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Review Article

Impact of Nasal Delivery Devices on Olfactory Drug Deposition

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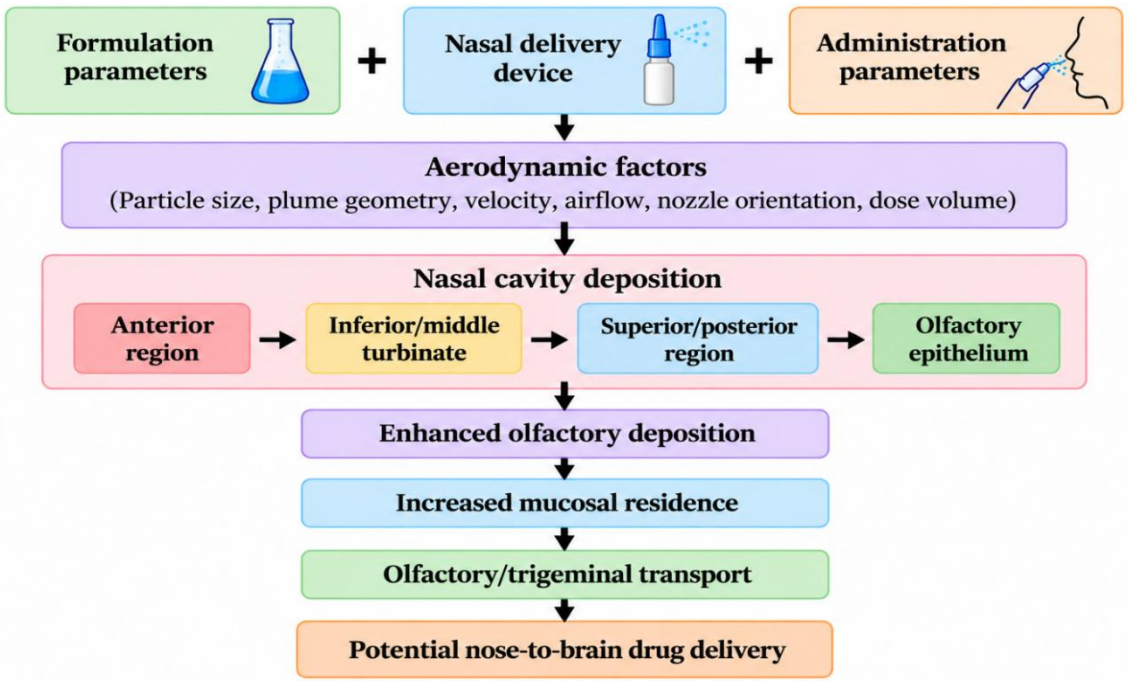
Abstract

Nasal delivery offers a promising non-invasive approach for targeting therapeutics to the brain through the olfactory region. However, conventional nasal administration frequently produces predominant deposition in the anterior nasal cavity, limiting drug access to the olfactory epithelium. Nasal delivery devices play a critical role in overcoming these anatomical and aerodynamic barriers by controlling spray velocity, droplet or particle size, plume geometry, airflow, dose volume and administration direction. This review examines the impact of conventional and advanced nasal delivery devices on olfactory drug deposition, with particular emphasis on metered-dose sprays, nasal drops, nebulizers, powder devices, atomizers, breath-powered bidirectional systems and specialized nose-to-brain platforms. The influence of device design and administration parameters on regional deposition, mucosal retention and potential nose-to-brain transport is discussed. Computational fluid dynamics, nasal cast models, imaging techniques and experimental approaches used for deposition assessment are also reviewed. Emerging personalized and digitally optimized devices may provide improved and reproducible olfactory targeting for future CNS therapeutics.

Keywords: Olfactory deposition, nasal delivery devices, nose-to-brain delivery, intranasal drug delivery, olfactory targeting

Graphical abstract



Highlights

✓ Device parameters influence aerodynamic transport and olfactory deposition.

✓ Optimized plume geometry and airflow can reduce anterior nasal impaction.

✓ Formulation properties affect aerosolization, deposition and mucosal retention.

✓ Patient anatomy and technique influence regional nasal drug deposition.

✓ Advanced devices may enhance olfactory targeting and nose-to-brain delivery.

1. Introduction

The nasal route has attracted considerable interest as a non-invasive pathway for delivering drugs to the central nervous system because the olfactory epithelium provides anatomical connectivity with the brain.[1] However, achieving therapeutically meaningful deposition in the olfactory region remains difficult because the nasal valve, turbinates, complex nasal geometry, mucus layer and mucociliary clearance can divert formulations toward the anterior cavity or nasopharynx.[2] Conventional nasal sprays generally produce greater deposition in the anterior and middle nasal regions, whereas specialized devices attempt to improve delivery toward the superior/posterior nasal cavity.[3] Device-related parameters-including nozzle geometry, spray angle, plume width, droplet size, velocity, airflow and administration technique-therefore represent critical determinants of olfactory deposition.[4] Recent research has increasingly shifted from simply selecting an intranasal formulation toward integrating formulation characteristics with device engineering and patient-specific administration.[5] Advanced breath-powered, bidirectional, atomization-based and personalized devices offer opportunities for more reproducible olfactory targeting.[6]

2. Nasal anatomy and the olfactory target

The nasal cavity is anatomically organized into the vestibular, respiratory and olfactory regions**,** with the olfactory epithelium predominantly located in the superior nasal cavity around the olfactory cleft.[7] This region is an important target for nose-to-brain delivery because its olfactory neurons provide a potential anatomical route toward the central nervous system.[8] However, achieving selective and efficient olfactory deposition remains challenging because of the nasal valve, complex turbinate structure, narrow olfactory cleft, limited olfactory surface area, mucociliary clearance, inter-individual anatomical variability, anterior leakage or swallowing and device-dependent aerosol behavior.[9]

3. Device-dependent determinants of olfactory deposition

3.1 Droplet/particle size

Particle or droplet size strongly influences nasal deposition. Very large droplets tend to impact the anterior nasal cavity, whereas smaller particles may penetrate deeper into the nasal passage depending on airflow and aerodynamic characteristics. Human nasal-cast and computational studies have identified particle size and flow conditions as important variables governing olfactory deposition.[10]

3.2 Plume geometry

A narrow and appropriately directed plume can improve penetration toward the superior/posterior nasal cavity. Plume angle and spray direction therefore represent important device-design variables.[11]

3.3 Airflow

Controlled airflow can transport aerosol beyond the nasal valve and improve posterior deposition. Breath-powered bidirectional devices are particularly relevant because exhaled airflow can facilitate movement toward the upper nasal regions while reducing unwanted pulmonary or oropharyngeal delivery.[12]

3.4 Nozzle orientation

Nozzle position and insertion angle affect the trajectory of the emitted formulation. Incorrect orientation can increase anterior deposition and reduce access to the olfactory cleft.[13]

3.5 Administration technique

Head position, breathing pattern, dose volume, nostril selection and administration angle can substantially alter regional deposition. Thus, device performance cannot be considered independently of user technique.[14] **Figure 1** illustrates the key factors governing nasal drug deposition and potential nose-to-brain transport, highlighting the influence of device, formulation and patient parameters on aerodynamic transport, olfactory deposition, mucosal retention and subsequent delivery toward the central nervous system.

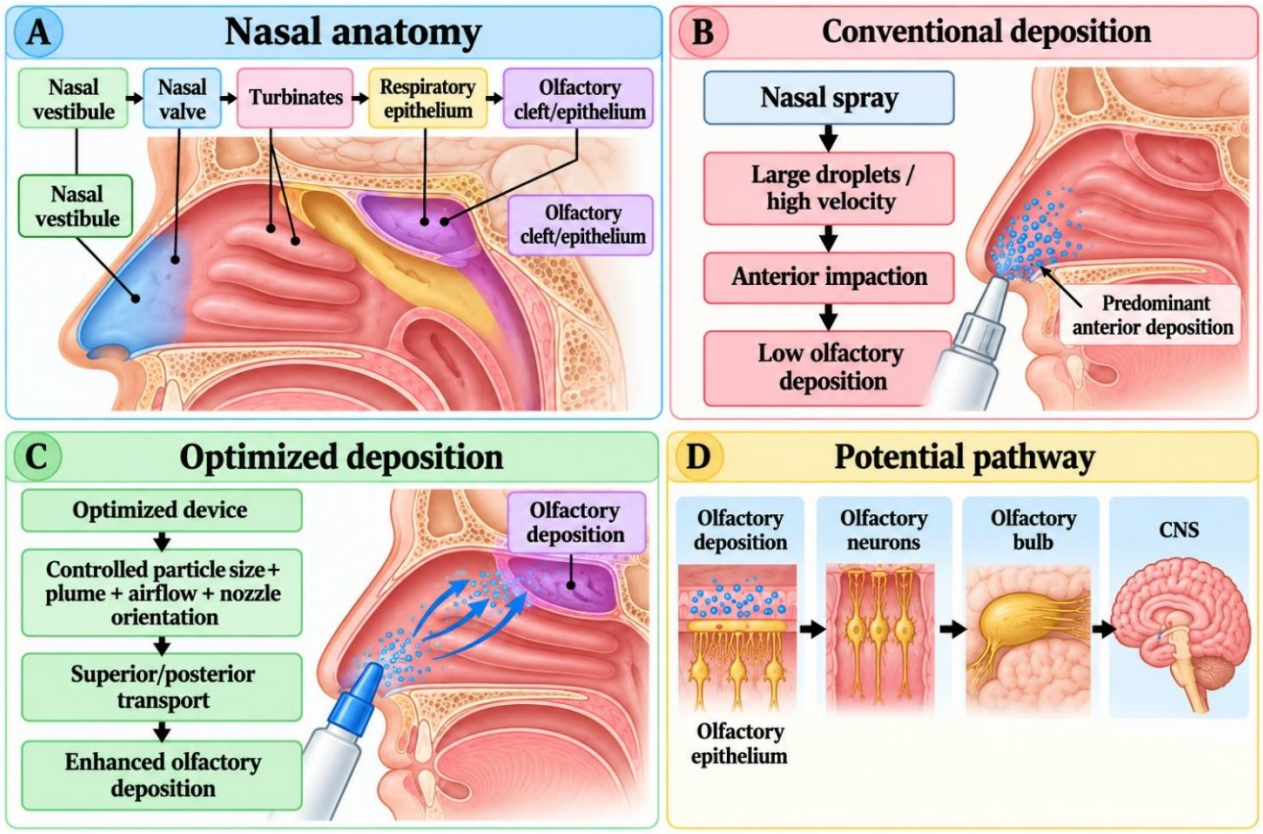


Figure 1. Anatomical and mechanistic basis of olfactory drug deposition

(Schematic illustration of nasal anatomy, conventional versus optimized deposition and the potential pathway of drug transport from the olfactory epithelium to the brain.)

4. Classification of nasal delivery devices

Table 1. Major nasal delivery devices and their deposition characteristics

Device	Primary mechanism	Typical deposition tendency	Olfactory targeting potential	Major limitation	Ref
Nasal drops	Gravity-driven	Variable; highly position dependent	Low-moderate	Runoff and poor dose precision	15
Conventional nasal spray	Mechanical pump	Mainly anterior/middle cavity	Low-moderate	Limited superior deposition	16
Metered-dose spray	Metered aerosol	Anterior/middle regions	Moderate with optimization	Device/formulation dependent	17
Nebulizer	Continuous aerosol generation	Can reach deeper regions	Moderate	Requires appropriate airflow	18
Nasal powder device	Dry-powder dispersion	Depends on particle properties	Moderate-high	Powder deagglomeration	19
Breath-powered device	Patient-generated airflow	Posterior/superior regions	High	Patient cooperation required	20
Bidirectional device	Controlled airflow through nasal cavity	Upper/posterior cavity	High	More complex administration	21
Specialized atomizer	Controlled aerosolization	Optimized regional deposition	High	Cost and device complexity	22
Personalized device	Anatomy-specific delivery	Targeted	Potentially very high	Limited clinical validation	23

5. Impact of conventional nasal devices

Conventional metered-dose nasal sprays are widely used because of their portability, dose reproducibility, ease of administration and rapid drug delivery.[24] However, the generated aerosol plume may undergo inertial impaction at the nasal valve and anterior nasal structures, resulting in predominant anterior deposition followed by mucociliary clearance or swallowing and consequently reducing drug exposure to the olfactory region.[25] Therefore, despite their established clinical utility, conventional nasal sprays have limited ability to achieve selective and efficient olfactory targeting.[26] **Figure 2** highlights the major device, formulation and patient-related factors that influence aerodynamic drug transport within the nasal cavity, determining whether deposition occurs predominantly in the anterior region or is directed toward the superior/posterior olfactory region, thereby affecting mucosal retention and the potential for nose-to-brain drug transport.

6. Advanced devices for olfactory targeting

Table 2. Advanced device strategies for improving olfactory deposition

Device strategy	Main principle	Expected effect	ReF
Breath-powered delivery	Uses controlled exhalation	Improves posterior/superior transport	27
Bidirectional delivery	Air enters one nostril and exits the other	Enhances upper nasal deposition	28
Vortex aerosolization	Generates controlled aerosol flow	Improves targeting of upper nasal regions	29
Specialized nozzle	Controls direction and plume	Reduces anterior impaction	30
Powder delivery	Optimizes aerodynamic particle behavior	Potentially improves regional penetration	31
Pulsating aerosol	Controls aerosol delivery over time	May improve deposition uniformity	32
Personalized nozzle	Adapted to patient anatomy	Potentially improves reproducibility	33
3D-printed device	Patient-specific geometry	Enables individualized targeting	34

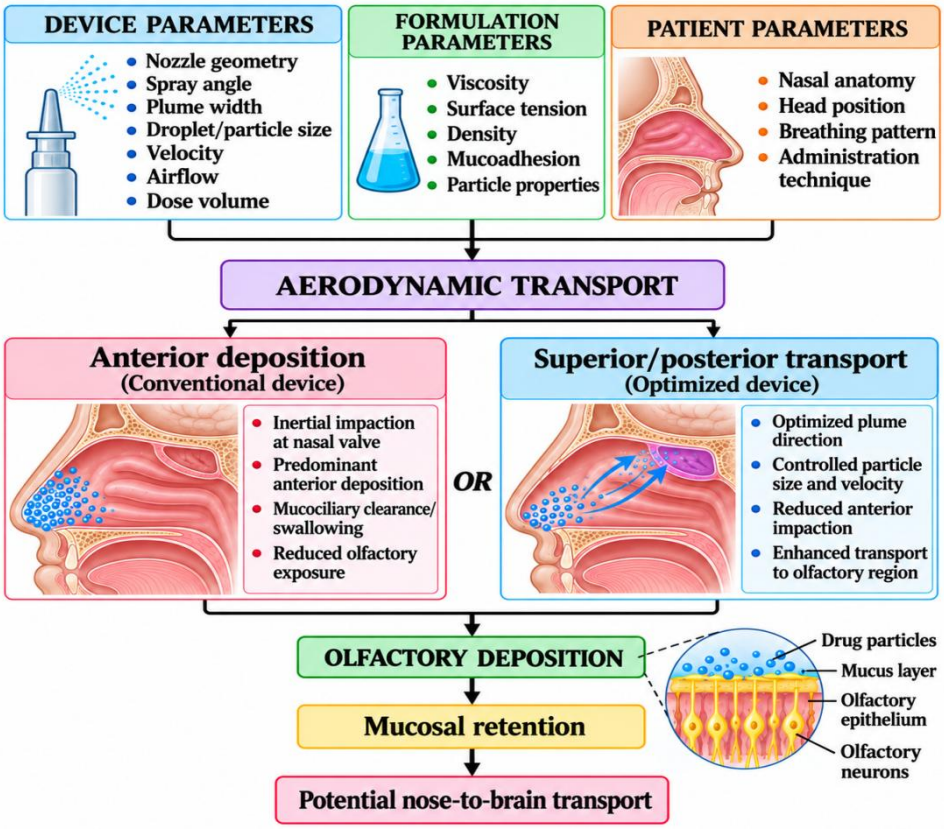


Figure 2. Device-formulation-deposition relationship

(Schematic representation of device, formulation and patient factors influencing aerodynamic transport, olfactory deposition, mucosal retention and potential nose-to-brain delivery).

7. Comparative evaluation of device performance

Table 3. Factors influencing olfactory deposition

Factor	Low/poor condition	Optimized condition	Influence on deposition	ReF
Droplet size	Excessively large	Optimized aerodynamic size	Controls regional impaction	35
Spray velocity	Very high	Controlled	Reduces anterior impaction	36
Plume angle	Broad	Narrow/controlled	Improves targeting	37
Nozzle orientation	Incorrect	Anatomically optimized	Improves olfactory access	38
Airflow	Uncontrolled	Controlled	Enhances posterior transport	39
Dose volume	Excessive	Optimized	Reduces runoff	40
Formulation viscosity	Very low/high	Optimized	Influences retention and spreading	41
Muco-adhesion	Low	Appropriate	Increases residence time	42
Head position	Non-optimized	Appropriate	Alters regional deposition	43
Patient breathing	Normal/uncontrolled	Device-guided	Influences aerosol transport	44

8. Breath-powered and bidirectional delivery

Breath-powered and bidirectional nasal delivery systems are promising approaches for olfactory targeting, as they use controlled airflow rather than relying solely on mechanical spray momentum to transport formulations deeper into the nasal cavity.[45] Experimental evidence suggests that bidirectional administration can enhance deposition in the upper and posterior nasal regions compared with conventional unilateral spray delivery, with one study reporting approximately 32% upper-posterior deposition using a bidirectional device compared with 11% using a conventional spray pump.[46] Thus, these systems may help overcome a key limitation of conventional nasal delivery-insufficient penetration beyond the nasal valve.[47]

9. Computational and experimental assessment

Table 4. Methods for evaluating olfactory drug deposition

Method	Application	Major advantage	Major limitation	ReF
Computational fluid dynamics (CFD)	Predicts airflow and particle trajectories	Non-invasive prediction	Requires validated models	48
Human nasal casts	Regional deposition studies	Anatomically relevant	Cannot fully reproduce physiology	49
Gamma scintigraphy	*In vivo* regional distribution	Quantitative imaging	Radiation exposure	50
Fluorescence imaging	Deposition visualization	Relatively simple	Mainly experimental	51
MRI/CT-based modeling	Patient-specific anatomy	Individualized modeling	Cost and complexity	52
Laser diffraction	Particle-size analysis	Rapid characterization	Does not directly measure deposition	53
Cascade impaction	Aerodynamic particle size	Detailed aerosol characterization	Laboratory based	54
In vivo pharmacokinetics	Exposure assessment	Biological relevance	Difficult to establish direct brain transport	55

10. Formulation-device interaction

Device optimization alone may not ensure enhanced olfactory deposition, as formulation characteristics-including viscosity, surface tension, density, particle size, muco-adhesion and rheological properties-also influence aerosolization and subsequent nasal transport.[56] Therefore, effective olfactory targeting requires coordinated optimization of both formulation and device attributes.[57] Recent studies combining machine-learning approaches with experimental optimization further suggest that formulation and spray characteristics can be jointly optimized to improve drug deposition in the olfactory region.[58]

Table 5. Formulation-device interactions affecting olfactory deposition

Formulation property	Device parameter	Deposition consequence	ReF.
Viscosity	Spray pressure	Influences atomization	59
Surface tension	Nozzle geometry	Influences droplet formation	60
Particle size	Airflow	Determines aerodynamic transport	61
Density	Spray velocity	Influences inertial behavior	62
Muco-adhesion	Dose volume	Influences retention	63
Rheology	Pump mechanism	Influences plume formation	64
Solid-state properties	Powder device	Influences dispersion	65
Drug concentration	Metering system	Determines delivered dose	66

11. Emerging personalized nasal delivery

A major future direction in olfactory drug delivery is the development of patient-specific nasal delivery systems, as considerable inter-individual variation in nasal anatomy can influence regional drug deposition and may limit the reproducibility of conventional devices.[67] Recent approaches have explored 3D-printed personalized devices designed to position drug-loaded formulations toward the olfactory region; however, their clinical translation still requires extensive human validation, particularly regarding drug-loading capacity and reproducibility.[68] In parallel, artificial intelligence (AI) and machine-learning (ML) techniques offer opportunities for individualized optimization by integrating patient anatomy, formulation properties, device parameters and deposition outcomes.[69] Such data-driven approaches may enable more precise prediction and optimization of olfactory deposition and support the development of anatomy-guided nasal delivery systems. Recent research has also demonstrated the potential of ML-assisted optimization of nasal spray characteristics for improving olfactory-region deposition.[70]

12. Current challenges and future perspectives

A key challenge in evaluating nose-to-brain delivery is that an increase in brain drug concentration does not necessarily confirm direct olfactory transport, because systemically absorbed drug may also reach the brain through the circulation. Therefore, future research should prioritize standardized olfactory-deposition metrics, patient-specific nasal models, validated CFD simulations, device–formulation co-optimization, reproducible administration techniques, long-term nasal safety and human imaging and pharmacokinetic validation. In addition, AI-assisted device optimization and regulatory standardization are needed to improve the reproducibility and clinical translation of advanced nasal delivery systems. Establishing a clear correlation between olfactory deposition and actual CNS exposure will be particularly important for demonstrating therapeutic relevance. Overall, translation remains challenging because laboratory models may not adequately reproduce human nasal anatomy and physiology, while standardized methods for characterizing regional deposition are still limited.

13. Conclusion

Nasal delivery devices are a critical determinant of olfactory drug deposition and consequently influence the potential effectiveness of nose-to-brain drug delivery. Conventional nasal sprays generally Favor anterior deposition, whereas specialized approaches-including breath-powered, bidirectional, atomization-based, powder and personalized devices-can improve transport toward the superior and posterior nasal cavity. Device parameters such as droplet size, plume geometry, spray velocity, nozzle orientation, airflow and dose volume must be optimized together with formulation properties and administration technique. Evidence from nasal-cast studies, CFD modeling, imaging and experimental investigations supports the concept that rational device engineering can substantially improve regional deposition. However, enhanced olfactory deposition should not automatically be interpreted as proof of direct brain delivery. Future progress will depend on patient-specific device design, formulation-device integration, standardized deposition assessment, AI-assisted optimization, and well-designed clinical studies. Thus, the future of olfactory drug delivery is likely to shift from conventional nasal administration toward precision, anatomy-guided and digitally optimized delivery systems.

Abbreviations:

AI : Artificial Intelligence
BBB : Blood Brain Barrier
CNS : Central Nervous System
CFD : Computational Fluid Dynamics
CT : Computed Tomography
CNS : Central Nervous System
CNSD : Central Nervous System Delivery
DP : Dry Powder
DPI : Dry Powder Inhaler
FDA : Food and Drug Administration
GIT : Gastrointestinal Tract
HPLC : High-Performance Liquid Chromatography
IV : Intravenous
LC-MS/MS : Liquid Chromatography-Tandem Mass Spectrometry

MD : Molecular Dynamics
ML : Machine Learning
MRI : Magnetic Resonance Imaging
N2B : Nose-to-Brain
NDD : Nasal Drug Delivery
NDS : Nasal Delivery System
PK : Pharmacokinetics
PD : Pharmacodynamics
PDE : Partial Differential Equation
PDI : Polydispersity Index
SEM : Scanning Electron Microscopy
TEM : Transmission Electron Microscopy
TGI : Trigeminal–Olfactory Interface
USP : United States Pharmacopeia
3D : Three-Dimensional

Declaration:

Ethics approval and consent to participate:

Ethical approval and informed consent were not applicable to this study because it was a narrative literature review that did not involve any original research involving human participants or animals.

Clinical Trial No:

As this manuscript is a narrative review based exclusively on previously published literature and does not involve any clinical trials, clinical trial registration was not required.

Consent for publication:

Clinical trial registration was not required because this manuscript is based solely on a narrative review of previously published literature and does not involve any clinical trials.

Availability of data and material:

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Rupesh Sahu: Literature review, data curation, validation & manuscript evaluation

Rahul Dev: Manuscript writing, review & editing and critical revision

Dharmendra Sahu: Concept development, methodology & critical review

Shiv Kumar Bhardwaj: Writing, methodology, visualization & final editing

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