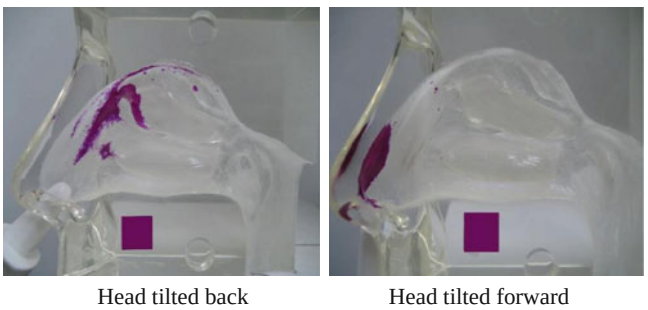

Fig. 6 Deposition pattern of Afrin nasal spray at different head positions (Insertion depth = 5 mm).

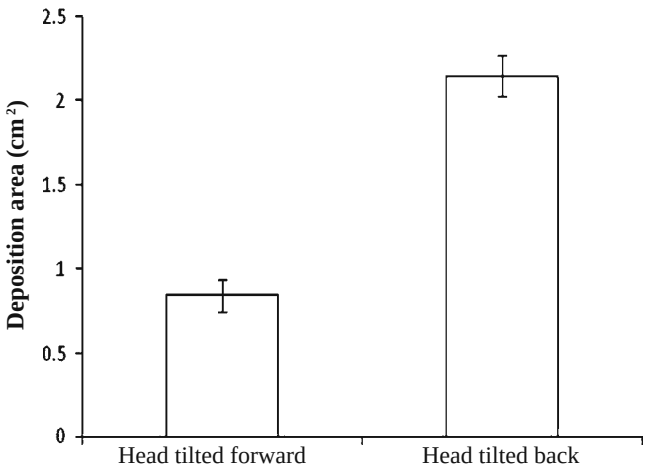

Fig. 7 Projected deposition areas of Afrin nasal spray at different head positions. All values are expressed as mean ± standard deviation of the mean ($n=5$).

Viscosity

The three formulations, Ayr, Afrin and Zicam, were all shear thinning: their viscosities decreased with increasing rates of shear. Viscosity data under rotation speeds of 1, 2, 3, 5 and 10 RPM are summarized in Table II. As shown in Table II, when rotation speed increased from 1 RPM to 10 RPM, the viscosity of Ayr decreased from 734.89 cP to 112.49 cP, the viscosity of Afrin decreased from 1042.04 cP to 284.05 cP, the viscosity of Zicam decreased from 1564.69 cP to 634.70 cP (readings at 10RPM were outside the measurement range).

Spray Pattern Measurement

Upon examination of spray patterns (Fig. 2a and b), it is possible to visualize dissimilarities between the three commercially available pumps. The results are quantified in Tables III and IV, and indicate that D_{max}, D_{min} and ovality ratios of the three nasal spray pumps were

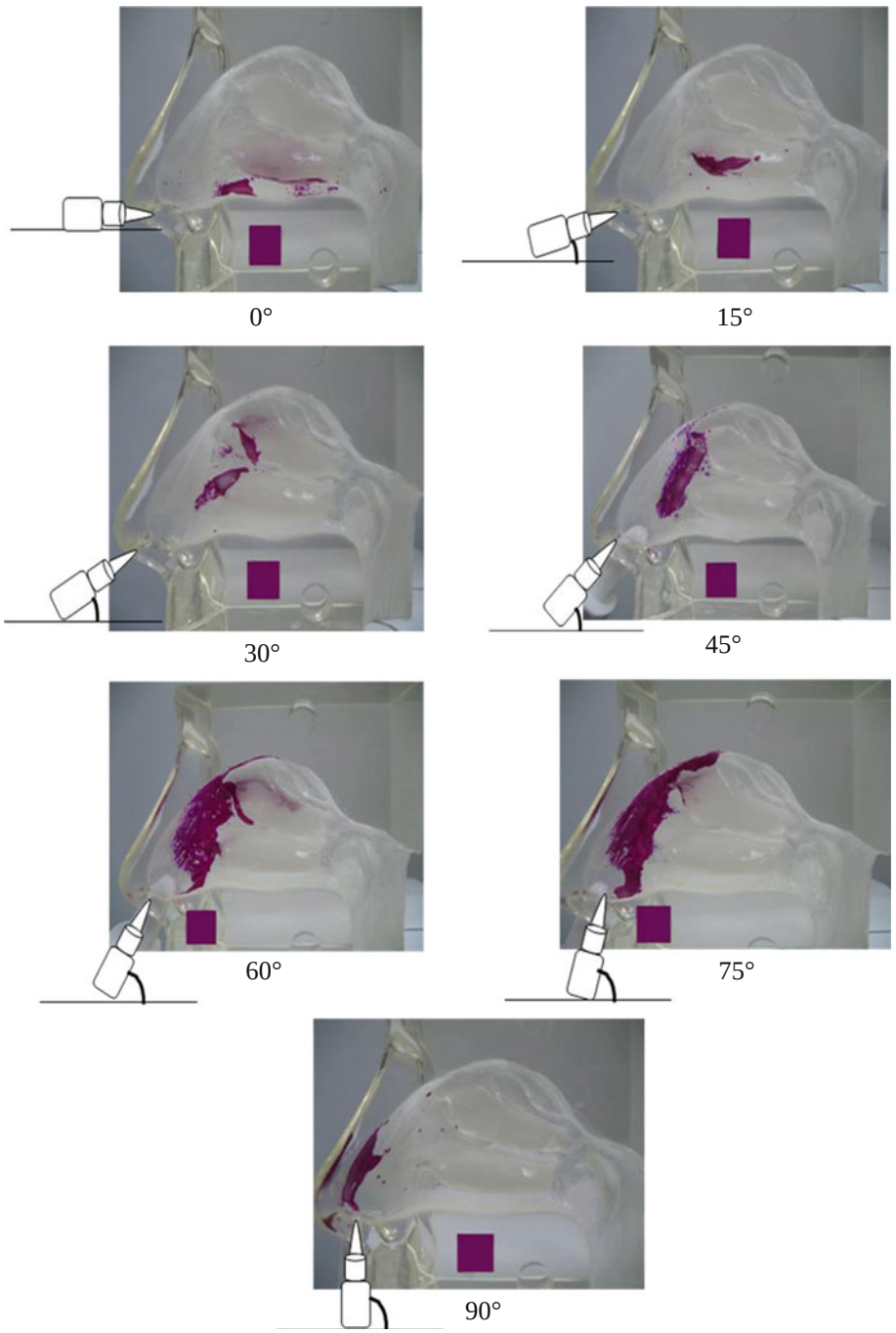

Fig. 8 Deposition pattern of Afrin nasal spray at different administration angles (Insertion depth = 5 mm).

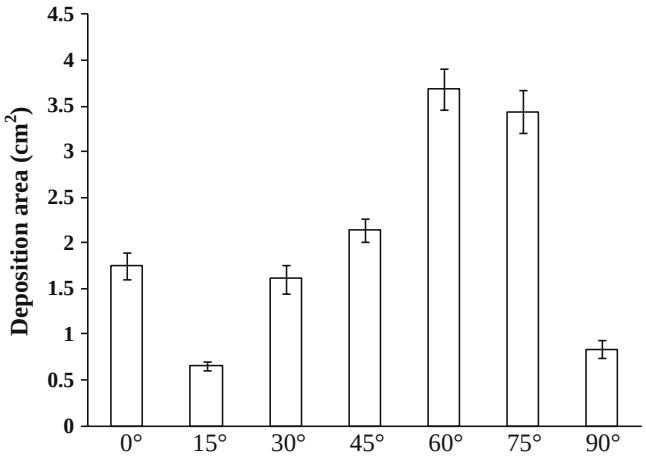

Fig. 9 Projected deposition areas of Afrin nasal spray at different administration angles. All values are expressed as mean ± standard deviation of the mean ($n = 5$).

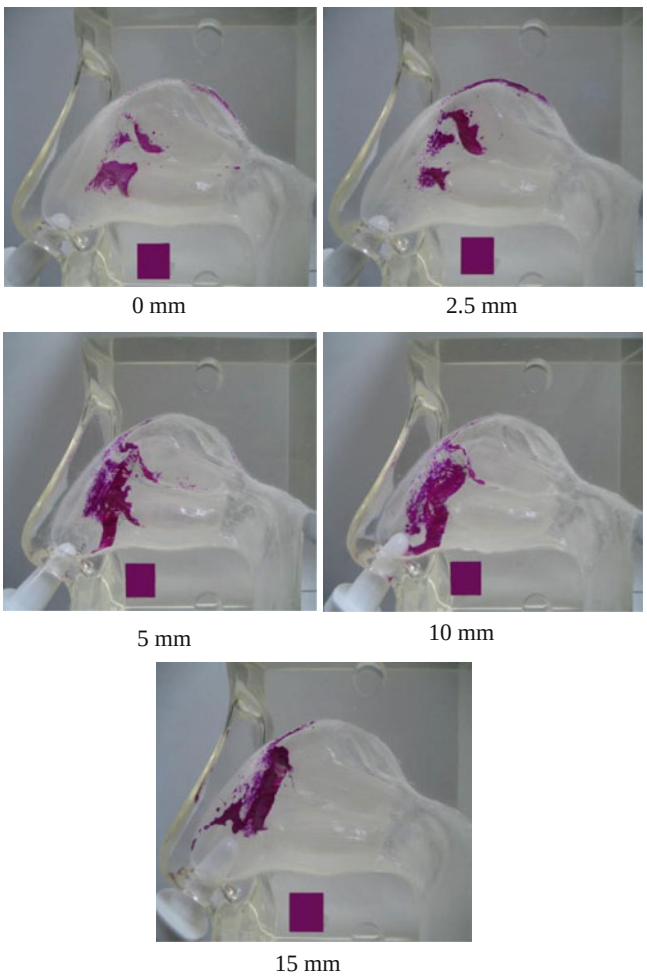

Fig. 10 Deposition pattern of Afrin nasal spray at different nasal spray insertion depths (Spray angle = 45°).

significantly different. An inverse relationship was observed between the viscosity and ovality ratio. Lower viscosity formulations (Ayr and Afrin) had higher ovality ratios compared to higher viscosity formulation Zicam.

Plume Geometry Measurement

Images of an emitted plume from Ayr and Afrin are shown in Fig. 3. Plume width and plume angle derived from these photographs are shown in Table V. Since the plume of Zicam nasal spray was similar to the width of laser beam, it was not possible to capture the plume images of Zicam nasal spray using ADSA. Comparison of plume width and plume angle indicated statistical differences between Ayr and Afrin nasal spray pumps.

Assessment of Deposition Pattern

Significant differences were observed between the deposition patterns of the three nasal sprays, and these are correlated with viscosity and sprayed droplet sizes. Images for the deposition pattern of Ayr, Afrin and Zicam nasal sprays without any air flow are shown in Fig. 4. The nasal spray deposition areas determined from these photographs are shown in Fig. 5.

Effect of Administration-Related Variables on Deposition Pattern

Head Position

The deposition pattern of Afrin nasal spray at different head positions are shown in Fig. 6. Deposition area of Afrin nasal spray at head tilted back position was significantly higher compared to the deposition area at head tilted forward position (Fig. 7).

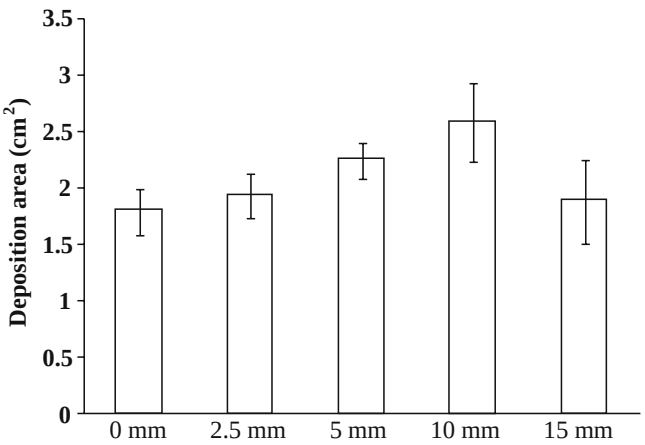

Fig. 11 Projected deposition areas of Afrin nasal spray at different insertion depths. All values are expressed as mean ± standard deviation of the mean ($n = 5$).

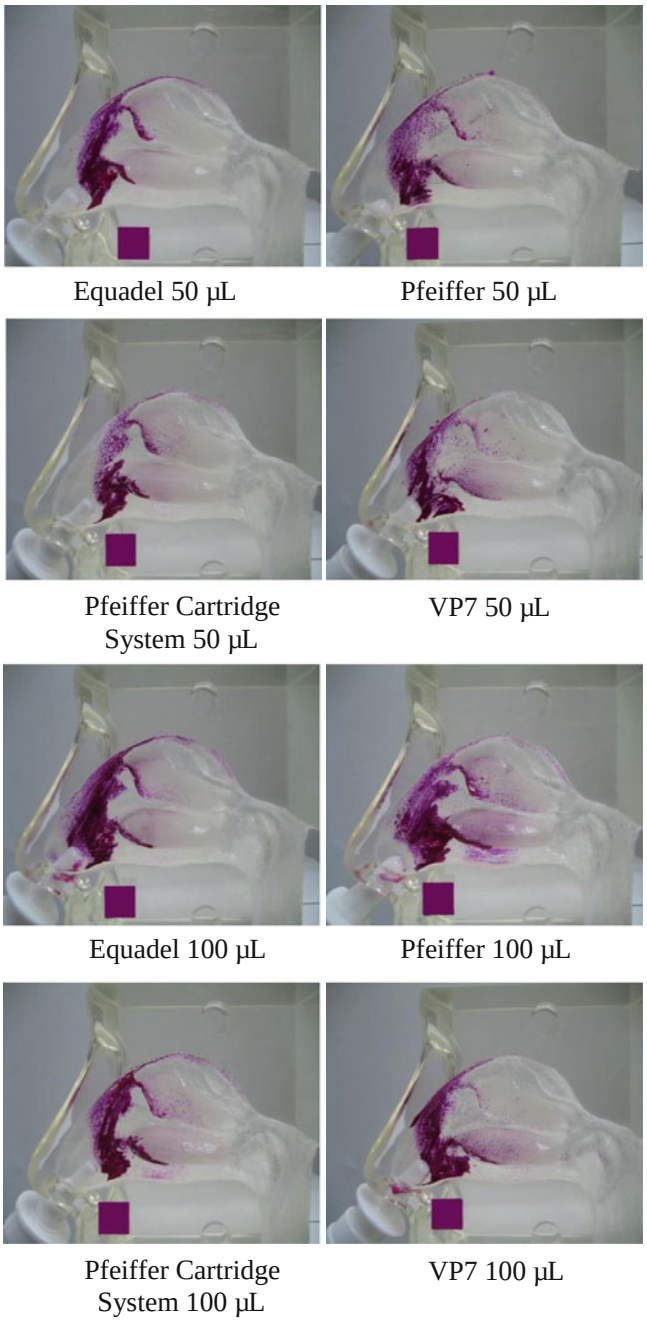

Fig. 12 Deposition pattern of water with different spray nozzle designs (Insertion depth = 5 mm; Spray angle = 45°).

Spray Administration Angle

Deposition pattern was measured using different administration angles (defined as the angle between the base of the nose model and the spray device tip). Changes in administration angle (0°–90°) had a significant effect on the deposition area. Images of the deposition pattern of Afrin nasal spray at different administration angles are shown in Fig. 8. The nasal spray deposition areas determined from these photographs are shown in Fig. 9

Nasal Spray Insertion Depth

Effect of various nasal spray insertion depths (0 mm–15 mm) on deposition pattern was studied (Fig. 10). Nasal spray insertion depth had significant effect on deposition (Fig. 11).

Effect of Nasal Spray Pump Design on Deposition Pattern

The influence of nasal spray pump design on deposition pattern was also assessed (Fig. 12). The spray was visualized by the incorporation of water into different nasal spray pump designs. Nasal spray pumps delivering larger volumes (100 µL) had significantly greater nasal deposition area compared to nasal spray pumps delivering 50 µL (Fig. 13).

DISCUSSION

These data suggest that the higher viscosity formulation Zicam was associated with significantly ($p<0.001$) less coverage compared to the lower viscosity formulations, Ayr and Afrin. The highest viscosity formulation produced the largest droplet size ($Dv_{50}=207.09\pm5.38$ µm) and the most focused plume—conditions which explain why most droplets impacted on the first oblique surface they encountered in the front of the nose. In contrast, the lower viscosity Ayr formulation showed more surface coverage

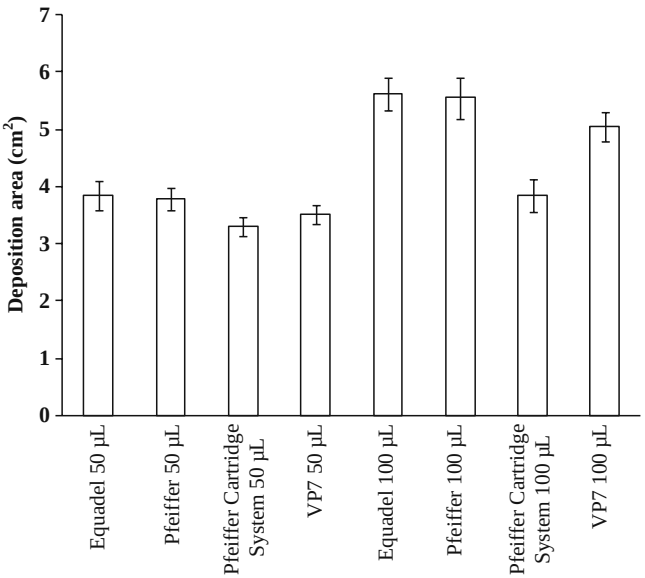

Fig. 13 Projected deposition areas of water with different spray nozzle designs. All values are expressed as mean ± standard deviation of the mean ($n=5$).

due to the production of smaller droplets ($Dv_{50}=53.11\pm3.09$ μm) and a wider plume angle (38.8±3.63°) (15). The viscosity data in the study were generated using a rotational rheometer. Pennington *et al.* conducted a study to approximate the viscosity values generated at the spray nozzle by correlating parameters such as spray area and droplet size analyses that can be measured efficiently during spray actuation. They found that the viscosities of shear thinning nasal sprays determined by both spray area and droplet size methods approached that of water at high shear rates and were shown to trend in accordance with the data generated from the rotational rheometer (16).

Results from the current studies suggest that with the tilted head forward position, deposition was mostly in the anterior part of the nose (the nasal valve), whereas with the tilted head back position, nasal spray reached even the middle regions of the nose.

In a study by Benninger *et al.*, which examined the patient instructions of seven commercially available nasal spray products, they found that diagrams accompanying some products showed administration angles between 30° and 45° (14). The nose model showed that higher administration angles (≥60°) resulted in the greatest deposition in the nasal valve region. Deposition areas from ≤45° spray angles indicated that droplets were better able to pass through the nasal valve. Moreover, lower administration angles (0°) had less deposition area compared to higher administration angles (75°), which might be due to the inability of the nasal spray to fully expand within the small surface area resulting in pooling of the formulation. This suggests that the administration angle is a critical factor, and based on the desired site of deposition, a target spray administration angle can be identified for optimal site-directed deposition. In contrast to the head position and spray administration angle, nasal spray insertion depth had a minimal (but statistically significant) effect on the deposition pattern with the deposition area being in a narrow range of 1.7–2.5 cm^2.

Analysis of the data revealed a significant difference in the deposition area between the nasal sprays delivering 50 μL and those delivering 100 μL, except for the Pfeiffer cartridge system, which is consistent with Newman *et al.*, who showed that 100 μL of nasal spray deposited over a larger area compared to 2×50 μL (3). By this method three out of four pump designs were essentially equivalent in terms of their ability to achieve coverage.

CONCLUSIONS

This study provided quantitative estimates of the effects that different formulation and administration variables have on the nasal model deposition area as judged from lateral, two-dimensional image. The angle at which the head is held relative to the nasal spray unit and the angle at which the nasal spray unit is presented to the nose appear to be more important determinants of spray coverage than nozzle insertion depth. Such results provide a basis for justifying patient instructions. Pump design was less influential than metering chamber volume, suggesting a way for generic manufactures unable to access the innovators pump to argue for use of an alternative design. Other authors have correlated formulation viscosity to droplet size in nasal products, but this paper links viscosity to deposition area, which is arguably more likely to correlate with efficacy.

The methods described in this paper allow patient-, device- and formulation-related variables to be quickly evaluated in an anatomically and physiologically (in terms of air flow through the nose) relevant way (10). They could be easily adapted to allow different views of the nasal cavity to be obtained, and we believe they have potential use as *in vivo* bioequivalence metrics or indicators of critical quality attributes.

REFERENCES

1. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today. 2002;7(18):967–75.
2. Suman JD, Laube BL, Dalby R. Comparison of nasal deposition and clearance of aerosol generated by nebulizer and an aqueous spray pump. Pharm Res. 1999;16(10):1648–52.
3. Newman SP, Steed KP, Hardy JG, Wilding IR, Hooper G, Sparrow RA. The distribution of an intranasal insulin formulation in healthy volunteers: effect of different administration techniques. J Pharm Pharmacol. 1994;46:657–60.
4. Vidgren MT, Kublik H. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev. 1998;29:157–77.
5. Food Drug Administration. U.S. FDA draft guidance for industry: bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action. Rockville: US Food and Drug Administration; 2003.
6. Harris AS, Svensson E, Wagner ZG, Lethagen S, Nilsson IM. Effect of viscosity on particle size, deposition, and clearance of nasal delivery systems containing desmopressin. J Pharm Sci. 1988;77:405–8.
7. Cheng YS, Holmes TD, Gao J, Guilmette RA, Li S, Surakitbanharn Y, *et al.* Characterization of nasal spray pumps and deposition pattern in a replica of the human nasal airway. J Aerosol Med. 2001;14:267–80.
8. Foo MY, Cheng Y, Su W, Donovan MD. The influence of spray properties on intranasal deposition. J Aerosol Med. 2007;20(4):495–508.
9. Kimbell JS, Segal RA, Asgharian B, Wong BA, Schroeter JD, Southhall JP, *et al.* Characterization of deposition from nasal spray devices using a computational fluid dynamics model of the human nasal passages. J Aerosol Med. 2007;20:59–74.
10. Kundoor V, Dalby RN. Assessment of nasal spray deposition in a silicone human nose model using a color based method. Pharm Res. 2010;27(1):30–6.

11. Poochikian G, Shah V. Pharmaceutical quality assessment system (PQAS): science and risk managed approaches for inhalation drug products. In: Dalby RN, Byron PR, Peart J, Suman JD, editors. Respiratory Drug Delivery 2006 (Book 1, ISBN 1-930114-95-8). Davis Healthcare, River Grove: Illinois; 2006;151–8.
12. Pharmaceutical cGMPS for the 21st century—a risk-based approach. Rockville: US Food and Drug Administration; 2004.
13. Doughty DV, Vibbert C, Bollinger ME, Kewalramani A, Dalby RN. Automated Actuation of Nasal Spray Products: Determination and Comparison of Adult and Pediatric Settings. Drug Dev Ind Pharm. 2010;37(3):359–366.
14. Benninger MS, Hadley JA, Osguthorpe JD, Marple BF, Leopold DA, Derebery MJ, *et al*. Techniques of intranasal steroid use. Otolaryngol Head Neck Surg. 2004;130:5–24.
15. Guo Y, Laube B, Dalby R. The effect of formulation variables and breathing patterns on the site of nasal deposition in an anatomically correct model. Pharm Res. 2005;22(11):1871–8.
16. Pennington J, Pandey P, Tat H, Willson J, Donovan B. Spray pattern and droplet size analyses for high-shear viscosity determination of aqueous suspension corticosteroid nasal sprays. Drug Dev Ind Pharm. 2008;34:923–9.