

Sensitivity analysis of Guided Stream Technology for targeting the olfactory area using an anatomically relevant nasal cast**Thomas Foliard¹, Sebastien Rabiller² & Alain Regard²**¹ Consultant for Nemera la Verpillière, 63 Avenue Tony Garnier, 69007 Lyon, France² Nemera la Verpillière, 63 Avenue Tony Garnier, 69007 Lyon, France**Summary**

Non-invasive nasal treatments exploiting the Nose-to-Brain pathway are a promising way of addressing central nervous system (CNS) diseases and diseases affecting brain tissue. A significant challenge of Nose-to-Brain delivery is associated with the targeted administration of the drug formulation to the olfactory cleft. Nemera has explored the ability of a narrow and straight liquid stream to deliver drug to the olfactory cleft leading to the development of the Guided Stream Technology (GST).

In vitro deposition tests have been performed with the GST device using a nasal cast designed by Nemera representative of a healthy patient's nasal cavity. The purpose of this study was to explore the impact of several key device administration parameters in a Design of Experiment (DoE): orientation of device relative to the cast during administration, depth of insertion in the nostril, and viscosity of the model formulation. The DoE generated qualitative and quantitative data on deposition outcomes in the nasal cast cavity in relation with the administration parameters and model formulation composition.

The results showed high levels of formulation deposition in the olfactory area (81% average from 81 depositions) with good experimental repeatability. Response surface analysis showed the influence of each administration parameter. The acceptable ranges of each parameter which consistently deliver a high percentage of deposition in the olfactory area of the nasal cast were defined.

Key Message

The Guided Stream Technology allows precise targeting of the olfactory cleft with liquid formulations in a non-invasive manner. This study shows low sensitivity to key administration parameters including viscosity of the formulation and confirms the potential clinical benefit of this technology.

Introduction

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 deliver drugs to the CNS and brain tissue is intrathecal, intracerebroventricular or intraparenchymal injections that deliver drugs directly to the cerebrospinal fluid. The last decades have witnessed a considerable interest in exploring the delivery of neuroactive therapeutics directly to the CNS and brain tissue by exploiting nerve and epithelial transport pathways associated with olfactory functions in the olfactory region [1].

The nasal sprays commonly used in nasal treatments show low levels of drug delivered to the olfactory cleft, e.g., 2.9% in a study conducted by Djupesland [2]. Various technological approaches have been explored to achieve targeted delivery of liquid formulations to this specific region, however to date and to our knowledge none of them have achieved more than 50 % deposition of the administered volume in the target region. Nemera has developed the Guided Stream Technology with the aim of delivering more than 50 % of the delivered volume to the olfactory area with a non-invasive and patient friendly device.

The present study used a 3-part nasal cast developed by Nemera specifically to evaluate deposition in the olfactory zone (the upper part). The sensitivity to three administration parameters was explored: sagittal angle, frontal angle and insertion depth, as well as the viscosity of the formulation.

Materials

A Guided Stream Technology prototype nozzle was associated with three Nemera® SP270+ pumps with 100 µL dose. Each device was filled with a different model formulation (water, Fluorescein 5g/L, Xanthan

Gum respectively 0.1, 0.8 and 1.2% w/w), to achieve various levels of viscosity. 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 of 50 cavities of 25 healthy patients (right cavities mirrored, the nasal cast being a left nasal cavity) from the Charité Medicine University of Berlin [3]. The nasal cast is divided in three detachable regions of interest: the nose, the olfactory area and the rest of the nasal cavity (respiratory & pharynx regions). The olfactory area is defined as the upper third of the nasal cavity [4].

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.



Figure 1: Deposition testing bench and nasal cast

Experimental method

The device administration tests were performed with a dry (no coating) 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. This actuation speed was previously defined as being representative of manual actuation speed based on stream front speed and impaction force measurements.

The four variable parameters were the angle of the device in the sagittal plane, the angle in frontal plane (as seen in Figure 2), the depth of insertion of the nozzle, and the concentration of xanthan gum in the formulation.

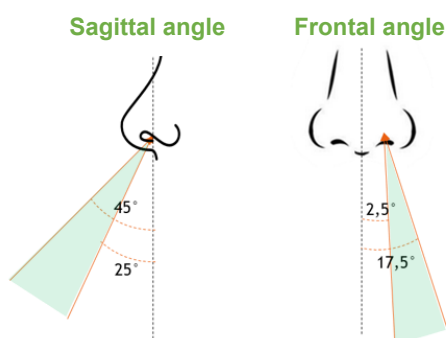


Figure 2: Definition of device orientation angles relative to the nasal cast during deposition tests

A low, medium and high setting for each parameter was defined in a preliminary study to guarantee a level of deposition in the olfactory area regardless of the combination of settings. Table 1 shows these levels for all four parameters. 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, for a total of 81 data points.

The model formulation was viscous enough to adhere to the nasal cast internal surface. Quantification of the mass of formulation deposited in each area was performed by weighing the three disassembled sections 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.

	Low	Medium	High
Insertion depth (mm)	5	10	15
Sagittal angle (°)	25	35	45
Frontal angle (°)	2.5	10	17.5
Thickener concentration (xanthan 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

Experimental results & discussion

The DoE enabled the generation of data of the mass of formulation and deposition pattern for each of the 27 tests. The deposition results were generally very high (on average 81% of dose delivered to the olfactory area), while showing good repeatability across three repetitions. Figure 3 shows the percentage of deposition in the olfactory area of the cast.

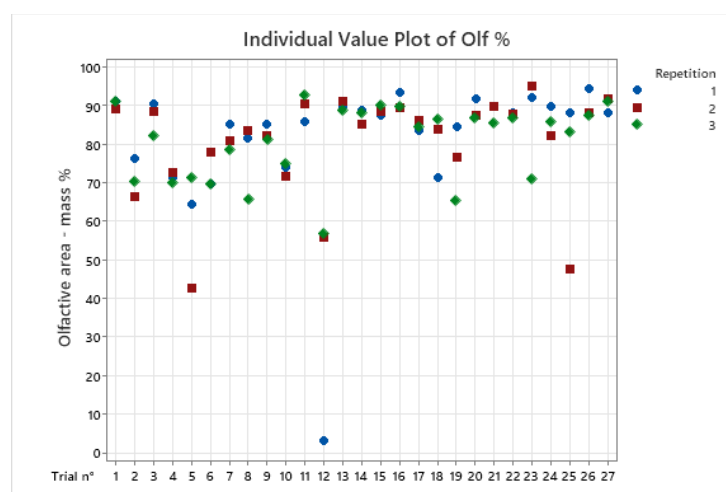


Figure 3: Deposition results (in mass %) in the olfactory area for each set of parameters tested.

While a majority of 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 3-section 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 olfactory area. A slight shift in the deposition pattern can cause large differences in measured weights. Figure 4 illustrates this effect.



Figure 4: Illustration of the discrepancies between repetitions – Boundary effect of the nasal cast parting line. (a) and (b): two repetition of the same border case, 47 and 83% respectively. (c):deposition pattern with optimal orientation, 90% in olfactory area

Deposition results were used to build a response surface – a model of the mass deposited in the olfactory cleft depending on the four deposition variables. It includes linear and quadratic terms in each variable,

and each product of variables. The Backwards Elimination method was used to retain only the statistically significant terms of the model.

Figure 5 is a visual representation of the response surface: for each of the three thickener concentrations, the modeled deposition percentage in the olfactory area is plotted against both orientation angles regardless of depth, which was shown to be statistically insignificant, $p=0.827$

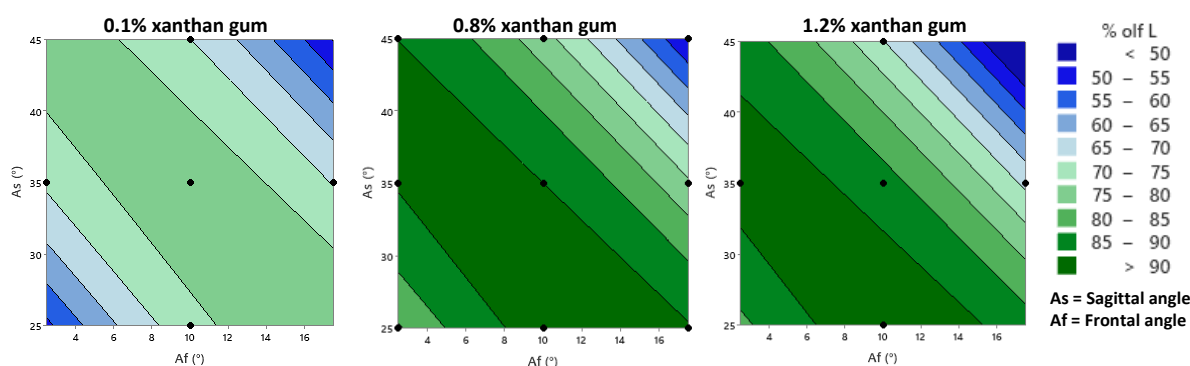


Figure 5: Response surface – modelled percentage of dose deposited in the olfactory area depending on both orientation angles of the device.

Our deposition objective (at least 50% in olfactory area) can be achieved with a relatively wide range of administration angles (15 to 20° in both directions). Performance was better with the two most viscous formulations compared with the least viscous one. Stream behavior at low viscosity differed due to multiple factors. The stream disperses more upon contact with the cast and undergoes reduced friction while sliding along the nasal wall. Also, the stream width varies in relation to viscosity. Images showed that the highest viscosity formulation tended to not be able to reach as far in the olfactory area. This suggests that higher viscosity formulations may be more difficult to deliver reliably to the olfactory cleft.

In addition, deposition performance decreases only when both angles increase or decrease at the same time. No critical value for either angle was found in the design of experiment window for which a good deposition becomes impossible regardless of other administration variables. Preliminary work was performed to ensure the range for each variable guaranteed non-zero deposition scores. As a result, the range of acceptable orientations, as well as user-related variation while using the device, may extend beyond the bounds of this study. More work will be conducted to understand the range of acceptable orientations and develop device solutions that ensure real administration angles stay in the optimal space.

Conclusions

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.

However, the current experimental method presents certain limitations, and further work is required to include the variability of the nasal anatomy, to refine the nasal model to be closer to in-vivo physiological conditions and to explore other formulation compositions.

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