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The Influence of Spray Properties on Intranasal Deposition

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ABSTRACT

While numerous devices, formulations, and spray characteristics have been shown to influence nasal deposition efficiency, few studies have attempted to identify which of these interacting factors plays the greatest role in nasal spray deposition. The deposition patterns of solutions with a wide range of surface tensions and viscosities were measured using an MRI-derived nasal cavity replica. The resulting spray plumes had angles between 29° and 80° and contained droplet sizes (D_{v50}) from 37–157 μm. Each formulation contained rhodamine 590 as a fluorescent marker for detection. Administration angles of 30°, 40°, or 50° above horizontal were tested to investigate the role of user technique on nasal deposition. The amount of spray deposited within specific regions of the nasal cavity was determined by disassembling the replica and measuring the amount of rhodamine retained in each section. Most of the spray droplets were deposited onto the anterior region of the model, but sprays with small plume angles were capable of reaching the turbinate region with deposition efficiencies approaching 90%. Minimal dependence on droplet size, viscosity, or device was observed. Changes in inspiratory flow rate (0–60 L/min) had no significant effect on turbinate deposition efficiency. Both plume angle and administration angle were found to be important factors in determing deposition efficiency. For administration angles of 40° or 50°, maximal turbinate deposition efficiency (30–50%) occurred with plume angles of 55–65°, whereas a 30° administration angle gave an ~75% deposition efficiency for similar plume angles. Deposition efficiencies of ~90% could be achieved with plume angles <30° using 30° administration angles. Both the plume angle and administration angle are critical factors in determining deposition efficiency, while many other spray parameters, including particle size, have relatively minor influences on deposition within the nasal cavity.

Key words: spray characteristics, spray angle, nasal spray, deposition pattern, intranasal administration

INTRODUCTION

THE NASAL CAVITY has been used as a route for drug administration for many decades, frequently for local decongestion or to ameliorate allergic conditions, but recently there has been an increasing interest in the systemic delivery of drugs via this route. In general, optimization of the delivery and subsequent absorption of nasally inhaled medications requires consideration of the

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interactions between the drug formulation, its mode of administration, the specific device and patient technique.[1,2] Various dosage forms have been utilized to deliver medications to the nasal cavity, including drops, powders, nebulized mists, and sprays. Due to their convenience and dose consistency, sprays have become the preferred mode of delivery for nasal products, and spray devices driven by propellants or hand-actuated pump systems have been developed to deliver drug-containing solutions or suspensions. Spray devices and drug formulations interact to produce a spray plume with unique geometric and droplet properties, and the characteristics of the resulting spray are believed to have a profound effect on the resulting nasal deposition patterns.[2,3]

One of the primary limitations to the efficient optimization of spray parameters for nasal administration is the ability to accurately measure deposition within the human nasal cavity. *In vivo* investigations of deposition using radiolabeled formulations are expensive to conduct and frequently provide only semiquantitative results, yet several investigators have successfully used these techniques to identify key spray parameters influencing nasal deposition. Newman et al.[4] demonstrated that a greater fraction of the total spray volume could penetrate into the ciliated region of the main nasal passage from a spray whose plume angle was 30° compared to a wider 60° spray (~70 μm median droplet size (D_{v50})). Similarly, Harris et al.[5] investigated the effects of changing droplet size using solutions with varying polymer concentrations and showed that there was greater anterior deposition of the larger droplets, and recently Suman et al.[6] used gamma scintigraphy to demonstrate that sprays possessing similar velocities and plume angles gave similar deposition patterns, regardless of the specific device used.

In an effort to study nasal deposition *in vitro*, the use of nasal cavity replicas has also been reported by numerous investigators.[7–12] A major advantage to the use of these *in vitro* models is the ability to systematically investigate nasal deposition under well-controlled conditions, yet a marked disadvantage is the absence of a responsive mucosal surface, which likely reduces the anatomical accuracy of the models. A pioneering study using a human silastic nasal cast from a human cadaver was described by Mygind et al.[7] These investigators compared the deposition of a dye formulation emitted from a metered-dose inhaler (MDI) (propellant-driven metered dose inhaler) and a pump spray device using both a slow inhalation (25 L/min) as well as a sniff-like inhalation (50–70 L/min). Their results showed that the MDI spray was deposited in a narrow zone in the anterior region of the cast, regardless of nasal flow conditions, while the pump spray was distributed over a larger total area and penetrated more deeply into the nasal cavity. Hallworth and Padfield[8] adapted a simplified glass nasal cast model without a complex turbinate feature and found that much of a spray administered using a 10-L/min inspiratory flow rate was deposited in the anterior region of the nose by inertial impaction, and only 4.5–8.5% of the spray penetrated more deeply into the nasal cast.

Recent technological advances have allowed digitized anatomical data obtained from magnetic resonance imaging (MRI) to be used to construct physical replicas of the human nasal airways.[9] These models have been successfully used to characterize regional deposition patterns of nasal spray formulations within the nasal passages, and Cheng et al.[10] used these data to conclude that narrow plume angles and small droplet sizes provide the greatest deposition beyond the nasal valve region. In a comparison of nasal formulations, Guo and colleagues[11] used a Plexiglas and silicone model reproduced from a human cadaver, and showed that a low viscosity nasal spray formulation (0.25% Avicel CL611) with a wider plume angle (69°) and smaller D_{v50} (47–86 μm) enhanced deposition in the turbinate region compared to higher viscosity formulation (2% methylcellulose; 32° plume angle; D_{v50} = 100–130 μm). *In silico* methods have also been developed to simulate spray deposition patterns in the nasal cavity.[12] The computational fluid dynamic model of the human nasal cavity developed by Subramaniam et al.[13] using FIDAP modeling software (Fluent, Inc, Lebanon, NH) was used by these investigators to simulate the trajectories of particles within the nasal cavity. Particles (D_{v50} = 20 or 50 μm) emitted from spray devices with plume angles of 32° or 79° were studied, and spray velocities of 1 or 10 m/sec and inspiratory airflow rates of 0 or 15 L/min were used in the simulations. Additional user technique-dependent parameters, including spray tip insertion distance (0.5, 1.0, and 1.5 cm) and spray administration angle (55°, 75°) were also investigated. In most of the simulations, deposition in

the nasal vestibule (anterior to the nasal valve) accounted for >90% of the particle trajectories, and in no case was turbinate deposition predicted to be greater than 20%. Improved deposition efficiencies were associated with the smaller particle size, the lowest spray velocity (1 m/sec), a spray tip insertion depth of 1 cm, and the presence of an inspiratory airflow, but no statistical differences were observed between the two plume angles tested.

Many of these previous investigations have suggested that plume angle, droplet size, droplet velocity, and inspiratory airflow rate all play a role in the deposition of nasal sprays. Studies where these codependent variables are carefully evaluated are needed to identify the factors controlling nasal deposition, however, since there is conflicting evidence regarding the role of each parameter. The studies reported here were undertaken to investigate the effects of particle size, plume angle, spray administration angle, and inspiratory flow rate on nasal deposition using three commercial pump spray devices. Formulations that provided a broad range of spray characteristics were prepared and evaluated to allow each parameter to be systematically investigated.

MATERIALS AND METHODS

Spray devices and formulations

Three aqueous nasal spray devices, designated as device A (Model 29606, Pfeiffer GmBH, Radolfzell, Germany); device B (Model VP7, Valois, Marly-le-Roi, France); and device C (Model 56283, Pfeiffer GmBH, Radolfzell, Germany) were used for spray plume generation. Mixtures of methanol (Fisher Scientific, Fairlawn, NJ), ethanol (AAPER, Shelbyville, KY), glycerin (Fisher Scientific), and rhodamine 590 tetrafluoroborate (Exiton, Dayton, OH) were used for formulation preparation and deposition evaluation.

Determination of droplet size

The droplet size emitted from each device was determined using a Malvern Mastersizer 2600 (Malvern Instruments Ltd, Malvern, UK). The 300 mm lens used was capable of measuring droplets between 5.8–564 μm in diameter. The spray device tip was aligned vertically at a distance of 4.5 cm below the center of the laser beam, and the distance between the spray tip and receiving lens was 9 cm (within vignetting distance). The spray devices were placed on an automatic actuation station (Medical Instrument Shop, University of Iowa) and were delivered with a force of 4.5 kg. Data collection was initiated when the beam obscuration exceeded 5% and data were collected for 1 sec (1000 sweeps). The data were analyzed using Malvern PS2600 (Ver. B22) software. Volume diameters (DV) defining 10%, 50%, and 90% of the cumulative volume distribution of the spray droplets were determined. Six repeated measurements were made for each device, and four units for each device were tested.

Determination of emitted plume angle

The spray actuation station was placed within a chamber whose walls were coated with a black, nonglossy interior finish. A 500-W bulb was mounted directly overhead for illumination. The nasal spray devices were placed into the actuation station and were actuated with a force of 4.5 kg. A laser was used to visualize a horizontal plane within the spray, 1 cm above the spray tip. Emitted plumes were captured as movie clips at a rate of 30 frames/sec by a digital video camera (DCR-TRV340, Sony, Tokyo, Japan). The frame containing the most fully developed plume was transferred to Paintshop Pro 7® (Corel Corporation, Ottawa, Canada) for image processing. The image was decreased to a 16-color gradient image based on color intensity, a transformation that provided more clearly defined plume boundaries. The angle formed between the two peripheral boundaries was measured using SigmaScan Pro® (Systat Software Inc., San Jose, CA). This measurement is similar to the plume geometry measurement recommended by the FDA and described in the draft guidance (Docket No. 99D–1738).[3] Six repeated measurements were made for each device, and four units of each device type were tested.

Human nasal airway replica

The human nasal airway replica was reconstructed from an MRI of a nonsmoking, 53-year-old Caucasian male with no pathophysiological conditions of nasal airway.[9] The model consisted of 72 sections (1.5 mm thick) of acrylic fastened together to form a three-dimensional nasal cavity replica. The posterior sections that form the nasopharynx were fitted to a vacuum line to allow air to be drawn through the cast (Fig. 1A).

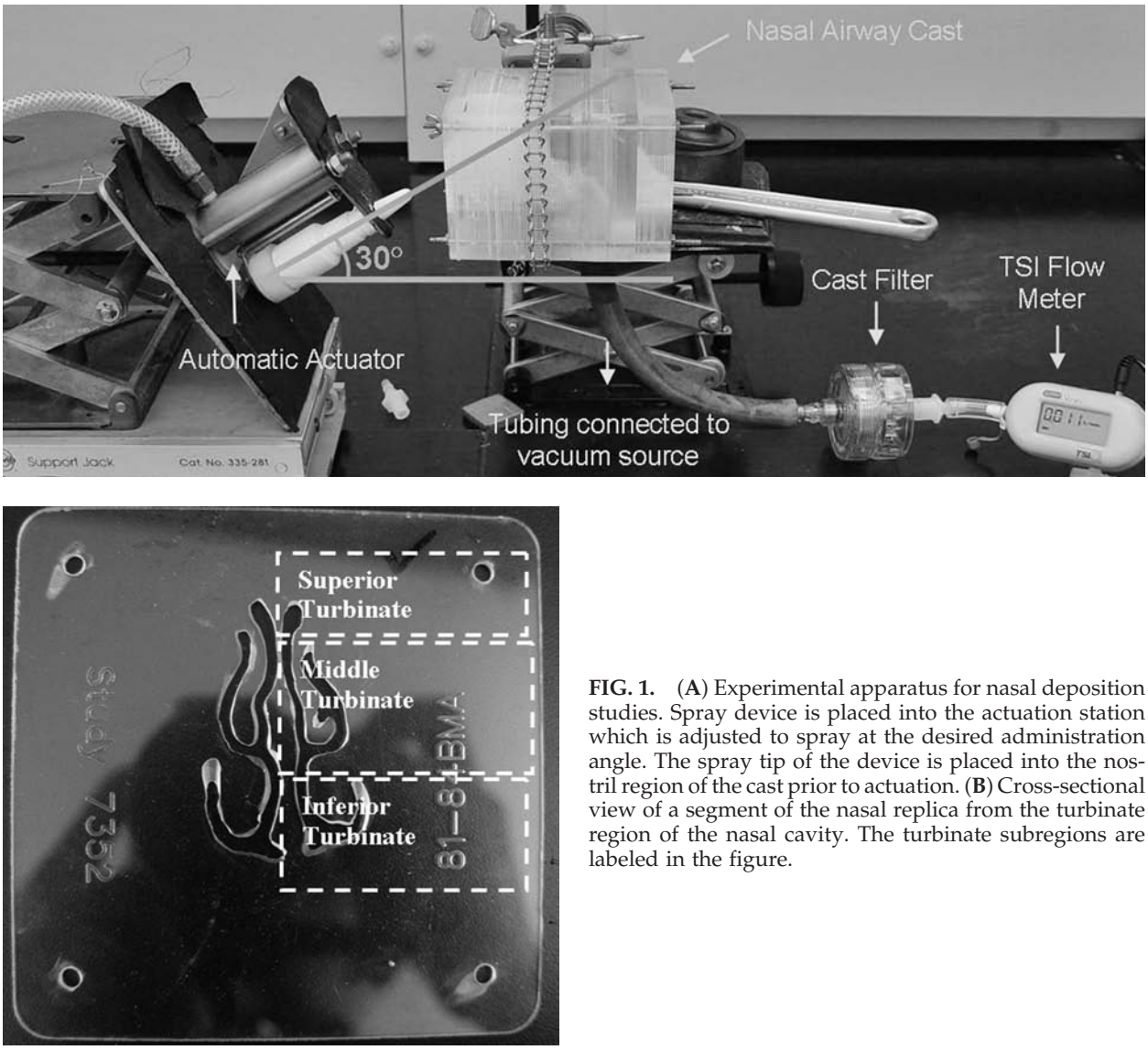

FIG. 1. (**A**) Experimental apparatus for nasal deposition studies. Spray device is placed into the actuation station which is adjusted to spray at the desired administration angle. The spray tip of the device is placed into the nostril region of the cast prior to actuation. (**B**) Cross-sectional view of a segment of the nasal replica from the turbinate region of the nasal cavity. The turbinate subregions are labeled in the figure.

The flow rate drawn by the vacuum was monitored with an in-line digital flow meter (Series 450, TSI Inc., Shoreview, MN). To ensure a leak-free seal between each adjacent acrylic plate, paraffin film was wrapped around the exterior surface of the cast. Deposition data of monodisperse particles obtained in this replica are in agreement with *in vivo* deposition data reported in the literature.[9] The agreement of the nasal deposition data for monodisperse particles suggests that the nasal replica can be used to obtain realistic particle deposition data.

Measurement of deposition in airway replica

To quantify spray droplet deposition within the nasal cast, a fluorescent marker, rhodamine 590 tetrafluroborate (0.42%), was added to each formulation prior to testing. Preliminary experiments demonstrated that addition of the marker had no effect on the viscosity or surface tension of the formulations. Ten milliliters of formulation were placed into each device, and the spray pump was primed at least six times before placing it in the actuation station. The spray device was tilted at an angle of 30, 40, or 50 degrees from the horizontal and the spray tip of the device was inserted into the right nostril of the replica to a distance 1 cm anterior to the nasal valve. A vacuum pump was used to draw an inspiratory airflow of 0, 20, or 60 L/min through the nasal cast. These flow rates were selected to represent breath holding, shallow breathing, and vigorous sniffing. The inspiration was initiated immediately before the device was actuated, and the inspiratory flow was maintained for 5 sec.

The cast was rapidly disassembled with care taken to minimize displacement of the deposited droplets. The anterior (first 22 plates) and nasopharynx (last 20 plates) regions were separated, and each was filled with a 50:50 water/ethanol solution and rinsed to recover any deposited formulation. This step was repeated several times (2–3) and the recovered volumes were combined prior to analysis. Segments from the turbinate region (30 plates, 33 to 78 mm from the nares) were removed as units of three sequential plates for a total of 10 units. The inferior, middle, and superior turbinate regions of each unit (Fig. 1B) were washed carefully by directing a stream of solvent (50:50 water:ethanol) over the region of interest. The volumes collected for each region were diluted to a final volume of 100 mL for analysis. Three repeated deposition measurements were made for each device, and three units for each device were tested.

Fluorometric analysis

The concentrations of rhodamine 590 tetrafluoroborate were measured using a fluorometer (Model 450, Tuner Inc, Sunnyvale, CA) with an excitation wavelength of 500 nm and emission wavelength of 515 nm. The limit of detection for this fluorometric analysis was found to be 0.042 ng/mL. A linear standard curve using concentrations from 0.042 to 63 ng/ml (representing 0.1% to 120% of the actuated dose diluted in 100 mL of wash solution) was used for quantification.

Calculation of deposition efficiency

The deposition characteristics of each spray device were determined from the amount of formulation recovered in the anterior, turbinate, or nasopharyngeal regions of the nasal replica. The delivery efficiency (DE) was calculated from the total amount of marker recovered within the nasal cavity relative to the amount of marker emitted from the device for each actuation [Equation (1)].

$$DE = \frac{A + T + N + F}{E} \quad (1)$$

where A is the amount of marker recovered from anterior region, T is the amount of marker recovered from turbinate region, N is the amount if marker recovered from nasopharynx region, F is the amount of marker recovered from the post-nasopharynx filter, and E is the amount of marker emitted from device (0.42 mg).

Because each turbinate contains three subregions,

$$T = \sum iT + \sum mT + \sum sT \quad (2)$$

where T is the summation of the amount of marker recovered from each of the turbinate subregions for each unit [i = inferior; m = middle; s = superior].

The regional deposition efficiency (RDE) in each anatomical region is expressed by Equation (3).

$$\text{Regional Deposition Efficiency (\%)} = \frac{A,T,N, \text{ or } F}{R} * 100 \quad (3)$$

where R is the the total amount of marker removed from the replica [$R = A + T + N + F$]

The subregion deposition efficiency (SDE)

Table 1. Plume Angles and Droplet Sizes Generated from Various Formulations Using Three Nasal Spray Devices

			Device A		*Device B*		*Device C*	
Formulation	*Viscosity (cP)*	*Surface tension (mN/m)*	*Plume angle (°)*[a]	D_{v50} *(μm)*[a]	*Plume angle (°)*[a]	D_{v50} *(μm)*[a]	*Plume angle (°)*[a]	D_{v50} *(μm)*[a]
Water	0.94	71.99	74.9 (2.3)	39.4 (3.2)	58.9 (2.0)	43.9 (2.3)	70.0 (2.0)	37.4 (3.3)
Methanol	0.60	22.80	79.6 (2.8)	38.5 (2.4)	61.9 (1.4)	40.8 (4.2)	74.0 (1.8)	38.3 (4.2)
Ethanol	1.16	22.16	75.1 (3.9)	39.2 (2.9)	59.0 (1.8)	36.7 (3.0)	72.1 (2.4)	39.1 (3.7)
30% glycerin	2.25	70.39	68.9 (4.2)	43.8 (2.4)	54.1 (2.2)	54.3 (2.8)	66.5 (1.8)	40.6 (1.7)
50% glycerin	5.26	68.85	58.5 (4.7)	65.6 (8.2)	41.8 (6.4)	104.1 (23.1)	51.4 (2.7)	72.2 (8.9)
60% glycerin	9.43	67.82	49.9 (4.3)	110.1 (15.7)	29.0 (4.0)	157.2 (29.3)	41.3 (3.0)	134.9 (17.1)

[a]Mean (standard deviation) for 24 replicate measurements.
Device A = Pfeiffer 29606.
Device B = Valois VP7.
Device C = Pfeiffer 56283.

within each turbinate subregion is expressed by Equation (4).

$$\text{Subregion deposition efficiency} = \frac{\sum iT, \sum mT, \text{ or } \sum sT}{T} * 100 \quad (4)$$

RESULTS

Spray characteristics

The plume angles measured for device A, B, and C were 74.9 ± 2.3°, 58.9 ± 2.0°, and 70.0 ± 2.0°, respectively, when water was sprayed from

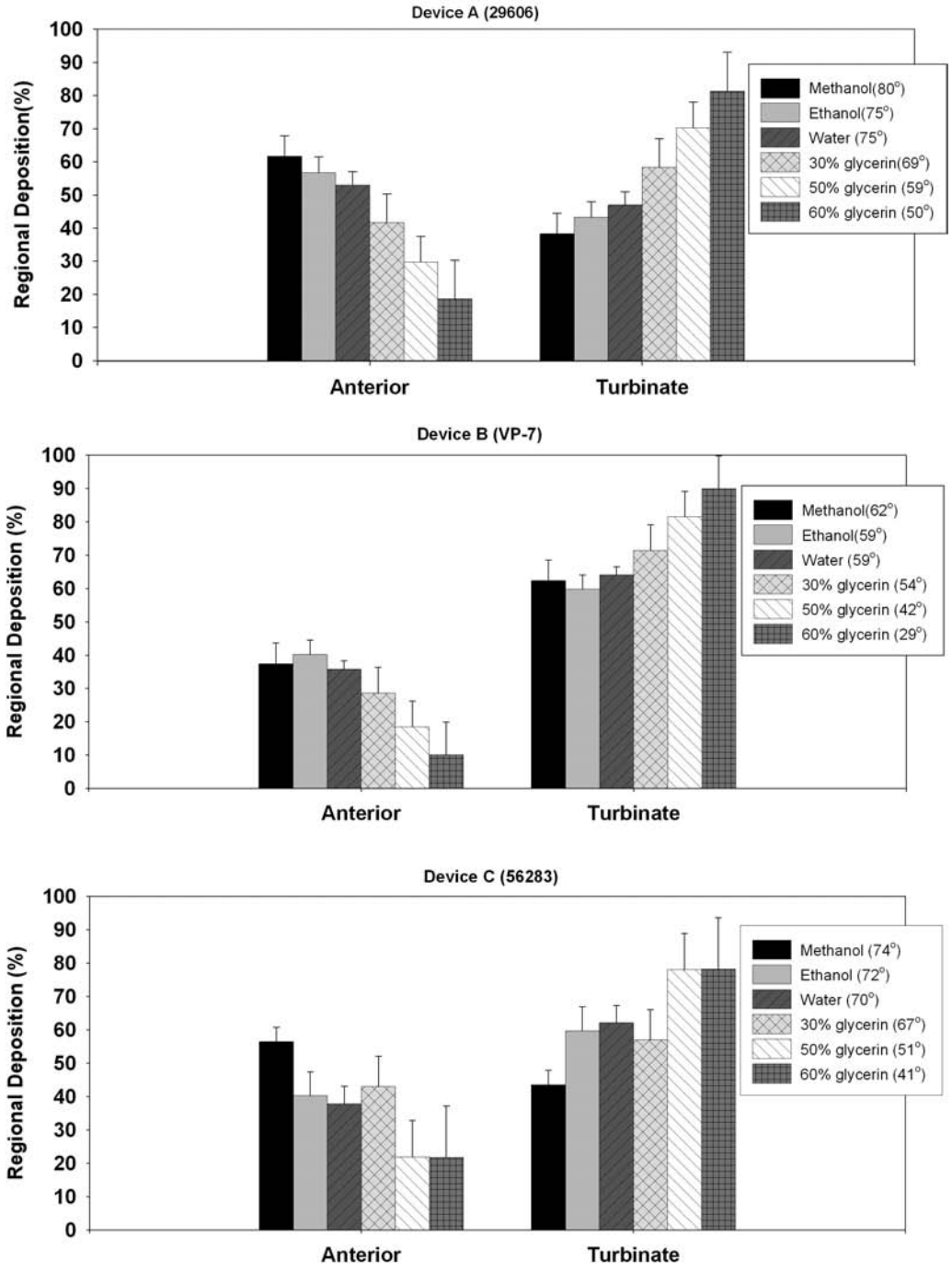

FIG. 2. Deposition in the anterior and turbinate regions of an MRI-derived nasal replica for formulations emitted from three different spray devices using a 30° administration angle. Values in each legend denote the plume angle of each formulation. The data represent the mean and standard deviation of nine replicates of each device:formulation combination.

each device. The volume median droplet size (D_{v50}) for devices A, B, and C were 39.4 ± 3.2 μm, 43.9 ± 2.3 μm and 37.4 ± 3.3 μm, respectively. A variety of additional formulations with various viscosities and surface tensions were measured, and their spray characteristics are summarized in Table 1. In general, increasing formulation viscosity decreased the plume angle and increased the droplet size. The surface tension of the formulation, however, showed little direct effect on the resulting spray properties.

Nasal deposition pattern

The DE ranged between 84% and 96%, with a relative standard deviation for each formulation ranging between 4% and 8%. This suggests that a small fraction of each spray may have been lost to the atmosphere or not completely recovered from the replica or transfer glassware. No bias in DE was observed for any particular device or formulation, however, and no formulation was detected beyond the nasopharynx or filter.

In general, deposition in the anterior region increased with increasing plume angle emitted from the device and, conversely, deposition in the turbinate region increased when the plume angle decreased (Fig. 2). For instance, the turbinate deposition from device A increased from 40% to 80% as the plume angle decreased from 80° to 50°. For device B, turbinate deposition increased from 62% to 90% as the plume angle decreased from 62° to 29°, and for Device C, turbinate deposition increased from 42% to 80% as the plume angle decreased from 74° to 41°.

When comparing between devices, it can be seen that similar deposition patterns were obtained for device/formulation combinations which gave nearly equivalent plume angles, regardless of the emitted particle size (Table 1, Fig. 3). For example, a 50% glycerin/water mixture emitted from device A and water emitted from device B both had plume angles of ~59° (D_{v50} = 66 μm and 44 μm, respectively) and their turbinate deposition efficiencies (RDE) were both ~68%. Regardless of plume angle or droplet size, all of the droplets were deposited within the first 22.5 mm of the turbinate region (total length of the 45 mm), and nearly 80% of the deposition was within the first centimeter of the region (Fig. 4). Examination of the vertical distribution of spray droplets within the nasal replica showed that the majority of the droplets were deposited in the middle and inferior turbinate regions of the replica while the fraction depositing near the superior turbinate in general decreased with decreasing plume angles (Fig. 5).

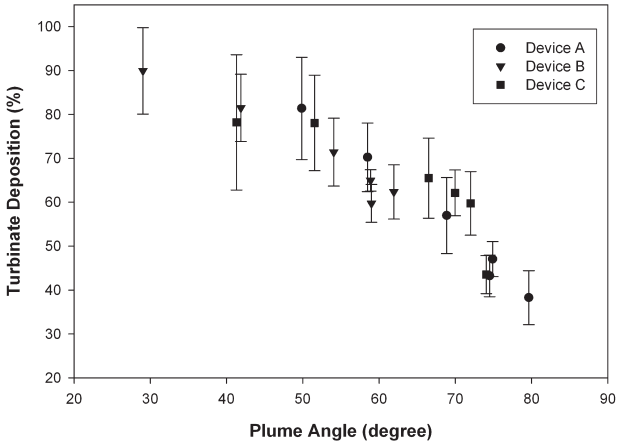

FIG. 3. Turbinate region deposition efficiencies of three pump spray devices administered at a 30° angle into an MRI-derived human nasal cavity replica. The plume angle was determined independently and is the direct result of the device:formulation combination. The data represent the mean ± standard deviation of nine replicates of each device:formulation combination.

Effect of inspiratory flow rate on deposition

Turbinate deposition efficiencies were measured using different inspiratory flow rates (0, 20, and 60 L/min) using methanol, water, and 60% glycerin vehicles in each of the test devices. For each device:formulation combination, there was no change in turbinate deposition efficiency when the inspiratory flow rate was increased (Fig. 6). Yet, as observed previously, there were significant differences in the deposition patterns among the various devices.

Effect of administration angle

Each of the previous experiments was carried out using a 30° administration angle (defined as the angle between the base of the nasal cavity replica and the spray device tip) (Fig. 1A). In actual clinical use, however, it is likely that various administration angles will be used. To determine the influence of the administration angle on deposition efficiency, two other angles, 40° and 50°, were also studied. Changes in administration angle had the greatest influence on the device:formulation combinations which had the narrowest plume angles. For example, methanol gave the widest plume angle for each of the devices, and

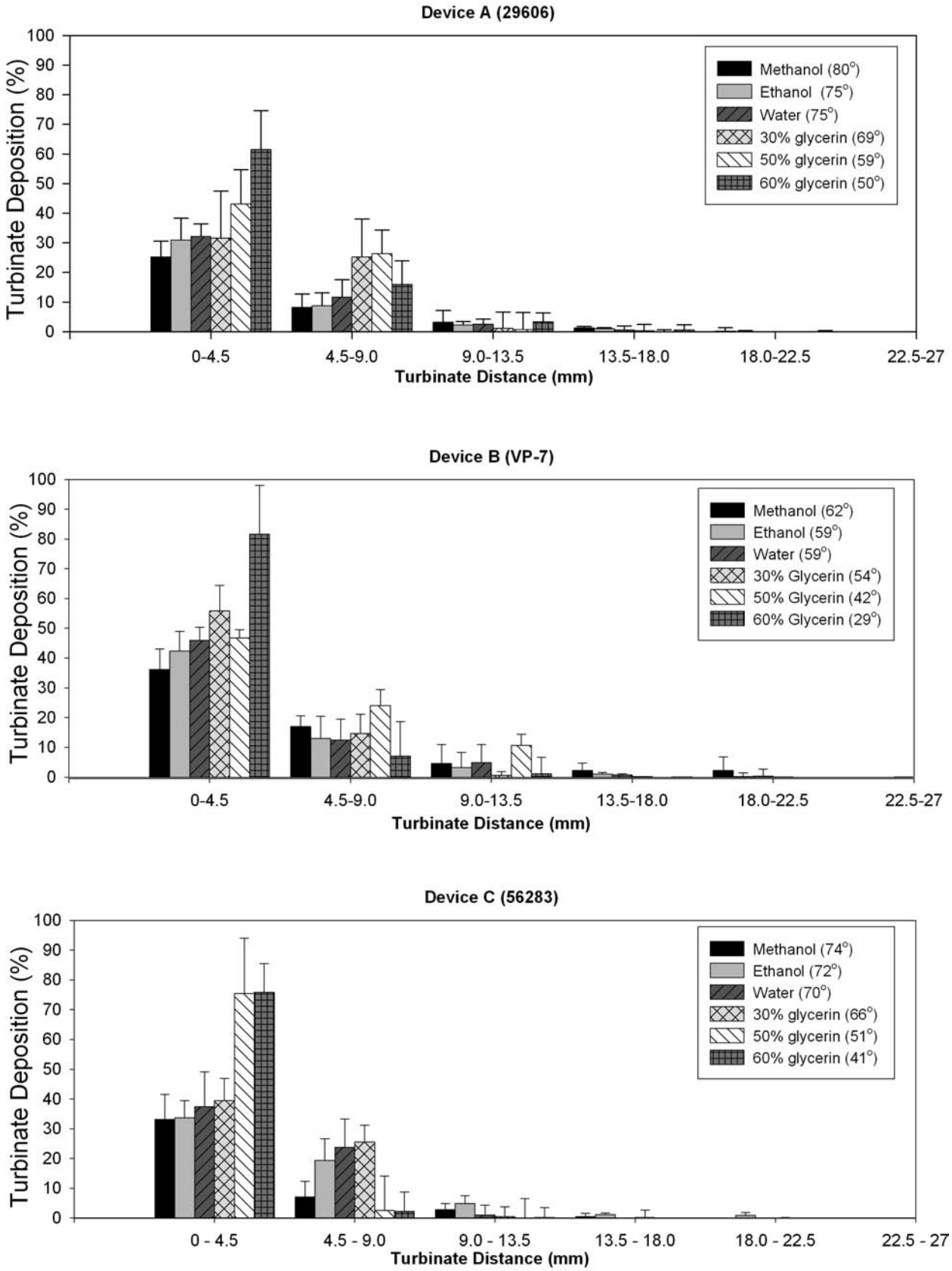

FIG. 4. Spray deposition (30° administration angle) within discrete segments (3 × 1.5 mm units) of the turbinate region of an MRI-derived human nasal cavity replica. Values in each legend denote the plume angle of each formulation. The data represent the mean and standard deviation of nine replicates of each device:formulation combination.

only a slight decrease in turbinate deposition efficiency was observed as the administration angle increased from 30° to 50°. In comparison, 60% glycerin produced the narrowest plume angle in all three devices, and the turbinate deposition efficiency for this formulation declined dramatically from ~80% to ~15% when the administration angle was changed from 30° to 50° (Fig. 7).

DISCUSSION

The nasal valve, a region of the nasal cavity ~3 cm posterior to the nostril opening, has the narrowest cross-sectional area of the entire nasal passage. Due to the airway constriction and turbulent airflow that occurs in this region, the nasal valve has been suggested as the limiting barrier

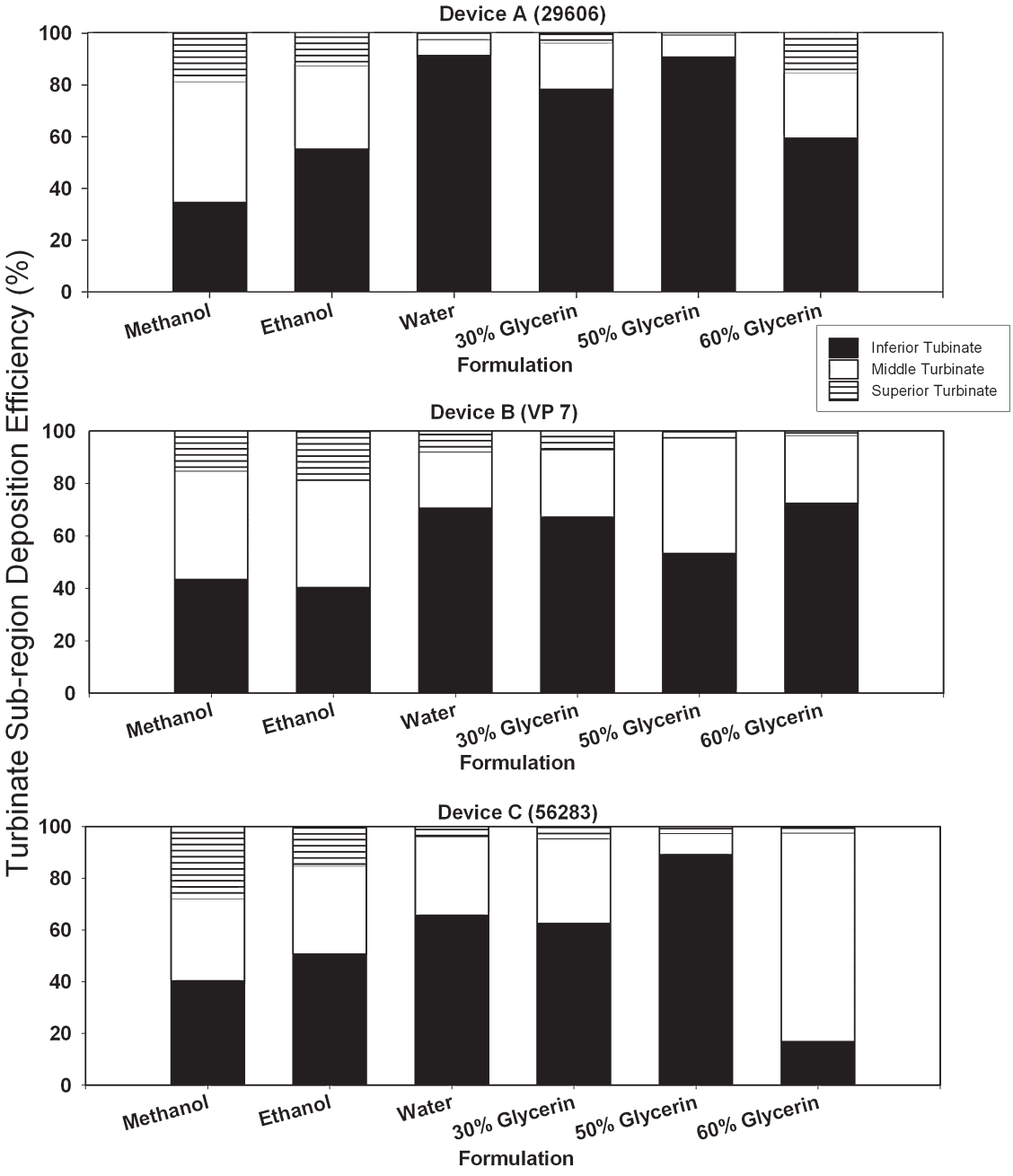

FIG. 5. Deposition pattern within discrete turbinate segments (30° administration angle). Formulation deposited within each subregion, inferior turbinate (filled rectangle), middle turbinate (open rectangle), and superior turbinate (stripe filled rectangle) was collected and efficiency was determined from the sum of the turbinate segments relative to the total amount of formulation deposited in the turbinate region. The data represent the mean regional depositions for nine replicate measurements of each device:formulation combination.

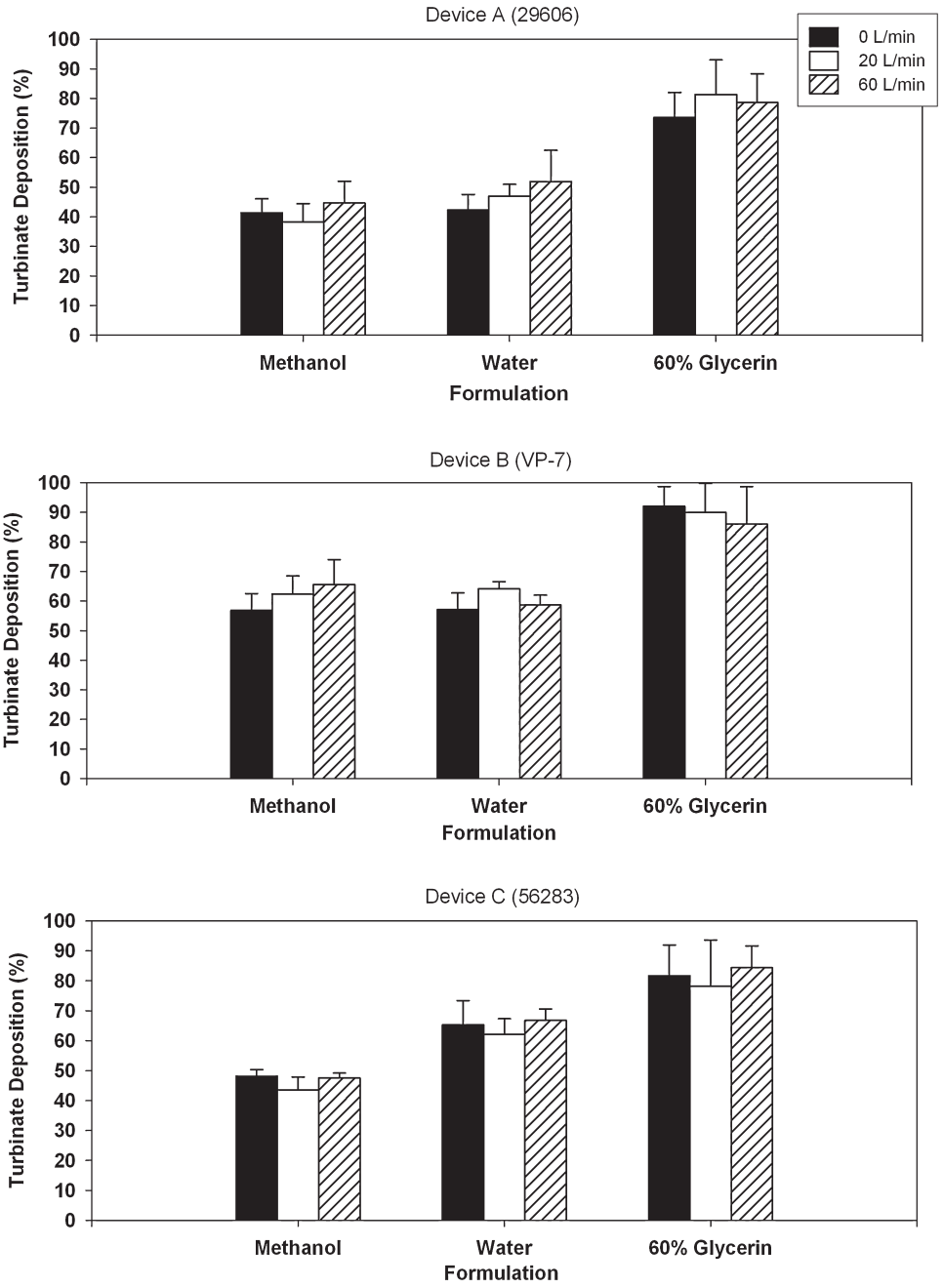

FIG. 6. Turbinate deposition for various device:formulation combinations under different inspiratory flow rate conditions, 0 L/min (filled bar), 20 L/min (open bar), and 60 L/min (stripe filled bar). The data represent the mean and standard deviation of nine replicates of each device:formulation combination. No statistical differences are observed within each device:formulation combination ($p < 0.05$) using one-way ANOVA.

for efficient delivery to the distal regions of main nasal cavity.[14,15] Following pump actuation, the emitted spray plume widens as the spray particles move away from the device tip. Within the nose, however, the airway instead narrows dramatically at the nasal valve. Particles whose trajectories carry them with the airstream through the nasal valve must then be able to pass around the anterior surfaces of the turbinates in order to reach the more distal regions of the main nasal cavity. Deposition patterns in the nasal replica confirmed that the widest plume angles (>70°) had the greatest deposition in the nasal valve region (anterior region; Fig. 2) while those with angles <50° were better able to pass through the nasal valve. The narrowest spray studied (29°;

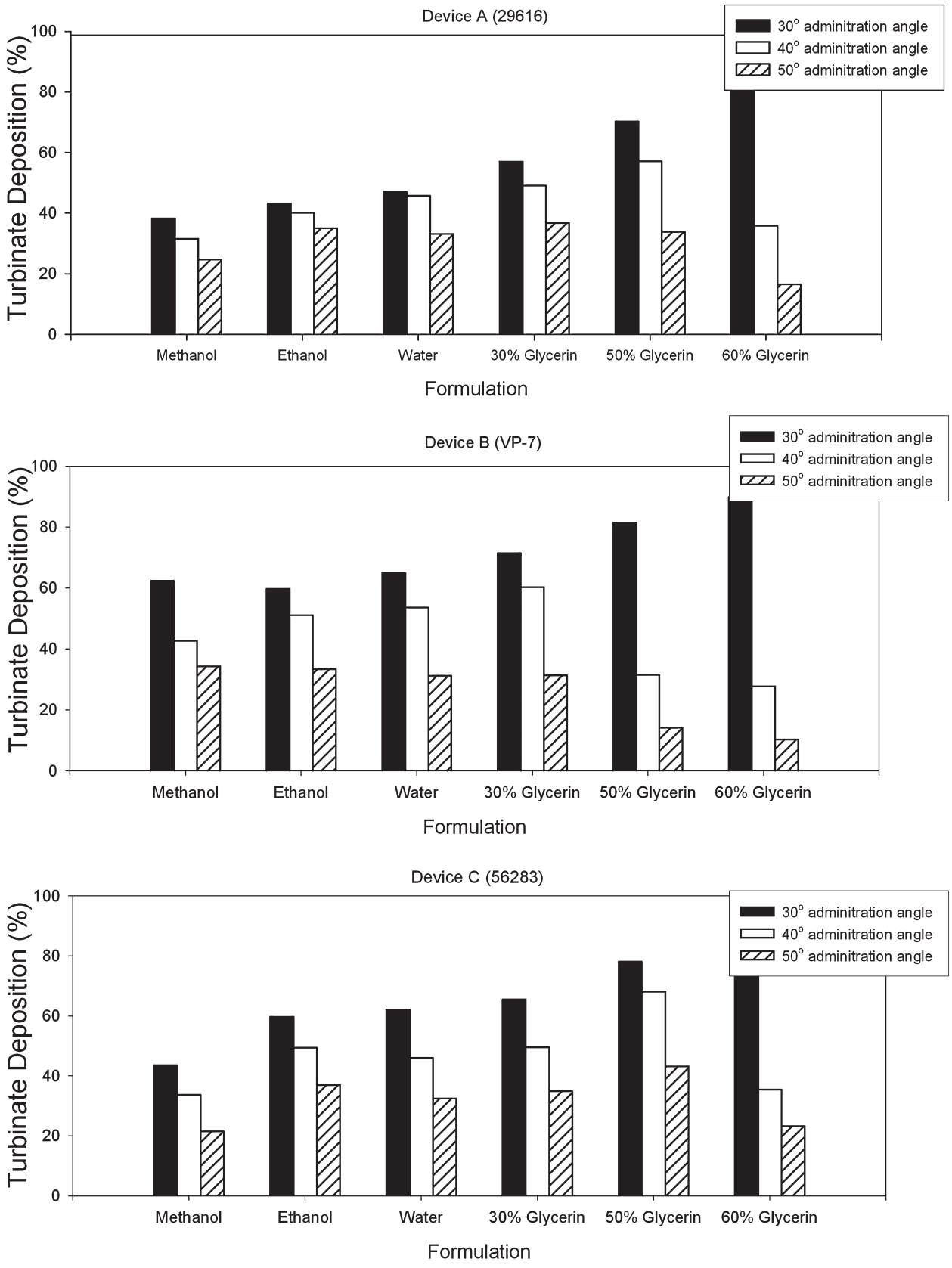

FIG. 7. Turbinate deposition efficiencies for various device:formulation combinations administered at 30° (filled bar), 40° (open bar), and 50° angles (stripe filled bar) into an MRI-derived human nasal cavity (nine replicates).

60% glycerin in device B; Fig. 2) was able to direct nearly 90% of the emitted spray to the turbinate region, demonstrating that a reduced spray plume angle is more compatible with efficient nasal deposition. Similar observations have also been reported in both *in vitro* and *in vivo* experiments.[10,14]

Newman et al.,[14] using gamma scintigraphy, reported that the deposition of a spray with a 35° plume angle gave improved posterior (turbinate) deposition compared to a spray with a similar droplet size (70 μm) but with a 60° plume angle. Cheng et al.,[10] using the same MRI-derived nasal replica as used in the current studies, also showed that sprays with narrower plume angles and smaller droplet sizes were deposited more posteriorly than those with wider plume angles. In comparison, Guo and colleagues[11] compared two cellulose-containing formulations; they observed an improved turbinate-region deposition from the spray with the wider plume angle (67° vs. 32°), and the *in silico* predictions of Kimbell et al.[12] failed to show any effect based on plume angle. The administration angles used in both of these studies were not specified, however, and this factor may have played a significant role in reducing the posterior deposition of the narrow plume angle spray.

Even though both plume angle and droplet size have been suggested to affect deposition patterns observed in the nasal cavity,[10,11] the typical codependence of these factors limits the ability to draw generalizations about the individual parameters. From these studies, it can be seen that the deposition patterns are quite insensitive to the specific device or formulation characteristics, and, in particular, the spray droplet size has little effect on deposition (Fig. 3). Instead, plume angle alone is a very accurate predictor of the resulting deposition pattern. Within the turbinate region, however, the subregion deposition patterns show a significant dependence on the device:formulation combination being used. In nearly all cases, the greatest fraction of the spray was deposited on the surfaces of the inferior turbinate, with significant amounts also impacting on the middle turbinate. This pattern was not unexpected because the inferior and middle turbinates protrude into the airway immediately posterior to the nasal valve. In fact, in some cases this deposition pattern may be clinically useful because increased middle turbinate deposition has been suggested to improve the effectiveness of topical treatments for chronic sinusitis.[16] Deposition in the superior turbinate region was low in all cases, as has been previously reported by Aggarwal et al.[17] due to the barrier-like nature of the inferior and middle turbinates. Although this deposition pattern is extremely effective in protecting the olfactory mucosa, which covers the superior turbinate and other nearby regions, it suggests that alternative delivery devices or platforms will be needed to efficiently target this region for agents utilizing the nose to brain transport pathways.[18]

In addition to the device and formulation properties that influence nasal deposition, user technique may also affect deposition in a manner similar to that observed in the lower airways. A cursory examination of patient instructions for several commercially available nasal spray products finds various recommendations for head position, angle of spray tip, and inhalation pattern relative to spray actuation. Most diagrams provided with these instructions show administration angles between 30° and 45°.[19] Results from the current studies suggest that the administration angle is a critical factor in the efficient delivery of a nasal spray, and should be clarified and emphasized in user instructions. The deposition efficiency decreased in a predictable manner with increasing plume angle when the sprays were administered at a 30° angle. Yet, for 40° and 50° administration angles, the overall deposition efficiencies were much lower (Fig. 8). It is inter-

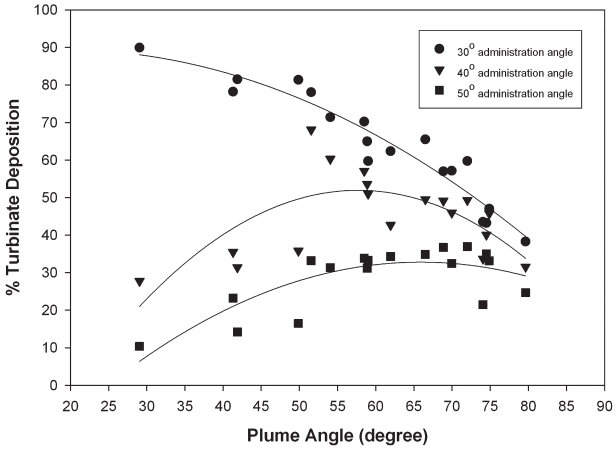

FIG. 8. Composite plot of turbinate deposition versus plume angle with different administration angles. Data points represent all device:formulation combinations tested at a fixed administration angle. Curves are provided for visualization only. No functional dependence is implied.

esting to note that narrow plume angles (30°) give the greatest turbinate deposition when administered at angles that direct the spray through the nasal valve, but for administration angles that direct much of the spray toward the walls of the nasal cavity, the plume angle must be sufficiently wide to allow a reasonable fraction of the spray plume to be directed through the nasal valve. As a result, wider plume angles will likely result in lower, but less technique-dependent, deposition patterns, while high efficiency delivery can only be accomplished with careful attention to the plume angle emitted from the device along with adherence to a clearly described administration technique.

The coordination of spray actuation and nasal breathing is another area of variability in current user instructions. The results of these studies clearly demonstrate that nasal deposition efficiency from pump spray devices is minimally affected by inspiratory airflow velocity. This is likely the consequence of the relatively large droplet sizes and high emission velocities (100–370 cm/s)[6,20] generated from pump spray devices producing particles with significant momentum entering the nasal cavity. The simulation results of Kimbell et al.[12] suggest a more significant dependence on the presence of an inspiratory airflow, however. In this case, the small particle size (20 μm) and the relatively low inspiratory airflow rate (15 L/min) may have enhanced the posterior deposition of these particles by enabling them to travel with the airstream deeper into the nasal cavity.

CONCLUSIONS

The results obtained from these studies provide a rational basis for device and formulation selection for nasal spray delivery systems. Based on the desired site of deposition, target plume and spray administration angles can be identified for optimal site-directed deposition. In addition, the necessity to coordinate specific breathing maneuvers with the spray actuation has been demonstrated to be unnecessary at typical inspiratory and spray velocities. These studies also demonstrate the importance of the inclusion of detailed information regarding administration technique in order to assure that well-characterized device:formulation combinations perform as designed when in the hands of typical users.

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