Development of *In Vitro* Nasal Cast Imaging Techniques to Predict *In Vivo* Nasal Deposition

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INTRODUCTION

Deposition studies in nasal casts models are continually evolving, as imaging and reconstruction software has made it possible to produce physical models with correct nasal geometry and dimensions in rigid materials by modern 3D printing techniques, like stereo-lithography. However, some caution is necessary as such casts may not realistically represent entirely the nasal valve dynamics, the specific physiology of the mucosa, or accurately represent the *in vivo* surface properties of the nasal mucosa, including the impact of mucociliary clearance [1]. Ultimately, human *in vivo* deposition, clearance studies, and relevant human clinical trials, would still be required for proof of deposition and efficacy of any nasal drug delivery device [2, 3]. However, *in vitro* nasal casts could serve as predictive tools for nasal deposition *in vivo,* but as such these casts should be validated.

This work describes the comparison of two analytical methods, an *in situ assay* method and an imaging method by gamma camera, to quantify radioactivity deposited in an *in vitro* nasal cast model to predict *in vivo* scintigraphy deposition.

METHODS AND MATERIALS

Nasal Cast Model

The nasal cast model used was constructed from epoxy plastic, based on computed tomography (CT) scans of a plastinated head model [4], previously validated as a predictive model for nasal aerosol deposition [5]. Figure 1A shows the four parts of the nasal cavity from the nose to the nasopharynx, allowing the *in situ* deposition of particles in each region of interest (Figure 1B). The

nose component was built using silicone to represent the flexibility of the human nostril. Based on Buck *et al.* [6], about 1/3 of the upper part of the nasal cavity, between the nose/nasal valve and the rhino-pharynx, was considered to be the area that defines the olfactory epithelium, often targeted for the nose to brain drug delivery pathway.

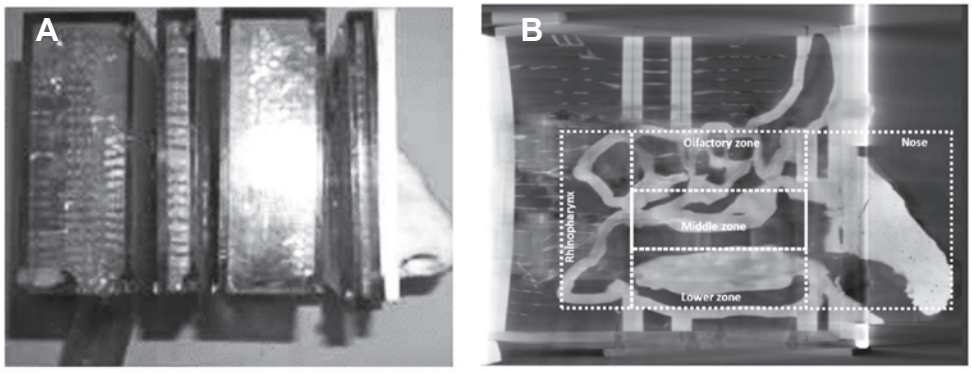

Figure 1. A: Nasal cast parts. B: Nasal cast regions of interest.

Nasal Spray Devices and Radiolabeled Formulations

Two different nasal devices and formulations were used to investigate deposition *in vitro*. A commercialized off-the-shelf liquid spray pump (VP7, Aptar Pharma) was used to deliver one dose of 50µL diethylenetriaminepentaacetic acid (DTPA) -Tc^{99m} radioactive liquid per nostril. After the labeling procedure, particle size distribution was measured by laser diffraction (Spraytec, Malvern) and characterized as: 19µm Dv10, 39µm Dv50, and 83µm Dv90, respectively.

An optimized unit dose powder device (UDS powder, Aptar Pharma) filled with lactose powder labeled with DTPA-Tc^{99m} was used to deliver one dose of 10 mg per nostril. The lactose particle size produced by the unit dose powder device was measured by laser diffraction after the labeling procedure and was characterized as: 31µm Dv10, 80µm Dv50, and 190µm Dv90, respectively.

***In Situ Assay* method**

After the radioactive aerosol administration, the nasal cast plates were removed and each region of interest (Figure 1B) was rinsed with a specific volume of water. The radioactive concentration in the resulting solution was obtained by using a radioactive counter (Isocompt). The deposited radioactivity was then deduced and normalized per region.

Imaging Method

After the radioactive aerosol administration, the nasal cast was imaged by a gamma camera. Radioactivity marks (scotch stained with radioactivity) were added on some anatomical points of the nasal cast in order to define the regions of interest. These regions were the same as defined in the *in situ* method. The radioactivity imaged in each region of interest was then determined and normalized per region.

RESULTS AND DISCUSSION

A difference in terms of radioactive distribution deposition was found in the nasal cast between the liquid nasal spray and the unit powder device. Although the *in situ* method and the imaging method did not show equivalent deposition measurements in each region of interest, higher deposition in the olfactory region was observed for the unit dose powder device, compared to the liquid nasal spray pump (Table 1 and 2). Figure 2 shows the radioactive deposition in the nasal cast obtained by single photon emission computed tomography (SPECT) image method. The deposition of radioactivity in the upper part of the nasal cast was higher with the unit dose powder compared to the liquid nasal spray.

Table 1.

Deposition in the nasal cast model with a liquid nasal spray pump (%) (n=4).

Regions of interest	***In situ* method** Radioactivity per region / total deposited radioactivity (%) (mean +/- SD)	**Imaging method** Radioactivity per region / total deposited radioactivity (%) (mean +/- SD)
Nose	76 ± 6	51 ± 6
Rhinopharynx	0 ± 0	1 ± 0
Lower zone	2 ± 0	13 ± 5
Middle zone	20 ± 6	30 ± 2
Olfactory zone	2 ± 1	6 ± 3

Table 2.

Deposition in the nasal cast model with a unit dose powder device (%) (n=4).

Regions of interest	***In situ* method** Radioactivity per region / total deposited radioactivity (%) (mean +/- SD)	**Imaging method** Radioactivity per region / total deposited radioactivity (%) (mean +/- SD)
Nose	20 ± 7	14 ± 4
Rhinopharynx	4 ± 2	6 ± 3
Lower zone	6 ± 2	8 ± 3
Middle zone	44 ± 7	37 ± 4
Olfactory zone	26 ± 9	34 ± 7

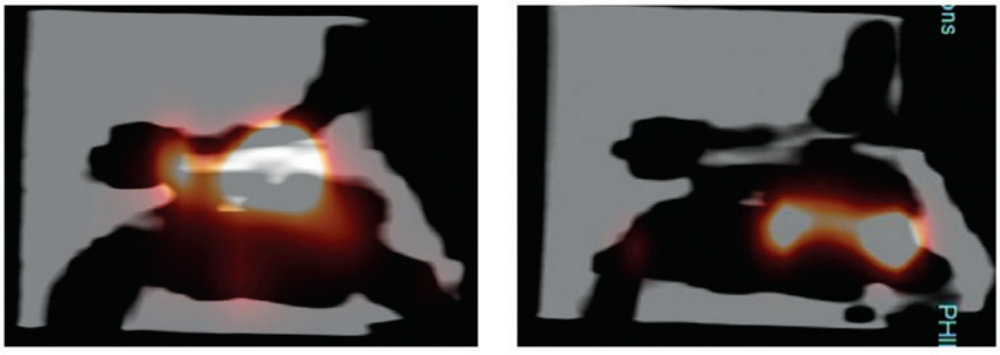

Figure 2. Deposition in the nasal cast model using SPECT with unit dose powder (left image) and nasal spray pump (right image).

CONCLUSIONS

A radiolabeling technique was successfully achieved for both liquid spray and unit dose powder nasal formulation delivery. The unit dose powder showed a higher deposition in the olfactory zone with the two *in vitro* measurement methods used. This work demonstrates that *in vitro* imaging techniques using nasal cast modes can be successfully used to assess nasal deposition for liquid and powder nasal delivery. Future imaging studies are required in order to directly compare *in vitro* nasal cast deposition to *in vivo* human deposition.

REFERENCES

1. Djupesland PG, Messina JC, Mahmoud RA: Nasal drug delivery devices: Characteristics and performance in a clinical perspective – A review. *Drug Deliv Transl Res* 2013, 3(1): 42-62.

2. Laube B: Devices for aerosol delivery to treat sinusitis. *J Aerosol Med* 2007, 20(Suppl): 5-18.

3. Suman JD, Laube BL, Dalby R: Validity of *in vitro* tests on aqueous spray pumps as surrogates for nasal deposition, absorption and biologic response. *J Aerosol Med* 2006,19: 510-21.

4. Durand M, Pourchez J, Louis B, Pouget JF, Isabey D, Coste A, Prades JM, Rusch P, Cottier M: Plastinated nasal model: A new concept of anatomically realistic cast. *Rhinology* 2011, 49(1), 30-36.

5. Le Guellec S, Le Pennec D, Gatier S, Leclerc L, Cabrera M, Pourchez J, Diot P, Reychler G, Pitance L, Durand M, Jamar F, Vecellio L: Validation of anatomical models to study aerosol deposition in human nasal cavities. *Pharm Res* 2014, 31(1): 228-37.

6. Buck L: Smell and taste: The chemical senses. In *Principles of Neural Science*. Edited by Kandel ER, Schwartzand JH, Jessell TM. McGraw-Hill; New York, NY: 2000: 625-52.