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DDL2025 DRUG DELIVERY TO THE LUNGS

SENSITIVITY ANALYSIS OF GUIDED STREAM TECHNOLOGY FOR TARGETING THE OLFACTORY AREA USING AN ANATOMICALLY RELEVANT NASAL CAST.

Exploring Nose-to-Brain Administration

Neurological disorders including neuro-degenerative diseases and psychiatric disorders could greatly benefit from the delivery of neuro-active therapeutics directly to the central nervous system and the brain to improve clinical and therapeutic outcomes. However, drug delivery to the brain via the systemic route remains a significant challenge due to the Blood-Brain Barrier (BBB). The current strategy to delivery drugs directly to the CNS and brain tissue are highly invasive. There is growing interest in **exploring drug delivery directly to the CNS** and brain tissue by exploiting nerve and epithelial transport pathways associated with olfactory functions **in the olfactory region** [1].

Aims & Objectives

- Assess the sensitivity of **Guided Stream Technology (GST)** in targeting the olfactory area.
- The sensitivity to three administration parameters was explored: sagittal angle, frontal angle and insertion depth, as well as the viscosity of the formulation.

Materials

- Three sets of Nemera® SP270+ pump, dose 100 µL + Guided Stream Technology prototype nozzle.
- Each device was filled with a different model formulation (water, Fluorescein 5g/L, and xanthan gum at the following concentrations to modify viscosity, 0.1, 0.8 and 1.2% w/w.
- The dynamic viscosity was characterised with cone / plane rheometer Kinexus® Ultra+ from Malvern® Instruments.
- The study was carried out with a nasal cast designed by Nemera® based on the average geometry from the Charité Medicine University of Berlin [2].
- The nasal cast is divided in three detachable parts: the nose, the olfactory area and the remaining nasal cavity (respiratory & pharynx regions). The olfactory area is defined as the upper third of the nasal cavity [3].
- An automated actuator Proveris® Vereo® NSx was used to actuate the devices. The angles of administration and insertion depth were controlled via an in vitro deposition testing bench, seen in Figure 1.

Nasal cast regions :

N: Nose
O : Olfactory region
R : Respiratory region

Figure 1 : Deposition testing bench and nasal cast

Experimental Methods

- Device administration tests were performed with **an uncoated dry nasal cast at room temperature, without airflow** simulating respiration. The model formulation was administered using an automated actuation system with an actuation speed of **85 mm/sec.**
- Four variable parameters were explored: The angle of the device in the sagittal plane, the angle in frontal plane (Figure 2), the depth of insertion of the nozzle, and the concentration of xanthan gum in the formulation.
- **A Box-Behnken design of experiment** was used to select a subset of combinations to be tested, resulting in **27 different tests.** The experiment was randomized with 3 replicates, generating a total of **81 data points.**
- Quantification of the mass of formulation deposed in each area was performed by weighing the three separated parts of the cast before and after administration. A photograph of the cast was taken immediately after actuation for qualitative visual assessment of the deposition pattern.

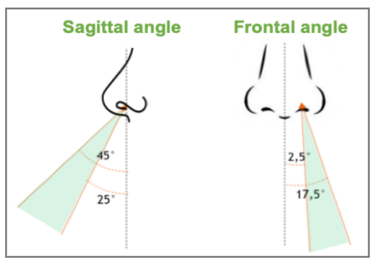

Figure 2 : Definition of device orientation angles relative to the nasal cast.

	Low	Medium	High
Insertion depth (mm)	5	10	15
Sagittal angle (°)	25	35	45
Frontal angle (°)	2.5	10	17.5
Xanthan concentration (w/w)	0.1%	0.8%	1.2%
Dynamic viscosity at 0.1s^{-1} shear rate (cP)	~120	~30 000	~80 000
Dynamic viscosity at 1000s^{-1} shear rate (cP)	3	22	44

Table 1: Administration parameters levels used in our design of experiment.

Results & Discussion

The deposition results were generally very high **(on average 81% of dose delivered to the olfactory area)**, with good repeatability across three repetitions (Figure 3).
Deposition results were used to build a response surface (Figures 4 & 5)

Our deposition objective (at least 50% in olfactive area) can be achieved with a **relatively wide range of administration angles (15 to 20° in both directions).** The deposition performance decreases only when both angles increase or decrease at the same time. **Higher performance** was observed with the two **most viscous formulations** compared with the least viscous one. (figures 3 & 4). **No significant impact of the insertion depth was found** (p=0.827).

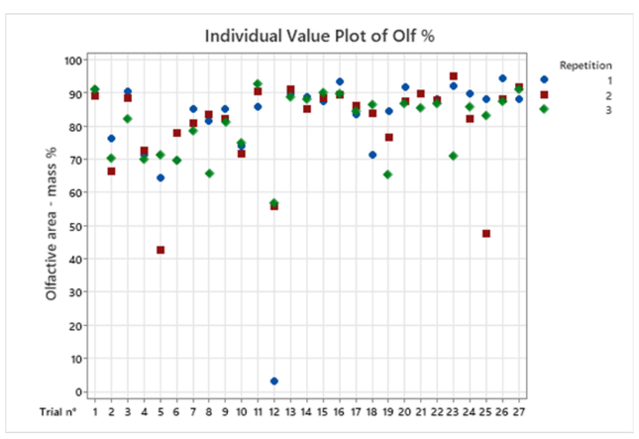

Figure 3: Deposition results (in mass %) in the olfactory area

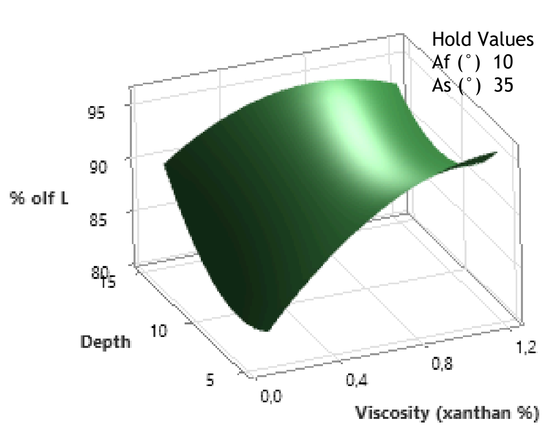

Figure 4: Response surface for medium values of administration angles.

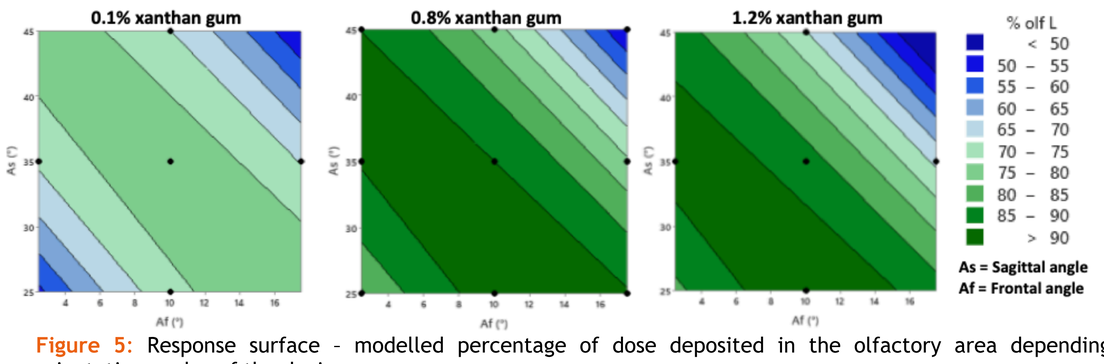

Figure 5: Response surface – modelled percentage of dose deposited in the olfactory area depending on both orientation angles of the device.

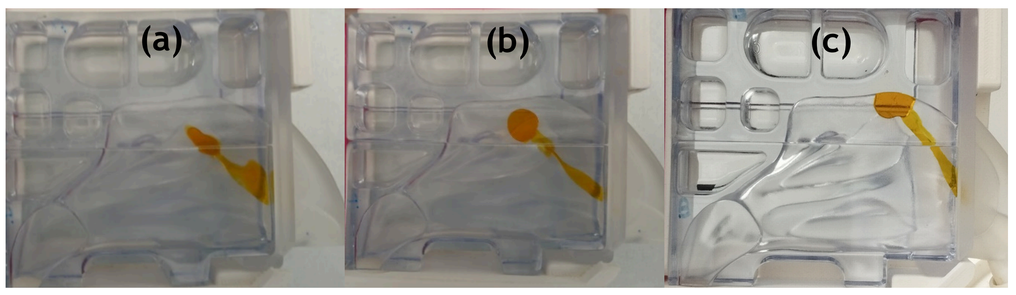

Figure 6: Illustration of the discrepancies between repetitions – Boundary effect of the nasal cast parting line. (a) and (b): two repetitions of the same border case, 47 and 83% respectively.
(c): deposition pattern with optimal orientation, 90% in olfactive area

While most of the tests delivered high repeatability (**less than 10% variation** in 20 out of 27 cases), a small number of tests produced larger discrepancies. We believe this was due to the modular design of the nasal cast, which leads to significantly different results depending on whether the deposited mass is just above or below the boundary of the olfactive area. A slight shift in the deposition pattern can cause large differences in measured weights. Figure 6 illustrates this effect.

Conclusion: Promising Track for Further Development

The Guided Stream Technology device used in this study shows ability to target the olfactory area with a range of formulation viscosities. The depositions were repeatable, and consistent with qualitative observations. Sensitivity to administration angle was low, and the results suggest that this technology allows some variability of the orientation of the device during the administration without hindering performance. In addition, the deposition pattern shows negligible sensitivity to the insertion depth of the device.
Our work continues in exploring the variability of the nasal anatomy (cf. poster #91), refining the nasal model to be closer to in-vivo physiological conditions and assessing other formulation variables.

References :

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