

Towards Standardized In Vitro Evaluation of Nasal Drug Deposition: An Analysis of Nasal Cast Methodologies and Implications for Pharmacopoeial Guidance: An IPAC-RS Viewpoint

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INTRODUCTION

Nasal drug delivery offers a versatile route for therapy, including topical treatments, systemic delivery and direct nose-to-brain targeting. Novel devices and formulations enable precise targeting in the nasal cavity, increasing the need to understanding regional deposition. Current regulatory guidance focuses on emitted dose, droplet size, spray pattern and plume geometry which ensure product quality and consistency but don't consider where drug deposition occurs, a critical parameter for certain therapies. *In vitro* nasal casts and CFD models have been adopted to enable investigation of deposition patterns and influencing factors, however, approaches are inconsistent and can lack clarity regarding validation techniques.

This work evaluates current methodologies, identifies gaps, and proposes a path toward harmonisation through non-mandatory pharmacopoeial guidance.

CRITICAL CONSIDERATIONS IN CURRENT APPROACHES

ANATOMICAL MODEL SELECTION

Patient-specific models provide high anatomical fidelity but are challenging for routine testing. Averaged nasal casts, constructed via geometric averaging or morphing of multiple CT or MRI images, preserve anatomical features while representing a population mean. In contrast, idealised nasal casts prioritise reproducibility via simplified geometries which normalise patient variability while representing key functional regions [5,6,7,8,] Averaged models are suited to mechanistic and clinically relevant studies, whereas idealised models offer advantages for routine testing [9]

CAST DESIGN

Nasal casts vary widely in geometry and segmentation, ranging from simple anterior/posterior divisions to detailed regional mapping. A lack of standardised segmentation complicates interpretation.

POPULATION REPRESENTATION

Nasal cast selection should consider patient population and how this impacts anatomy, for example, differences between paediatric and adult populations [10,11,12,13]. Disease states further alter airway geometry, impacting airflow and deposition patterns [14]. No consensus exists on how population and intrasubject variability should be incorporated into in vitro testing.

ADMINISTRATION METHODOLOGY

In vitro deposition is sensitive to administration parameters, including nozzle angle, insertion depth and actuation force. Small variations can significantly alter outcomes but these parameters are often inconsistently controlled and reported. Differences between manual and automated actuation further contribute to variability [15]. Standardized administration protocols are needed to improve reproducibility.

DEPOSITION MEASUREMENT

A range of techniques is used to quantify deposition, including gravimetric, spectroscopic, chromatographic, colorimetric, and imaging-based methods but there is limited consensus on which approaches provide the most relevant information.

INTEGRATION WITH CFD

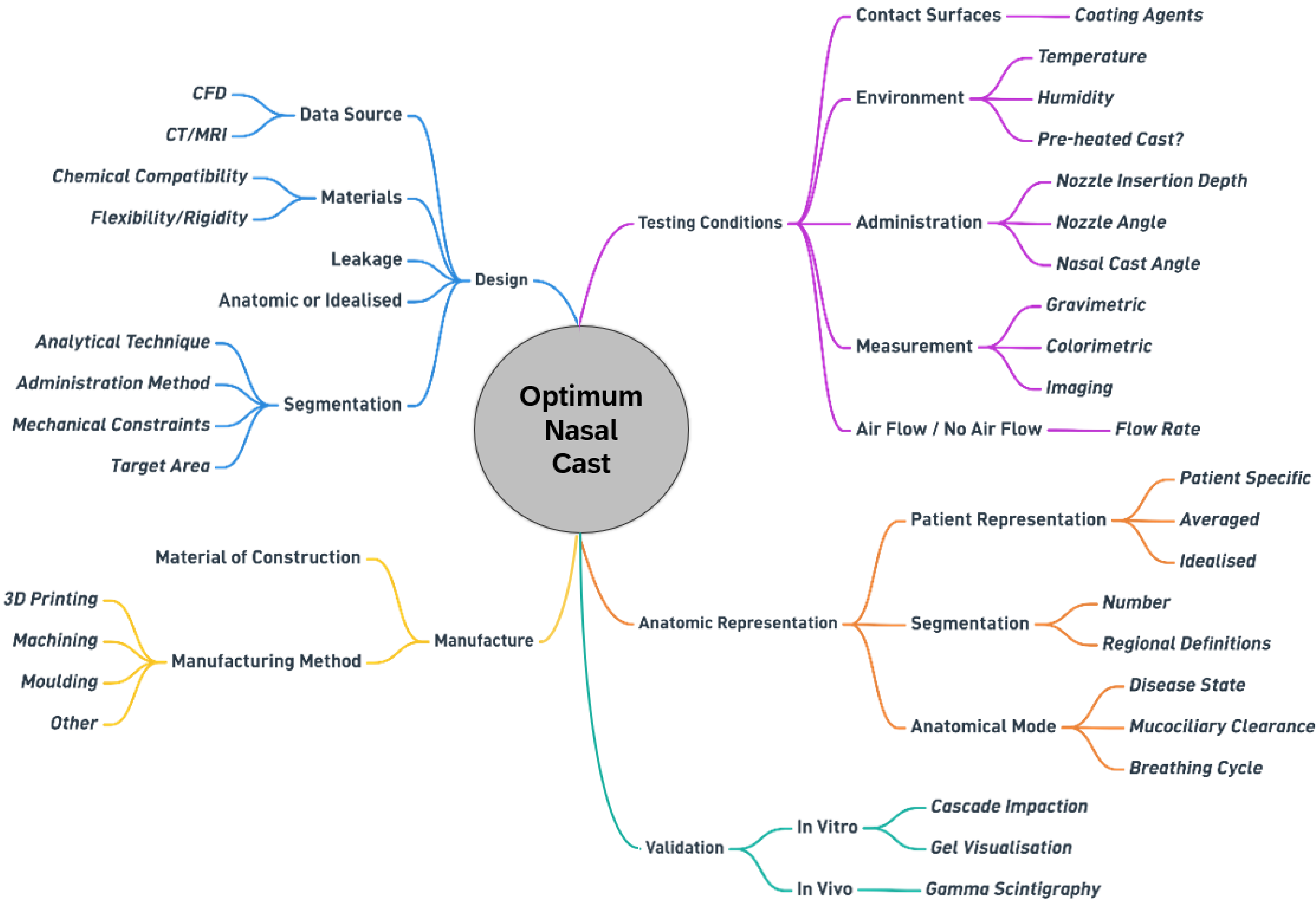
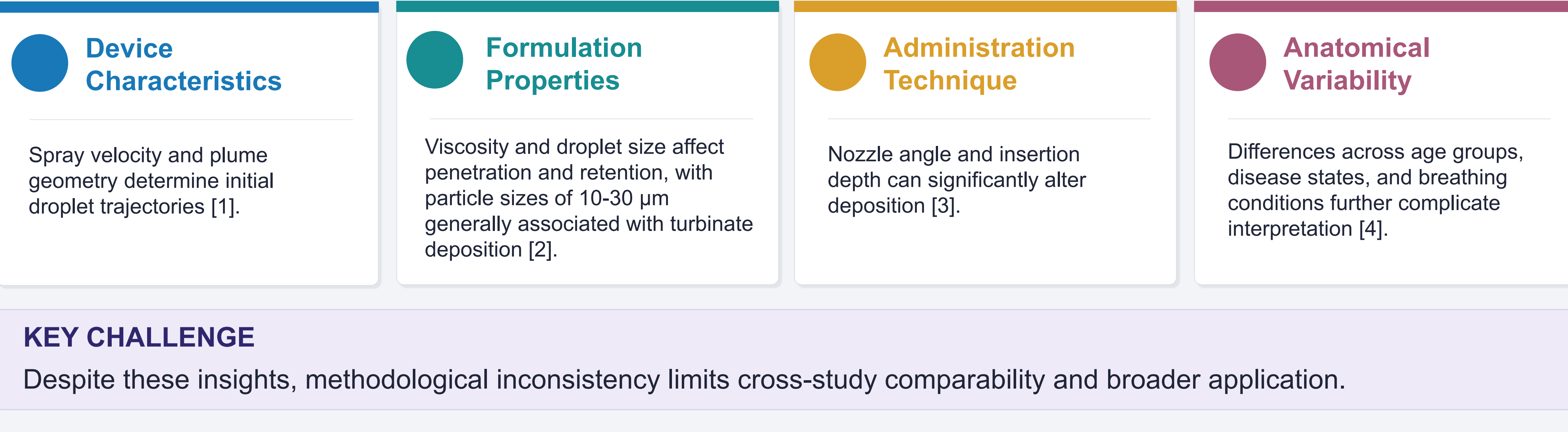
CFD enables exploration of airflow and deposition in complex geometries and can simulate variability across populations [16]. However, results are highly dependent on model assumptions and require validation against experimental data [17].

KEY CONCLUSIONS

- Nasal drug delivery presents challenges not addressed by current pharmacopoeial guidance. While nasal casts and CFD have advanced understanding of regional deposition, lack of standardization limits their application.
- An informative pharmacopoeial chapter could establish guiding principles for nasal deposition testing, including clinically relevant nasal regions, cast selection, population considerations, administration protocols, CFD use, validation, and reporting standards.
- A harmonized framework is needed to improve reproducibility, comparability, and clinical relevance, representing a practical step toward more consistent evaluation of regional nasal deposition.

STATE OF THE ART

A literature review indicates that differences in model selection, segmentation strategies, and administration protocols introduce deposition site variation. A summary of the factors that drive variability is shown in Figure 1. Such factors mean that reported deposition values may reflect experimental design rather than product performance.



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