# Development of an In Vitro Method for In Vivo Prediction of Regional Deposition of Nasal Powders

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## Introduction

In vitro models of realistic nasal cavities have previously been used to study regional deposition of nasal solution and suspension spray products. Determination of regional deposition from inhaled drugs is important for understanding in vivo performance because absorption and mucociliary clearance vary by region, and some drug products may target specific regions. Dry powder nasal drug products have not been tested in these types of in vitro models, due to a lack of these products on the U.S. market. However, two products were recently approved, sumatriptan succinate nasal powder for treatment of migraines in 2016 [1] and glucagon powder for severe hypoglycemia in 2019 [2], and there is also current interest in predicting regional deposition of nasally insufflated opioid abuse deterrent formulations (ADFs). The objective of this study was to develop an in vitro method capable of accurately quantifying regional deposition of nasal powders and validate against existing in vivo nuclear imaging data from the literature [3].

## Materials and Methods

A patient-specific 3D nasal model was designed based on computed tomography scan data, configured for bidirectional delivery, and decomposed into nasal cavity regions that correspond to regional definitions from Djupesland and Skretting [3]. The resulting design was built using a stereolithography technique (Formlabs Form 2, clear resin) (Figure 1). The model was printed to allow for alternating between right or left nostril actuations. The internal nasal cavity pieces were coated with a 1:2 glycerol:methanol mixture and allowed to air dry prior to assembly.

Onzetra Xsail (Currax Pharmaceuticals LLC, Brentwood, TN, USA) devices from the same lot (Lot no. 0017R) were used in this study. Used nosepieces were disassembled and cleaned/dried prior to reassembly with hydroxypropyl methylcellulose (HPMC) capsules (Quali-V®-I, Qualicaps® Inc., Whitsett, NC, USA) loaded with 16 mg lactose monohydrate (LMH) (Lactohale® LH210 median particle diameter [D50] = 16 µm, or LH100 [D50] = 132 µm, DFE Pharma, Goch, Germany) (Figure 2). The capsules were loaded with LMH rather than the active ingredient in Onzetra Xsail (i.e., sumatriptan succinate) to closely replicate the methods used in Djupesland and Skretting [3] that utilized capsules filled with 99mTc-labeled lactose powder. One dose (i.e., one nosepiece) was actuated using an exhalation flow rate of 100 L/min of laboratory compressed air applied to the mouthpiece for 3 seconds during each experiment. Nasal cavity pieces were carefully disassembled and washed with 10 or 20 mL of the diluent/mobile phase (degassed 18 MΩ water). High performance liquid chromatography (HPLC) equipped with a Refractive Index Detector (RID) was used to quantify LMH recovery from particles deposited on individual pieces of the nasal model. The LMH weight was used to determine recovery percentage for each region within the nasal model. Experiments done in high humidity conditions (temperature [T] = 73°F, relative humidity [RH] = 95-98%) were completed in a glove box with an ultrasonic mist generator. Low humidity conditions were set at T = 73°F and RH = 16-36%.

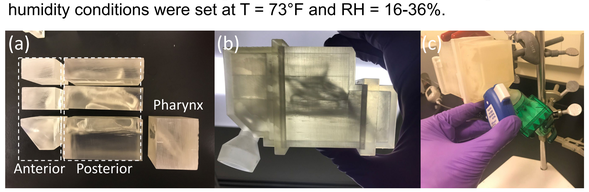


**Figure 1.** Representative depictions of the (a) in vitro resin pieces built using stereolithography of all internal nasal cavity regions (anterior, posterior, and pharynx), (b) the fully assembled in vitro model with outer casings and filter adapter (lower left) and (c) the setup for bidirectional delivery with filter attached (green).

## Takeaway: The in vitro method developed in this study using a 3D printed nasal cavity model showed a good in vivo representation for regional deposition of nasal powders.

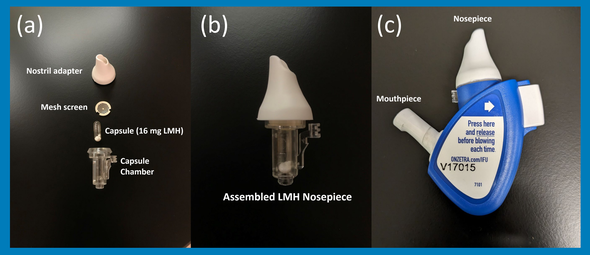


**Figure 2.** Representative images of (a) a disassembled nosepiece showing the individual components and capsule containing 16 mg of lactose monohydrate (LMH), (b) fully assembled nosepiece, and (c) Onzetra Xsail delivery device loaded with one nosepiece.

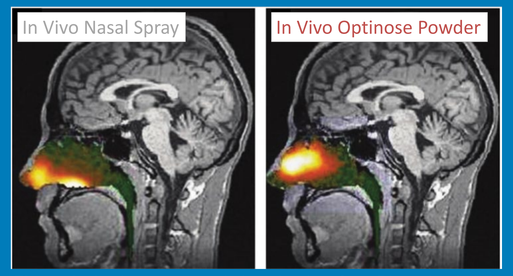


**Figure 3.** In vivo gamma scintigraphy data from Djupesland and Skretting [3] showing deposition profiles (in % gamma scintigraphy intensity) using nasal spray (left) and Optinose device (right).

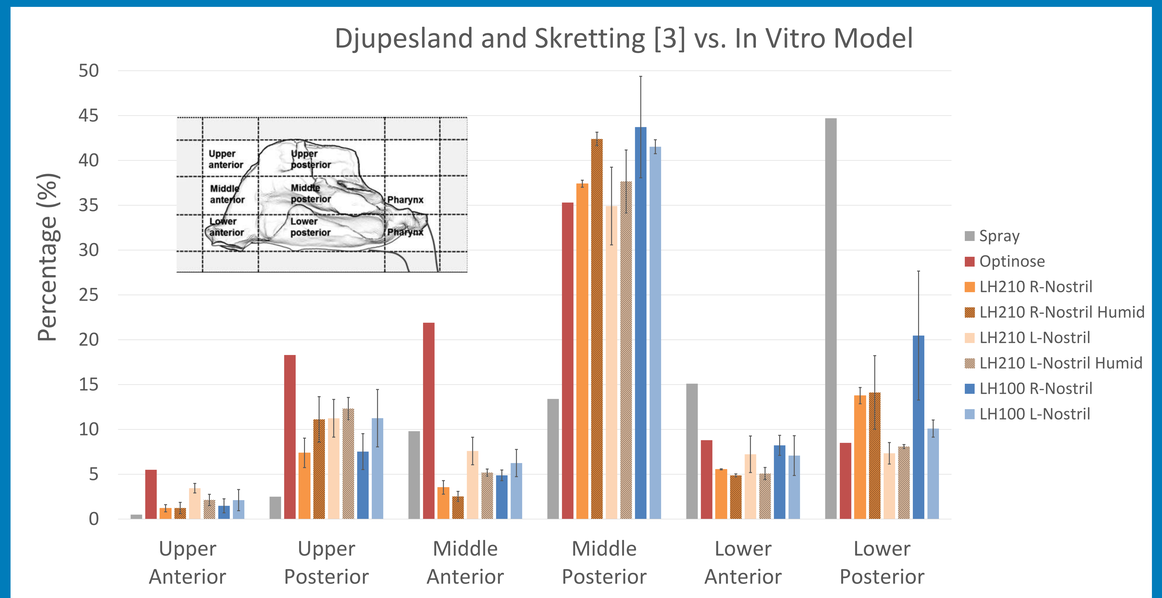


**Figure 4.** All LMH data (LH210 and LH100), collected with either the right (R) or left (L) nostril in vitro model and given as mean ± standard deviation (n = 3), compared to mean in vivo literature data (n = 7) [3]. Percentage for LMH data (LH100 and LH210) is the percentage of emitted dose collected, whereas percentage for in vivo data (Spray and Optinose) is a normalization of the regional image intensities.

## Results and Discussion

Data were collected using either the right (R) or left (L) nostril in vitro model from fine LH210 (orange) and coarse LH100 (blue) powders (Figure 4). Results show the models capture approximately 90% or greater of the emitted LMH dose with less than 5% depositing in the filter or outer casings (i.e., pharynx holder and holders). It should be noted that small amounts of deposition were expected on the casings as the pharynx holder is used to block the pharynx region during bidirectional delivery and the filter adapter is also exposed during collection.

Both R and L nostril models showed large deposition in the middle posterior region regardless of the particle size or humidity conditions. There was a slight increase in deposition in the upper posterior region when using the left nostril model, which could be due to the asymmetrical cavity of this specific nasal model. High humidity conditions (RH = 95-98%) had little effect on the deposition profile with a slight decrease in the anterior region and slight increase in the posterior region.

Comparisons between fine and coarse powders (i.e., LH210 and LH100, respectively) were difficult due to the high variability of LH100 powder using the right nostril model. The largest deviations occurred in the middle posterior, lower posterior, and pharynx regions. Considering the same percent emitted dose collected between experiments, this powder/model combination distributed the powder unevenly within these three regions.

Figure 4 additionally shows the comparison of the fine powder data (LH210) and in vivo gamma scintigraphy data from Djupesland and Skretting [3] from a nasal spray and the Optinose device (Figure 3). The LH210 powder has a similar particle size distribution ([D50] = 16 µm) to the radiolabeled particles used in the in vivo experiments (mean D50 = 15 µm), allowing for a direct comparison. All LH210 data generally agrees with the in vivo Optinose, i.e., Onzetra Xsail, deposition pattern data (Figure 4, red), showing largest deposition in the middle posterior region and low deposition in the lower posterior region, a major region for typical nasal sprays to deposit (Figure 4, gray).

## Conclusions

- The in vitro method developed in this study using a nasal cavity model showed a good in vivo representation for regional deposition of nasal powders.
- The method may be insensitive to substance type, but additional data would be needed to confirm this claim.

## References

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3. Djupesland PG, Skretting A: Nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. J Aerosol Med Pulm Drug Deliv 2012, 25:280-289.

## Disclaimer

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.