The relevance of non-standardised in vitro nasal cast models in product development

Lucas Silva[1] **& Gonçalo Farias**[2], Nathalie Hauchard[2], Nuria Manzano[1]

[1]Nanopharm, An Aptar Pharma Company, Grange Road, Cwmbran, NP44 3WY, United Kingdom

[2]Aptar Pharma, Route des Falaises, Le Vaudreuil, 27100, France

Key Message

Two distinctly different, validated nasal cast models were able to similarly discriminate differences in the regional deposition of two nasal products. Different nasal cast models could be used during product development studies as long as these have been validated with in vivo studies.

Introduction

Similar to orally inhaled drug products, the regional deposition of nasal droplets plays a major role in absorption and bioavailability [1]. Thus, both in silico models and realistic in vitro tests have been proposed to better understand the regional deposition of nasal drug products [2,3].

One key challenge of using a nasal cast to evaluate regional deposition is the difficulty of standardisation: it might be challenging to make a representative nasal cast that covers a wide range of people given the tremendous interindividual differences in nasal geometry and to account for the mucus and mucociliary clearance [4]. Furthermore, several actuating parameters should be controlled such as the tilt angle, actuation force, insertion depth in the nostrils and airflow applied. To overcome some of these challenges, different solutions have been envisioned such as the development of idealised models based on computational fluid dynamics (CFD) simulations and validating sophisticated models with in vitro in vivo correlation studies [5,6].

Experimental Methods

The regional deposition of model formulations being dispersed with two different nasal devices was investigated. A multidose liquid nasal spray pump (VP7 pump fitted with a 232 actuator, Aptar Pharma) was used to deliver 50 µL of a fluorescein solution. A unit dose powder device (UDSp powder, Aptar Pharma,) was used to deliver 10 mg of pure fluorescein sodium powder. No flow rate was applied to any of the experiments.

In vitro deposition of model formulations being dispersed from two nasal devices was characterised in an adult male nasal cast (**Aeronose™,** courtesy of Aptar/DTF/Univ. of Tours) with chemical quantification (Figure 1 A).

One device was manually actuated into both nostrils of the nasal cast with an accurately defined insertion depth of 10 mm for the liquid device and 15 mm for the powder device and a delivery angle (horizontal plane) of 45° and a fixed angle from the centre wall of 5° for both products. The analysis was performed in triplicate per configuration (three devices for the multidose pump and six devices for the unit dose powder device).

The Alberta Idealized Nasal Inlet (**AINI**, Copley Scientific Ltd.) was also used to characterise the regional deposition of both products with chemical quantification.

One device was manually actuated into the single nostril of the nasal cast with an approximated angle of 45° and insertion depth around 10 mm for both devices since it was not possible to achieve higher insertion depths (visually assessed).

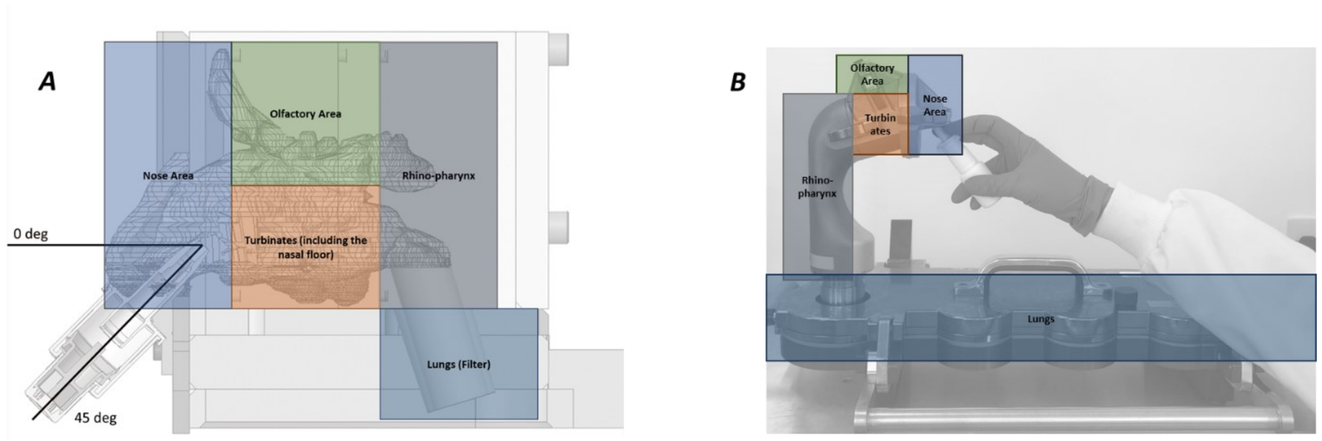

Figure 1 - (A) 3D representation for the nasal cast Aeronose™ and nasal regions used for quantification. (B) Experimental set-up of AINI nasal cast and nasal regions used for quantification.

Results and Discussion

Figure 2 presents the regional deposition of two nasal sprays (VP7/232 and UDSp) in two different nasal cast models (Aeronose™ and AINI). All configurations had a negligible postnasal deposition (deposition lower than 5%). The liquid nasal device had a higher deposition area in the nose (~54%) compared to the powder device (~24%) which was comparable between both casts. Consequently, the nasal deposition in the posterior region (turbinates, olfactory area and rhinopharynx) of the nasal cavity was significantly higher (student's t-test, $p < 0.01$) for the UDSp (~76%) compared to the VP7/232 device (~46%) which was comparable between both casts. Nonetheless, a higher deposition on the olfactory area for the Aeronose was observed compared to the AINI, particularly for the UDSp (~47% for Aeronose compared to ~2% for the AINI). This gap of deposition in the olfactory region may be related to the differences in adhesion of the powder into the nasal cast (different materials and coating agents), differences in the cavity (particularly on the volume / surface area) and, less probably, due to the inability of reaching equivalent insertion depths. Evaluating further coating agents with further replicates might be required to confirm this differences in deposition in the olfactory region.

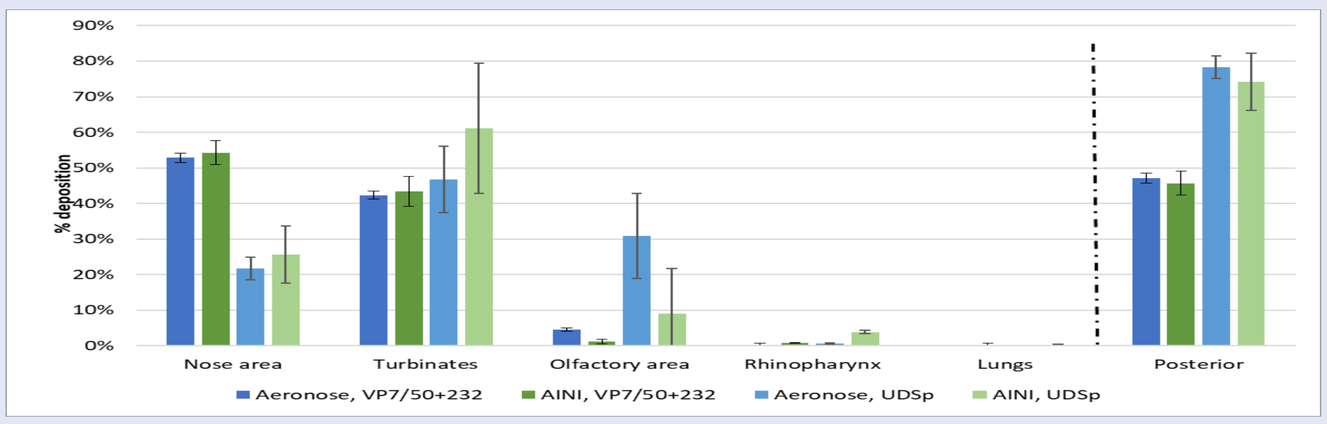

Figure 2 - Mean *in vitro* deposition from two different nasal sprays (VP7/232 and UDSp) in two different nasal cast models (Aeronose™ and AINI). Error bars show standard deviations (n = 3). The posterior region corresponds to the deposition in the turbinates, olfactory area and rhinopharynx.

Conclusion

Although standardisation might be a challenge for nasal cast deposition studies, this study suggests that different nasal cast models are able to equally discriminate differences in the regional deposition of two different nasal drug products (powder and liquid). Hence, these realistic in vitro tools could provide valuable insights into the regional deposition by facilitating device and formulation screening studies during early development stages of nasal drug products Although an idealised nasal cast model could be more important for quality control type of testing, a sophisticated and complete geometry individual model could also be considered, particularly when targeting specific anatomies and when developing personalised drug product applications. Nevertheless, in vitro in vivo validation studies should be considered during the development of these realistic in vitro tools.

References

1. Forbes B, Bommer R, Goole J, Hellfritzsch M, De Kruijf W, Lambert P, Caivano G, Regard A, Schiaretti F, Trenkel M, Vecellio L, Williams G, Sonvico F. A Consensus Research Agenda for Optimising Nasal Drug Delivery. Expert Opinion on Drug Delivery 2020, 17 (2): pp. 127–132.
2. Le Guellec S, Ehrmann S, Vecellio L. In vitro – in vivo correlation of intranasal drug deposition. Advanced Drug Delivery Reviews 2021, 170: pp. 340-352.
3. Rygg A, Hindle M, Longest PW. Linking Suspension Nasal Spray Drug Deposition Patterns to Pharmacokinetic Profiles: A Proof-of-Concept Study Using Computational Fluid Dynamics. Journal of Pharmaceutical Sciences, 2016, 105(6): pp. 1995–2004.
4. Salade L,Wauthoz N, Goole J, Amighi K. How to Characterize a Nasal Product. The State of the Art of In Vitro and Ex Vivo Specific Methods. International Journal of Pharmaceutics, 2019, 561, pp. 47–65.
5. Williams G, Cabrera M, Graine L, Le Guelle S, Hauchard N, Jamar F, Pardessus J, Le Pennec D, Reychler G. In Vitro and In Vivo Assessment of Regional Nasal Deposition using Scintigraphy from a Nasal Spray and a Nasal Powder. Respiratory Drug Delivery 2021, 1: pp. 135 –40.
6. Finlay WH, Chen J, Kiaee M, Martin AR. Development of an Idealized Nasal Geometry for Estimation of Regional Deposition of Nasal Sprays. Respiratory Drug Delivery 2021, 1: pp 127-134.