Evaluating simulated patient use in realistic nasal airway models for the *in vitro* characterization of nasal spray products

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Introduction

In this paper, we seek to present a review of efforts to characterize nasal spray products and highlight some of Virginia Commonwealth University's (VCU's) studies in this area aimed at developing relevant realistic *in vitro* testing methods.

The nasal route of administration presents an enormous opportunity for pharmaceutical drug delivery and yet remains a significant challenge. Effective intranasal drug delivery for the treatment of local and systemic diseases requires that medications overcome natural barriers, including the complex nasal airway geometry of the upper respiratory tract, to penetrate through the anterior nasal region.[1] For the majority of local and systemic delivery applications, drug should be delivered to the nasal middle passages where the middle meatus and the middle and superior turbinates are located.[2] It is also important that there is minimal delivery of drug into the lungs and deposition is confined to the intended site of action.[3-4] The natural anatomical barriers to efficient delivery include the presence of the nasal valve region with its small surface area and changes in airway flow direction toward the turbinate regions. For conventional sinus drug delivery, this is practically impossible, as drug must penetrate through the small sinus ostia, which are in the range of 3-5 mm in diameter for the maxilliary sinus. These ostia are often blocked in sinusitis, and the sinuses remain a poorly ventilated region that makes them difficult to reach with nasal drug products.[5-6]

Specific regional deposition within the nasal upper passages also offers opportunities for nose to brain delivery if the olfactory region can be targeted. Once the nasal barrier functions are overcome, absorption and therapeutic effect can also be affected by the presence of mucociliary clearance, which can result in translocation of the drug to the posterior region of the nasal cavity and nasopharynx within 10-30 min.[7] In addition to the complex nasal passage airway geometry and its inherent defense mechanism to trap the incoming particles/droplets, there is significant inter-subject nasal geometry variability with respect to race, sex and age. Intra-subject variability can also increase variability in the delivered nasal drug dose.[8-9] Finally, it is important to recognize that the nasal spray formulation and device characteristics will also play an important role in determining the regional deposition within the nasal cavity.

The use of clinically relevant *in vitro* tests, which offer the ability to assess the regional nasal deposition for nasal delivery devices, may be advantageous to the pharmaceutical industry in the production of new nasal drug delivery products and to accelerate the development of generic products. Current *in vitro* testing is focused on quality control assessments of droplet particle size (by laser diffraction), plume geometry, spray pattern, priming/re-priming, drug in small particles/droplets and spray dose content uniformity.[4, 10-11] However, none of these tests, which are performed as standalone characterizations, reflect the multi-factorial complexity of nasal drug administration, in which interactions between the (i) patient nasal airway, (ii) patient-use conditions and the (iii) formulation/delivery device will ultimately determine the fate of the delivered drug. It is therefore critical that these three variables are realistically simulated in any *in vitro* study of nasal drug devices and assessment of their delivery performance together with validating that the *in vitro* measurements are reflective of *in vivo* delivery.

Patient nasal airway: Nasal models/casts

Recently, anatomical nasal airway models or casts have been considered as effective tools for clinically relevant *in vitro* testing of nasal spray therapies.[12-14] Initially, the airway models were cadaver-based, which were casts or digitized copies of casts, however there was some concern that these geometries were inaccurate due to post-mortem changes in the airways. Guilmette et al.,[15] described increases in airway passage volume that were attributed to shrinkage of the turbinates in the cadavers. With advancements in the speed and resolution of medical imaging (e.g. MRI and CT) and, more recently, rapid prototyping techniques, there are a growing number of airway models being developed for a variety of emerging applications, including drug deposition and toxicological dosimetry studies.[16-17] Delivery of nasal spray products in realistic airway physical models can potentially allow determination of drug deposition efficiency or even equivalence between products for generic purposes, which may offer significant benefits in the product development process.

However, as mentioned previously, there is significant inter-subject variability in the nasal airways of the patient population and capturing this variability using *in vitro* airway models poses a significant challenge.[18-21] Various approaches to building airway models have been employed including (i) the use of single anatomies from individuals[19-26] or (ii) development of a group of anatomies to represent a range of inter-subject variability or (iii) combined anatomies from several subjects to develop an idealized or average model.[9, 27-30] Two main approaches have been considered for developing idealized/average nasal airway models. One approach is based on finding a characteristic dimension that reduces the inter-subject variability in nasal deposition among a population and making a nasal geometry that represents the average of the characteristic dimension of the population.[30] For example, Javaheri, et al. used hydraulic diameter as the primary dimension that was thought to determine deposition in an idealized infant nasal model.[30] Equally, once a mean characteristic dimension is identified, a patient-specific model can be selected from a group of models that satisfies the mean value. The second approach has been based on averaging the dimensions (mainly cross-sections through the length of nasal airway) of multiple subjects (e.g., 26[29] or 30[28] subjects) and developing a single model that represents the average dimension. For instance, the most recent average nasal model was obtained using a deformable template method for aligning and averaging the nasal airway geometry from computed tomography (CT) scans of 26 individual adults.[29] For this approach, multiple subjects can be considered (e.g., 30) with several anatomies selected to represent a range of characteristic dimensions.[31, 32]

In addition to the contribution of nasal anatomy to inter-subject variability, different approaches to segmenting or defining the so-called regions of interest

Figure 1

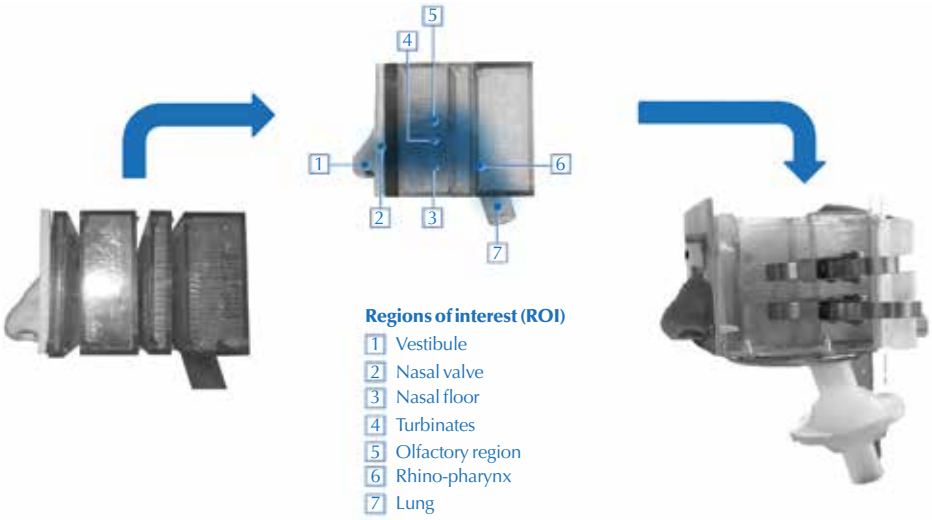
VCU's Human Nasal Model 1[34]

(ROI) for analysis of deposition in the different regions of the nasal cavity adds to the variability in the assessment of sprays using nasal airway models. Some models may have only one or two segments or ROIs,[33, 34] as shown in Figure 1.[34] In contrast, some anatomical models have multiple ROIs,[35] (see Figure 2)[35] with one model having 77 sections.[14] Models of this type can be used to assess parameters such as deposition with liquid or powder nasal drug delivery devices, or the effect of patient-use parameters such as delivery orientation or insertion angle.[12, 36-38] Quantitative assessments of regional drug deposition can be made using drug formulations, model compounds such as fluorescein, or radiolabels, together with the use of water-sensitive gels on the surface of the airway model to visualize deposition.[33, 35, 39, 40]

It is important to recognize that there are some limitations of *in vitro* nasal airway models. Due to their rigid, inflexible structure, they are unable to simulate the forces present due to the Bernoulli principle during inhalation, which cause narrowing of the nasal valve with increasing inspiratory flow rate.[6] However, despite this drawback, the models appear useful to evaluate the initial site of drug deposition. The ability to investigate the fate of the deposited drug is limited in the physical model due to the lack of a mucociliary clearance (MCC) function. Therefore, it is not possible to determine the translocation of drug following deposition, which will ultimately control local nasal respiratory epithelial uptake and systemic drug absorption. Alternative approaches include computational fluid dynamic modeling, which can be used to predict the fate of suspended drug particles in nasal spray droplets from the point of nasal deposition to the systemic absorption. Rygg et al., predicted spray droplet deposition locations in a three-dimensional (3D) nasal cavity, which were then translated into a nasal dissolution absorption and clearance model (nasal-DAC) and coupled with an integrated compartmental pharmacokinetic (PK) model to generate systemic plasma concentration/time profiles. The drug deposition prediction in the 3D model of the human nasal cavity was validated

Figure 2

Aptar Pharma & DTF/University of Tours (CEPR-INSERM U1100) Human Nasal Model[35]



using *in vitro* nasal deposition study in a physical airway nasal model with identical dimensions and geometry to the computational model.[41]

Patient-use conditions: Experimental considerations using human nasal airway geometries

For *in vitro* testing of novel delivery devices or comparison of innovator and generic nasal products, studies must be performed using test conditions that are designed to simulate patient use, with a realistic nasal airway model that will allow for a range of different patient-use variations. For most of these products, patients are advised to clear the nostril before use. The priming and re-priming instructions vary between products given that they have been developed based on a particular spray pump model. There are no uniform instructions provided to the patients with respect to head position (vertical, tilted forward, tilted backward), nasal spray position within the nostril (insertion depth, insertion angle) or nasal inhalation (inhalation rate, inhalation timing) provided in patient information leaflets. It is interesting to observe that instructions for use of commercially available, locally acting, corticosteroid nasal sprays have both similarities and some significant differences across spray devices, which may make describing uniform *in vitro* testing conditions problematic. However, studies have clearly shown that the selection of appropriate, simulated, patient-use conditions is important, as it will play a significant role in determining the deposition site of the nasal spray.[17, 42, 43]

A number of studies have investigated the effects of patient-use parameters on the deposition of nasal sprays in realistic airway models. The patient-use variables have included the position of the nasal spray and airway model, inhalation profiles and the nasal spray actuation conditions.[17, 34, 42, 43] However, the conclusions regarding the significance of each parameter with respect to determining nasal deposition are sometimes contradictory. As an example, there are a number of *in vitro* studies that have failed to show any change in *in vitro* nasal deposition profile using either constant inhalation air flow or realistic inhalation profiles and when testing in the absence of inhalation flow.[12, 40, 43] Other studies have indicated that the presence of an inhalation during nasal spray actuation does have a significant effect on the nasal drug deposition profile.[34, 37] These apparently contradictory findings may be due to differing experimental conditions that were employed to perform these studies.

Validation approaches of nasal airway models

One approach taken to develop and validate such an anatomically correct nasal model has been to create a plastinated nasal model from a human male cadaver. This model was validated anatomically, geometrically and aerodynamically using techniques such as endoscopy, CT scans, acoustic rhinometry and rhinomanometry.[44] The model was further validated with *in vivo* data by comparing the *in vitro* regional deposition of a radiolabeled nasal spray in the model (developed from a 3D scan) to deposition measured in seven healthy volunteers using scintigraphic imagining.[33, 45] In order to measure regional drug deposition in the model, the nasal cast was divided into several sections including vestibule/nasal valve, nasal floor, turbinates, olfactory region, nasopharynx regions and lung (Figure 2). These kinds of approaches can provide realistic models of nasal airways and can be very useful tools to study nasal air flow, drug delivery and aerosol deposition studies *in vitro*. However, well established *in vivo/in vitro* correlations between spray deposition across the range of nasal models and human subject studies have yet to be developed and further studies are needed.

Study of the effects of patient use and formulation variables on nasal deposition

We performed a multi-factorial, *in vitro,* realistic nasal deposition study to identify critical patient-use variables that should be controlled during testing. The study was also used to demonstrate the range of nasal deposition that can be achieved in a single airway model with just manipulation of two factor experimental conditions and their interactions.

Methods and materials

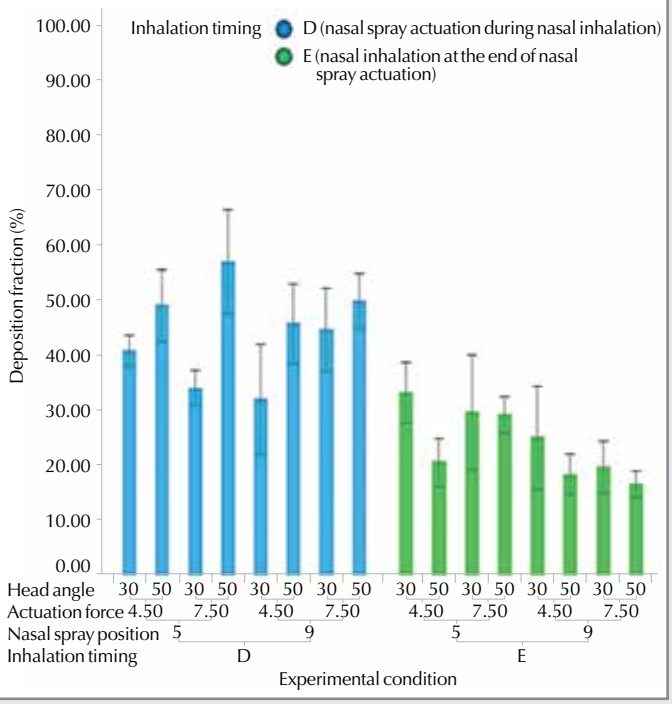
Nasonex® nasal spray (Merck & Co. Inc., Whitehouse Station, NJ) containing 50 µg mometasone furoate (anhydrous) per spray was used as the model suspension nasal spray formulation. The variables considered were aspects of the nasal spray actuation: nasal inhalation timing (actuation during inhalation (D) or inhalation at the end (E) of actuation), head angle (30º or 50º), nasal spray position (5 mm or 9 mm from the front of the nostril) and actuation force (4.5 kg or 7.5 kg).[17, 34] Drug distribution in the anterior nose and the combined middle passage and nasopharynx regions was evaluated during *in vitro* regional deposition testing, which utilized an automated nasal spray actuator to control the actuation parameters, a realistic physical model of the nasal cavity (VCU model 1; Figure 1) attached to a low-resistance inspiratory filter and a breath simulator to facilitate the nasal breathing. A nasal breathing profile with a peak inspiratory flow rate of 35.8 L/min was used.[43] For each experiment, two actuations were administered into one nostril while the other nostril was blocked. A validated high performance liquid chromatography (HPLC) method for mometasone furoate was used to measure the drug deposited on the nasal spray device, in the nasal model and on the low-resistance inspiratory filter at the end of the model throat. Drug was extracted by washing using an appropriate volume of methanol/water (50:50 %v/v).[17]

Results

The mean (standard deviation; SD) drug recovery ranged from 87.3% (1.7%) to 100.6% (5.8%) of the label claim. Figure 3 shows the mean (SD) *in vitro* drug delivery to the combined middle passage and nasopharynx region in the multi-factorial study, which ranged from 16.6% (2.4%) to 57.1% (9.4%) of the recovered dose. Previous reports for *in vivo* deposition results revealed that regional nasal drug deposition varies widely for nasal spray products, with mean middle-passage deposition for the Nasonex product being reported as 65% and about 35%.[46, 47] The outcome measure for statistical analysis of the *in vitro* results was defined as the combined middle passage and nasopharynx deposition. Performing full factorial ANOVA on the results demonstrated that the nasal spray actuation during nasal inhalation (D) could increase drug delivery up to three-fold to the posterior part of the nasal cavity and significantly reduce the fraction of drug deposition in the anterior region of the nose compared to the situation when nasal breathing started after nasal spray actuation (E) (p value < 0.0001). Other critical factors were recognized as the position of nasal spray within the nostril (p value = 0.0048) and the possible interaction between nasal inhalation timing and head angle (p value < 0.0001) for the tested nasal spray product.[17, 34] The importance of the spray plume release point controlled by nasal spray positioning in the nose or head angle was also previously deemed to be important and recognized in many *in vitro* and CFD studies.[34, 42] Clearly, it has been demonstrated that simulated patient-use experimental conditions can significantly influence the *in vitro* regional drug deposition of nasal spray products in realistic nasal models. While isolating individual patient-use variables is relatively simple in the laboratory, it is still largely unknown how these variables translate to the observed *in vivo* nasal deposition as a patient uses the nasal spray in practice, due to confounding issues such as inter-subject variability.

Figure 3

Mean (error bars are standard deviation, n = 4) combined drug deposition in middle passage and nasopharynx regions in VCU's nasal model 1 (expressed as percent of recovered dose) for Nasonex® nasal spray. The x-axis represents the experimental conditions in four lines: 1) head angle (30º or 50º), 2) actuation force (4.5 kg or 7.5 kg), 3) nasal spray position (9 mm or 5 mm) and 4) nasal inhalation/nasal spray actuation timing (D: nasal spray actuation during nasal inhalation, E: nasal inhalation at the end of nasal spray actuation with an inhalation rate of 35.8 L/min).



Device and formulation: Comparison of innovator and generic nasal spray products

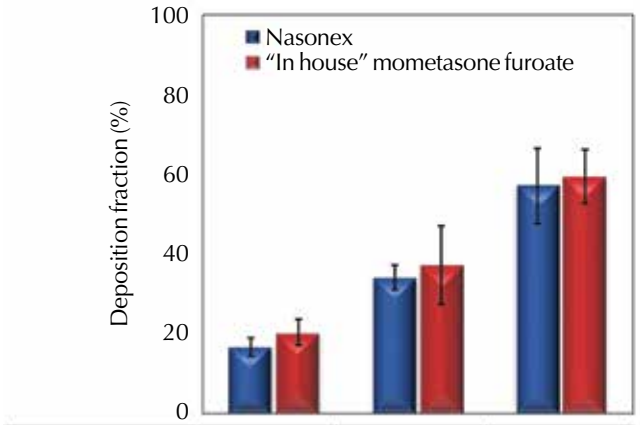
The combination of device, formulation and the effect of the resultant spray plume on nasal deposition should also be assessed using realistic *in vitro* test methods. An example of such an application is use of realistic *in vitro* test methods to compare innovator and generic nasal spray products.

Methods and materials

Using the methods and materials described above, this approach has been adopted to investigate the similarity of two products in a single nasal airway model (VCU's Model 1) by employing patient-use conditions that produce "low" (about 20%), "intermediate" (about 40%) and "high" (about 60%) combined middle passage and nasopharynx region deposition. With this approach, the possible "*in vivo*" deposition variability for two device/formulation combinations were

Figure 4

Mean (error bars are standard deviation, n = 4) combined drug deposition in middle passage and nasopharynx regions in VCU's nasal model 1 (expressed as percent of recovered dose) for Nasonex and "in house" mometasone furoate nasal spray products. Simulated patient-use conditions were used to generate low (~20%), intermediate (~40%) and high (~60%) deposition, respectively. The x-axis represents the experimental conditions in four lines: 1) head angle (30º or 50º), 2) actuation force (4.5 kg or 7.5 kg), 3) nasal spray position (9 mm or 5 mm) and 4) nasal inhalation/nasal spray actuation timing (D: nasal spray actuation during nasal inhalation, E: nasal inhalation at the end of nasal spray actuation with an inhalation rate of 35.8 L/min).



Head angle	50	30	50
Actuation force	7.5	7.5	7.5
Nasal spray position	9	5	5
Inhalation timing	E	D	D

Experimental condition

simulated and the regional nasal deposition of an "in house" generic mometasone furoate nasal spray formulation (Aptar VP3/93 pump with 404E/A4 internal gasket, 908 EVA neck gasket and 40 mm visible dip tube; AptarGroup Inc., Le Vaudreuil, France) which was Q1/Q2 equivalent to the innovator product, Nasonex nasal spray, against which it was compared. Three sets of simulated patient-use experimental conditions were chosen to produce low, intermediate and high combined middle passage and nasopharynx region drug delivery to the middle passage of VCU's nasal model 1.[17]

Results

The mean (SD) combined middle passage and nasopharynx region drug deposition for "in house" mometasone furoate nasal spray product was 20.2% (3.2%), 37.0% (9.9%) and 59.1% (6.8%), respectively, which was not significantly different from the observed values for Nasonex when tested under identical patient-use testing conditions in VCU's nasal model 1 (Figure 4). These initial investigations appear to indicate that using this *in vitro* test method with nasal spray devices/formulations with similar spray plume characteristics (data not shown here) produces similar regional nasal deposition profiles when tested using a range of simulated patient-use conditions.

Conclusions

Realistic *in vitro* nasal model protocols should be based on recommended patient-use information and *in vitro* experimental conditions should be precisely controlled if reproducible results are to be obtained. If nasal *in vitro* tools are developed in this way, they could eventually play an important role in nasal product developments and they could provide reliable *in vitro* tools that can predict and compare deposition patterns in the nasal cavity. It will be important to examine the nasal drug delivery efficiency of the products in a series of nasal airway models representing the variability observed in the patient population with respect to airway geometry. This systematic evaluation of geometric variability may also allow the identification of a useful averaged model. The ability of these *in vitro* nasal models to distinguish nasal spray products with clinically meaningful differences in spray plume properties also needs to be established. Perhaps a series of nasal spray formulation/device combinations with a different range of spray plume geometry (angle, width as well as spray area) and droplet sizes can be used to establish the usability of these models. Standardization of the nasal airway model geometry and test methods will contribute to the development of this approach as a regulatory tool for assessing new products in development and generic nasal sprays.

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