

Emerging Trends in Nasal Spray Development: Tools for Future Success

A Brief History of Nasal Drug Delivery
Nasal drug delivery has significantly evolved since its inception several decades ago. Initially, it was primarily used for locally acting treatments related to decongestion and rhinitis, with some of the earliest multi-dose sprays appearing in the 1950s and 1960s. A major milestone was reached in 2003 with the approval of the first nasal vaccine, FluMist® Quadrivalent. Since then, pharmaceutical developers have pursued intranasal drug administration as a viable alternative to traditional routes. It has become an attractive option for various indications, including rescue therapies, infectious disease prevention, pain management, central nervous system conditions, and more.

Recent breakthroughs, such as Narcan® for opioid overdose reversal and the antidepressant Spravato® for treatment resistant depression, demonstrate a growing interest in novel nasal therapies. Additionally, the emergence of the COVID-19 pandemic in 2020 spurred vaccine development, renewing interest in intranasal and inhaled vaccine administration due to ease of administration and rapid action.

Advantages of Intranasal Drug Delivery

The nasal cavity is an ideal target for administering drugs locally and systemically, particularly to the central nervous system (CNS). The nasal mucosa is highly vascularised, providing a direct route for drug absorption into the bloodstream, which facilitates rapid onset of action. This efficient absorption can lead to reduced

dosages compared to oral administration, as it bypasses first-pass metabolism in the liver. Moreover, intranasal administration is non-invasive and can usually be self-administered, enhancing patient compliance. These benefits underscore intranasal drug delivery as a valuable alternative for achieving rapid and effective therapeutic outcomes in various clinical settings.

Key Regulations and Consideration for Nasal Drug Development

The approval process for nasal drug products is governed by strict regulatory testing and development guidelines. Major regulatory bodies, such as the Federal Drug Administration (FDA) and the European Medical Association (EMA), require comprehensive *in vitro* characterisation tests and *in vivo* clinical evaluations. While there are a variety of paths to approval depending on the drug product and region, there are several essential *in vitro* tests for nasal spray products that include Pump Delivery, Spray Pattern, Plume Geometry, Dose Content Uniformity, Aerodynamic Particle Distribution, and Droplet Size Distribution. These tests are essential for characterising the emitted nasal spray and crucial for proper development and approval of nasal drugs products.¹

When delivering drugs to the nasal cavity, it is critical to understand the relationship between the formulation, device, and the patient and to control their effects on both *in vitro* spray characteristics and potential implications for *in vivo* therapeutic outcomes. When developing a nasal drug product, it is essential to monitor the effects of these factors on spray characteristics to maintain equivalence to a reference product or internally defined product performance standards. These three factors dictate the

location, amount, and therapeutic outcome of nasal drug products, making their development uniquely challenging.

The Device

The device is more than primary packaging to contain and administer a formulation; it is a tool operated by a patient to deliver medication to the target site. A nasal spray device contains multiple components, such as the nasal pump, dip-tube, pump assembly, and internal swirl chamber, and has a specific nozzle length and diameter. Developers must consider all these mechanical factors during development, as they can influence the performance of nasal sprays both *in vitro* and in clinical studies. For example, changing the diameter of the orifice and swirl chamber design of a nasal spray, while all other factors are held constant, can lead to drastically different *in vitro* performance.²

The Formulation

Formulations play a significant role in nasal spray performance. In addition to the Active Pharmaceutical Ingredient (API), the physical characteristics of the emitted spray are critical to therapeutic outcomes and critical *in vitro* spray characteristics. Formulation factors, such as the viscosity and the presence of excipients, can lead to distinct spray characteristics and deposition and absorption behavior in the nasal cavity. We have shown that an increase in formulation viscosity decreases the Spray Pattern area and an increase in droplet size. The inverse of this relationship holds true, where a decrease in formulation viscosity leads to an increase in Spray Pattern area size and a decrease in particle size.³ From a therapeutic perspective, highly viscous formulations can remain in contact with nasal epithelium longer, allowing for increased time



1950



1960



2003

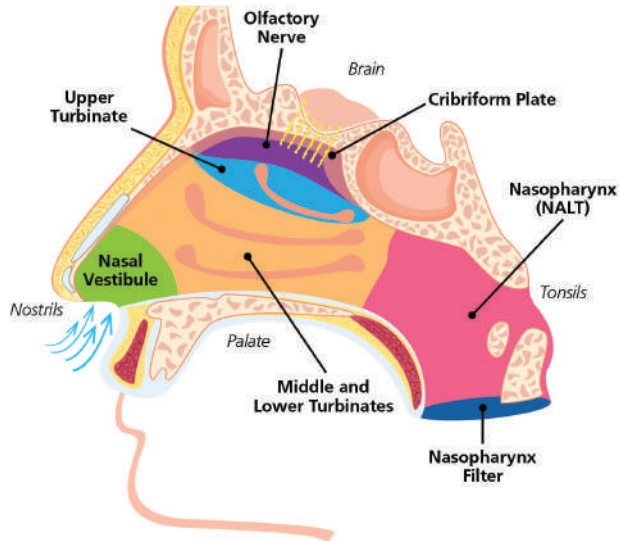


2015



2024

Evolution of Nasal Spray Devices Through the Years



Anatomical Regions of the Human Nasal Cavity

regions of interest include the olfactory and the Nasal Associated Lymphatic Tissue (NALT) regions.

- **Olfactory Region:** This region is thought to provide a non-invasive means to bypass the Blood Brain Barrier (BBB) for direct administration to the CNS.
- **NALT Region:** This region is an ideal target for effective non-invasive means for vaccine administration.

The rise of targeted nasal delivery products and the complex nature of the human nasal cavity make development testing under human-realistic conditions essential. The use of tools like human-realistic nasal casts and controlled administration are needed to advance nasal drug development. Using nasal casts early and throughout development with automated actuation reduces the risk and time to market by providing clinical indications before human testing begins. Advancements in manufacturing and imaging technology have improved the utility of nasal casts, enabling the creation of more complex and human-realistic geometries. The enhanced nasal casts provide deeper insights compared to traditional idealized models.

Pairing *in vitro* development testing with *in vitro* human-realistic deposition testing can enhance nasal product development, reducing the risk and time to market. Tools known as nasal casts have been used for decades to replicate human usage, considering factors such as insertion angle and depth, orientation, and the influence of breathing.

for absorption before mucociliary clearance from the nasal cavity. While most nasal drugs are spray formulations, dry powders are also growing in use due to certain advantages, such as formulation stability, longer residence time in contact with nasal mucosa, and better control over particle characteristics.

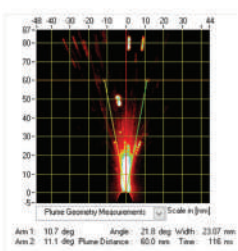
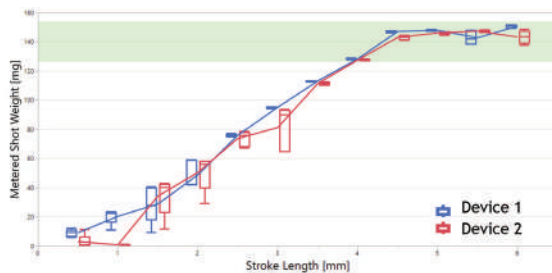
The Patient

Human Factors are another critical factor for nasal spray performance. Unlike other modalities, nasal drug products are highly influenced by human factors, making human-realistic testing essential for product efficacy and approval. The way a patient administers the spray, known as actuation, can be studied and then replicated through specialised instruments known as Automated Actuators. Regulatory agencies recommend automated

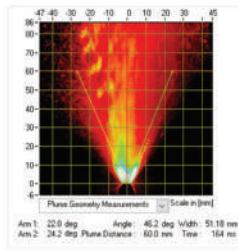
actuation for *in vitro* characterisation tests to eliminate human variability in manual testing and create robust, repeatable methods for development and regulatory submission. It is important to define a demographically relevant actuation profile to be used throughout development and regulatory testing. For example, actuation profiles determined from adult and pediatric patients yield significantly different performance in critical *in vitro* tests like Spray Pattern and Droplet Size Distribution, when using the same device-formulation.⁴

Advancements and Opportunities in Targeted Nasal Drug Delivery

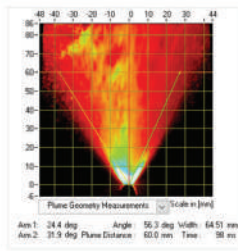
There is growing interest in targeted nasal delivery, which opens the nasal route to new therapies and innovative products. Specific



Low Velocity



Medium Velocity



High Velocity

Methodologies and Technology Utilised in the Proveris by Design Process





Proveris Nasal Cast attached to Vereo® Automated Actuator

Navigating Development with Proveris Laboratories: The Proveris Advantage for Nasal Product Success

The successful development and launch of a nasal drug product requires strict adherence to regulatory guidelines and a thorough understanding of the three factors that influence nasal drug efficacy: the device, formulation, and patient. Proveris Laboratories, a division of Proveris Scientific Corporation, offers a comprehensive approach to *in vitro* nasal product development. Our Orally Inhaled and Nasal Drug Product (OINDP) expert scientists utilise the Proveris by Design™ approach, proven to reduce timelines and streamline submission. As targeted and novel nasal therapies rise, Proveris Laboratories not only adheres to industry best practices using gold-standard Proveris equipment, but also advances the science of aerosol and spray delivery with innovative tools.

Proveris Laboratories further enhances the nasal development process by integrating human-realistic nasal cast deposition testing early and throughout development. This method enriches nasal product development by providing deeper insights into product performance. Conducting nasal cast deposition studies during the formulation and device optimisation phases allows for an understanding of nasal deposition before progressing to *in vivo* testing, significantly reducing the risk of failure due to poor *in vivo* performance.

The Proveris Nasal Cast: Revolutionising Human-Realistic Nasal Deposition Testing

The Proveris Nasal Cast is a human-realistic adult model of the nasal cavity, complete with five extractable regions and a nasopharynx filter, allowing for the quantification of API in each region. During nasal deposition testing,

Proveris Laboratories employs human-derived automated actuation and studies the effects of device insertion angle and depth, as well as human-realistic breathing, when applicable.

Proveris Nasal Cast studies provide rapid results and are particularly useful for those developing targeted nasal therapies, novel device designs, and innovative delivery techniques. The Proveris nasal cast is an accurate model of realistic complex geometries and barriers that are important to account for when targeting specific regions like the Olfactory region and the NALT region. Developers must ensure that the target region receives the required amount of drug products and nasal cast studies are the most efficient way to determine this without *in vivo* testing.

Next-Generation Nasal Spray Products with Proveris Laboratories

The next generation of nasal spray products has advanced well beyond primarily localized treatments like decongestants and rhinitis therapies. Innovative products now target specialised regions within the nasal cavity with novel formulations and devices. By understanding and controlling the complex relationship between device, formulation, and patient, Proveris Laboratories offers a comprehensive development process that leverages innovative tests and technologies, reducing timelines, and enhancing insights.

Proveris Laboratories performs traditional testing with demographic-specific human actuation parameters, paired with Human-Realistic Nasal Cast testing, to elevate development. This approach allows for the assessment of therapeutic indications before clinical trials. Trust our experts to work for you and start a partnership with Proveris, an

industry leader in OINDP instrumentation and laboratory services, for over 25 years.

REFERENCES

1. FDA Guidance for Industry (2002) Nasal Spray and Inhalation Solution, Suspensions, and Spray Drug Product – Chemistry, Manufacturing, and Controls Documentation <https://www.fda.gov/files/drugs/published/Nasal-Spray-and-Inhalation-Solution--Suspension--and-Drug-Products.pdf> Accessed June 27, 2024.
2. Impact of actuator design on multi-dose nasal spray characteristics. Poster presented at Respiratory Drug Delivery Conference 2018. Chauhan H, Liu-Cordero S, Liao L, Werbeck J; Respiratory Drug Delivery 2018. Volume 2, 2018: 497-502.
3. Synergies of inhalation product development and spray characterisation. Catalent Incorporated, Proveris Scientific Corporation. Workshop presented at Respiratory Drug Delivery Conference 2023 (RDD2023). RDD Europe 2023 – Workshops (rddonline.com)
4. Automated actuation of nasal spray products: effect of hand-related variability on the *in vitro* performance of Flonase nasal spray. Doughty, D. V., Hsu, W., & Dalby, R. N. (2013). <https://doi.org/10.3109/03639045.2013.777735>



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