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Nose-to-brain drug delivery: A new frontier in targeted therapeutics

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ABSTRACT

Delivering therapeutics to the Central Nervous System (CNS) remains a major challenge in drug development, largely because the blood–brain barrier (BBB) limits brain exposure for most systemically administered agents. Among alternative delivery routes, intranasal administration has attracted significant interest because it leverages direct anatomical connections between the nasal cavity and the brain, thereby reducing reliance on BBB permeability. This review examines the nasal route, focusing on how olfactory and trigeminal neural pathways contribute to drug transport into the CNS. Rather than assuming a single dominant route, the relative role of extracellular perineural diffusion, intracellular neuronal transport, perivascular movement, and cerebrospinal fluid–associated distribution are evaluated in light of existing experimental evidence. Key factors that limit or enhance intranasal brain delivery—including mucociliary clearance, local enzymatic activity, drug physicochemical properties, formulation design, and patient-specific variability—are discussed with attention to their practical implications. Recent advances in formulations, such as mucoadhesive and in situ gelling systems, particulate and lipid-based carriers, dendrimers, and stimuli-responsive platforms, are reviewed alongside developments in nasal delivery devices that influence regional deposition.

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Introduction

Despite sustained advances in neuroscience and pharmacotherapy, effective treatment of neurodegenerative and psychiatric disorders remains limited by the difficulty of achieving adequate drug exposure within the Central Nervous System (CNS). A major constraint is the blood–brain barrier, which restricts the passage of many therapeutically relevant molecules and slows clinical translation of CNS-active agents. To address this limitation, alternative delivery routes have been explored to improve brain targeting while minimizing systemic exposure. Among these, intranasal (IN) administration has received increasing attention because it enables drug transport from the nasal cavity to the brain through direct anatomical connections, thereby reducing reliance on BBB permeability and potentially lowering peripheral side effects (1). From a formulation perspective, nasal delivery platforms range from simple liquid and semi-solid preparations to more complex carrier-based systems. Conventional approaches include solutions, suspensions, emulsions, gels, and drug-loaded nasal powders. In contrast, newer strategies incorporate mucoadhesive formulations, microspheres, nano- and microemulsions, polymer-based powders, and stimuli-responsive gels designed to enhance residence time and drug absorption within the nasal cavity (2).

Several physiological barriers collectively limit the effective delivery of therapeutic agents to the CNS. Foremost among these is the blood–brain barrier (BBB). This highly selective interface protects neural tissue from potentially harmful substances but also restricts the entry of many pharmacologically active compounds (3, 4). In addition to its tight junctions, the BBB expresses active efflux transporters, including P-glycoprotein, which reduce intracerebral drug accumulation by transporting substrates back into the systemic circulation (5). Beyond barrier-related constraints, systemic pharmacokinetics further complicate CNS drug delivery. Rapid hepatic metabolism and clearance by peripheral tissues can significantly lower circulating drug levels, thereby limiting the fraction of the administered dose that ultimately reaches the brain (6). Together, these factors contribute to subtherapeutic CNS exposure and pose persistent challenges in developing effective treatments for neurological and psychiatric disorders.

Intranasal administration has gained attention as an effective method to bypass the blood–brain barrier (BBB) and deliver therapeutic agents directly to the CNS. This route takes advantage of the anatomical connections provided by the olfactory and trigeminal nerves, which extend from the brain to the nasal cavity and terminate in the olfactory and respiratory epithelium. Preclinical and clinical studies have consistently shown that this delivery pathway can achieve rapid and targeted drug transport to the brain, highlighting its potential for treating neurological disorders (7). Drugs must be administered to the brain to treat CNS disorders.

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The permeability concerns of the endothelial membrane that divides central interstitial fluid from systemic circulation, known as the Blood-Brain Barrier (BBB), typically cause hydrophilic and high-molecular-weight medications to have trouble getting to the brain. Because they cannot reach sufficient levels in the brain through systemic circulation, numerous therapeutic medicines have been discontinued. If taken orally, proteins and peptides—macromolecular biologics—are quickly broken down by liver cytochromes or gastrointestinal enzymes because they are too large and hydrophilic to cross the BBB from systemic circulation. Therefore, a non-invasive treatment would be preferred for patients, especially those with conditions requiring long-term medication. Studies on humans and animals have demonstrated that transporting exogenous elements straight from the nose to the brain is a possible way to get beyond the BBB (8).

This review primarily presents the foundational concepts and recent developments in nose-to-brain drug delivery, highlighting its potential to address the significant obstacle posed by the blood–brain barrier (BBB) in CNS therapy. It aims to summarize current understanding of nasal anatomy, physiological transport pathways, and formulation strategies that enable direct drug delivery to the brain through the olfactory and trigeminal nerves. Additionally, the review considers the role of nanotechnology and advanced delivery platforms in improving drug stability, permeability, and targeted action. The discussion further encompasses pharmacokinetic and pharmacodynamic considerations, therapeutic applications, regulatory aspects, and emerging research directions to establish nose-to-brain delivery as a precise and clinically relevant approach for CNS-targeted therapeutics.

Methods

This review was conducted as a narrative synthesis of published literature. We searched PubMed, Scopus, Google Scholar, and Web of Science databases for articles published between January 1990 and October 2025. The search strategy used combinations of the following keywords: "nose-to-brain delivery," "intranasal drug delivery," "olfactory pathway," "trigeminal nerve," "blood-brain barrier," "nanoparticles," "lipid carriers," "in situ gels," "mucoadhesive," and "clinical trials." We also manually screened the reference lists of retrieved articles to identify additional relevant studies. We included peer-reviewed original research articles, review articles, and clinical studies published in English. We excluded non-English articles, conference abstracts, and unpublished data. Because this is a narrative review, we did not perform a formal quality assessment or meta-analysis. Similar methodology has been used in previously published reviews on this topic.

Anatomy and physiology of the nasal cavity

Nasal regions: Vestibular, respiratory, and olfactory

The nasal cavity is divided into three primary functional regions: the vestibular, respiratory, and olfactory areas, each distinguished by its epithelial structure and physiological role. The respiratory region, characterized by its extensive surface area and rich vascular network, serves as a major site for drug absorption. Although the olfactory region occupies a smaller portion of the nasal cavity, it contains specialized neurons that establish a direct anatomical link to the CNS, enabling potential nose-to-brain transport (9). Because of its keratinized epithelium, the vestibular region mainly provides protection and makes a negligible contribution to medication absorption. The pseudostratified ciliated epithelium lining the respiratory mucosa facilitates mucociliary clearance, which has a major impact on the duration of drug residency. Bipolar olfactory neurons in the olfactory epithelium enable specialized nose-to-brain transport systems (10).

Olfactory epithelium as a gateway to the brain

The olfactory mucosa provides an accessible route for CNS drug delivery because its neurons project straight through the cribriform plate to the olfactory bulb. The blood–brain barrier can be circumvented by drugs that are deposited on the olfactory surface through intracellular or perineuronal transport. The olfactory region's neurological connections make it essential for nose-to-brain transmission despite its tiny surface area (11). The olfactory pathway (Figure 1) allows molecules to be delivered quickly to the CNS without the need for systemic circulation. Drug deposition in the olfactory bulb and related brain areas is greatly influenced by axonal transport from the olfactory neurons. Drug diffusion and absorption are influenced by the mucus layer that covers the olfactory mucosa, which acts as both a barrier and a medium (12).

Trigeminal nerve pathway

For intranasal medications to reach deeper brain areas like the brainstem, the trigeminal nerve (Figure 1) offers an alternate neural pathway. Its maxillary and ophthalmic branches innervate the olfactory and respiratory areas, increasing the possibility of neural drug absorption. Research indicates that when medications are mainly deposited in the respiratory mucosa, trigeminal-mediated transport may predominate (13). Trigeminal nerve pathways support both intracellular axonal transport and extracellular diffusion along perineural gaps. Drug distribution through

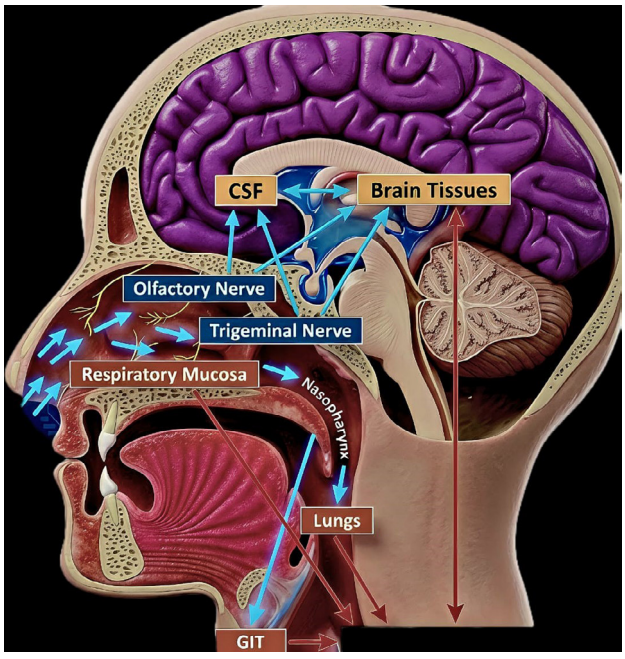

Figure 1. Gateways for nose-to-brain drug delivery
GIT: gastrointestinal tract; CSF: cerebrospinal fluid

trigeminal pathways frequently causes deposits throughout linked tissues, including brainstem nuclei. Variations significantly influence the predominance of either olfactory or trigeminal transport in the place of deposition (14).

Role of endocytosis in nose-to-brain transport

While passive diffusion and perineural transport are well-recognized routes for nose-to-brain delivery, endocytosis plays an equally important but often underappreciated role in the transport of macromolecules and nanocarriers across the nasal epithelium (15). Several distinct endocytic pathways have been identified in olfactory and respiratory epithelial cells, each with different capacities for carrying drugs and particles of varying sizes and surface properties (16).

Clathrin-mediated endocytosis is the best-characterized pathway. It involves the formation of clathrin-coated pits on the cell membrane that pinch off to form intracellular vesicles. This mechanism is particularly relevant for nanocarriers that are surface-modified with targeting ligands such as transferrin, lactoferrin, or antibodies. When these ligands bind to their corresponding receptors on olfactory epithelial cells, the receptor-ligand complex is internalized via clathrin-coated vesicles, allowing the drug or nanoparticle to enter the cell (16). Studies have demonstrated that clathrin-dependent endocytosis is the major pathway involved in nanoparticle uptake in olfactory tissues, with this mechanism being particularly dominant in the dorsal part of the olfactory epithelium. This pathway is well-suited for transporting molecules and particles up to approximately 150-200 nm in size (16).

Caveolae-mediated endocytosis operates independently of clathrin and involves flask-shaped invaginations called caveolae. These structures are rich in cholesterol and the protein caveolin. One advantage of this pathway is that it often bypasses lysosomal degradation, allowing internalized cargo to be transported across the cell and released intact on the opposite side via transcytosis (17). Research on drug-loaded nanoparticles has shown that caveolae-mediated endocytosis is a primary uptake mechanism for certain nanocarriers crossing the nasal mucosa. This makes caveolae-mediated endocytosis particularly attractive for delivering therapeutic proteins and sensitive biologics to the brain without degradation inside the cell (18).

Macropinocytosis is a non-specific, fluid-phase uptake mechanism that involves the formation of large, irregular vesicles called macropinosomes. Unlike clathrin- or caveolae-mediated pathways, macropinocytosis does not require specific receptor-ligand interactions. It is triggered by growth factors or by the interaction of certain nanoparticles with the cell surface (19). This pathway can internalize relatively large particles and macromolecular complexes, including viruses, gene therapy vectors, and large nanoparticles up to several micrometers in size (15). Studies have shown that macropinocytosis contributes significantly to the uptake of certain nanoparticles in respiratory tissues (20).

Receptor-mediated endocytosis is a broad category that includes clathrin- and caveolae-dependent mechanisms and other specific uptake processes. It is a highly efficient route for targeted drug delivery. For example, nanoparticles decorated with ligands for the transferrin receptor, low-density lipoprotein receptor, or lectin receptors on olfactory neurons have shown significantly improved uptake and transport to the brain after intranasal administration compared with untargeted particles (21). The expression of specific receptors on olfactory epithelial cells can be exploited to enhance nose-to-brain delivery through this pathway (15, 22).

The relative contribution of each endocytic pathway depends on several factors. Particle size is a key determinant: smaller nanoparticles (under 100 nm) tend to enter via clathrin-mediated pathways, whereas larger particles may rely more on macropinocytosis (19). Surface charge also matters: cationic particles often show higher cellular uptake due to electrostatic interactions with negatively charged cell membranes, but they may also cause greater toxicity (16). Studies have shown that surface modification of nanoparticles can significantly alter endocytic uptake, as polyethylene glycol-modified particles show different tissue accumulation patterns compared to unmodified particles (22). Ligand density and receptor expression on target cells further influence which pathway is engaged (18).

For formulation scientists, understanding these endocytic mechanisms provides practical guidance. If a drug or nanocarrier is intended to reach the brain intact, designing it to undergo caveolae-mediated transcytosis may be advantageous (17). If rapid cellular uptake is the goal, clathrin-mediated endocytosis may be preferred (19). If the target cells express specific receptors, ligand conjugation can harness receptor-mediated endocytosis to enhance delivery (15, 18). Several studies have demonstrated the relevance of endocytosis to nose-to-brain delivery. Transferrin-decorated chitosan nanoparticles showed enhanced uptake in nasal epithelial cells via receptor-mediated endocytosis (18). Drug-loaded, chitosan-coated PLGA nanoparticles demonstrated caveolae-mediated endocytosis as their primary cellular uptake mechanism, leading to improved brain delivery after intranasal administration (21). Similarly, studies using nanoparticle tracers confirmed that clathrin-dependent endocytosis, macropinocytosis, and caveolae-dependent pathways are all involved in nanoparticle transport across the nasal mucosa, with the relative contribution of each pathway varying between respiratory and olfactory tissues (16, 19).

Factors influencing drug transport

Mucociliary clearance

According to studies, mucociliary clearance can eliminate intranasal formulations in 15 to 20 min, greatly shortening the time available for drug absorption. The time medications stay in contact with the nasal epithelium is influenced by two important factors that determine the clearance rate: ciliary beat frequency and mucus viscosity. Formulations that interact with mucus or increase viscosity can improve absorption potential by prolonging nasal residence duration and slowing elimination (23). Effective mucociliary clearance shields the respiratory system, but by moving substances quickly toward the nasopharynx, it poses a challenge to medication delivery. Drug absorption varies based on several factors, including temperature, environmental irritants, and disease status. Mucoadhesive polymers improve nose-to-brain transport efficiency by interacting with mucins to promote formulation retention (24).

Enzymatic degradation

Peptidases, proteases, and CYP450 isoenzymes are

expressed in the nasal mucosa. These enzymes break down medications before they are absorbed, lowering the amount that may be delivered to the brain. Significant enzymatic degradation occurs in peptide and protein treatments, requiring protective formulation techniques such as enzyme inhibitors or nanoparticles. Drug stability at the deposition location is influenced by the different metabolic environments found in the respiratory and olfactory regions (25). Macromolecular medications have significant challenges from enzymatic breakdown in the nasal cavity, which limits their therapeutic effectiveness unless appropriate carriers stabilize them. Protease inhibitors and mucoadhesive excipients have been shown to increase the stability of peptides meant for CNS targeting. The choice of formulation for nose-to-brain transport is influenced by the fact that lipophilic medicines often degrade less than hydrophilic big molecules (26).

Physicochemical properties of the drug

Small, moderately lipophilic molecules are more likely to enter the CNS because they pass through the nasal epithelia more quickly. Transport is significantly influenced by molecular weight; molecules with a molecular weight of less than 1,000 Da have better permeability via nasal epithelia. Drug diffusion is impacted by ionization at nasal pH, where unionized species often show increased membrane permeability (12). High-molecular-weight and hydrophilic medications mostly depend on paracellular transport, which is naturally restricted in the nasal mucosa. Lipophilicity enables faster diffusion into both systemic and cerebral routes, improving transcellular transport. Poorly absorbed compounds can have their permeability improved by chemical modification, such as prodrug synthesis (8).

Formulation characteristics

By prolonging contact with epithelial surfaces, mucoadhesive systems improve medication absorption via the trigeminal and olfactory routes. By turning into a gel when exposed to nasal temperature or ions, in situ gelling technologies offer extended residency. When administered correctly, permeation enhancers like bile salts and surfactants temporarily weaken the integrity of the epithelium tight junction, enhancing drug transport without causing long-term harm (27). Particle size plays a critical role in determining deposition patterns within the nasal cavity. Particles in the range of approximately 10–50 µm are generally considered optimal, as they promote retention within the nasal passages while reducing the likelihood of pulmonary deposition. In addition to size, the regional localization of deposited drug—whether within the respiratory or olfactory epithelium—is strongly influenced by device-related factors such as spray pattern, plume geometry, and the type of delivery system used. Formulations and devices designed to enhance deposition in the upper nasal cavity can improve access to the olfactory mucosa and, consequently, increase the efficiency of nose-to-brain transport (28).

Nasal physiology and patient-specific factors further contribute to variability in intranasal drug absorption. Pathological conditions such as rhinitis, sinusitis, and mucosal inflammation can impair ciliary function and alter epithelial thickness, thereby affecting drug residence time and penetration. Increased mucus production during infectious or inflammatory states may further hinder absorption by accelerating drug clearance from the nasal cavity. In addition, inter-individual anatomical differences, including septal deviation, can influence airflow patterns and drug distribution, leading to variability in therapeutic outcomes following intranasal administration (29). Transport pathways may change as a result of nasal epithelial structural remodeling brought on by chronic respiratory conditions. Allergic inflammation increases vascular permeability, which can improve systemic absorption while decreasing CNS-directed uptake. The efficiency of nose-to-brain transport is greatly impacted by age-related changes in mucosal hydration and epithelial permeability (30).

Mechanisms of nose-to-brain drug transport

Olfactory pathway (Intracellular and extracellular transport)

Both intracellular and extracellular drug transport are made possible by the olfactory mucosa, which acts as a direct anatomical link between the brain and the nasal cavity. Endocytosis allows drugs deposited in the upper nasal cavity to enter olfactory sensory neurons, where they are then slowly transported by axons to the olfactory bulb. Nonetheless, research repeatedly demonstrates that most chemicals pass through extracellular perineural channels that encircle the olfactory neurons, providing significantly quicker access to the CNS. These perineural gaps serve as low-resistance diffusion channels that enable compounds, such as peptides and nanoparticles, to enter the olfactory bulb within minutes, long before intracellular axonal movement takes place. Taken together, these findings demonstrate that the primary mechanism causing early brain exposure following intranasal delivery is extracellular olfactory transport (11).

Trigeminal nerve pathway

The trigeminal nerve offers a supplementary but extremely important conduit for drug transport from the nose to the brain in addition to the olfactory route. Drugs deposited even in the lower nasal cavity can still reach the CNS because the ophthalmic and maxillary branches of the trigeminal nerve innervate both the respiratory and olfactory regions. According to experimental findings, the brainstem, midbrain, and pons are among the deeper brain regions that may be reached by molecules migrating via the trigeminal nerve, extending the distribution possibilities of intranasal therapies beyond the olfactory bulb. Because the trigeminal system still facilitates significant CNS administration, this channel is particularly important for traditional nasal sprays that rarely exactly target the olfactory area (8).

Perineural, perivascular, and extracellular bulk flow pathways

Beyond neuronal transport, extracellular routes that link the nasal mucosa to perivascular spaces and cerebrospinal fluid (CSF) account for a substantial amount of intranasal drug movement. Molecules can quickly diffuse into the subarachnoid space after entering the perineural or perivascular compartments. Convective CSF bulk flow then allows molecules to spread throughout the brain. The amazing rapidity of these non-neuronal routes has been demonstrated by imaging and tracer investigations, which have revealed that intranasally delivered chemicals can arrive in the CSF and perivascular channels within 5-30 min. These results suggest that, in addition to olfactory and trigeminal

pathways, perivascular and CSF-mediated dispersion play a crucial role in the extensive CNS distribution that occurs after intranasal treatment (31).

Influence of drug physicochemical properties on transport mechanism

The physicochemical properties of the supplied medicine significantly affect the effectiveness and dominance of each nose-to-brain transport route. Nasal epithelial membranes are easily penetrated by small, somewhat lipophilic substances, providing effective access to extracellular and neural routes. On the other hand, hydrophilic proteins, peptides, and macromolecules exhibit restricted transcellular permeability and, as a result, depend more heavily on perineural and perivascular transport to reach the brain. A drug's preference for olfactory neural transport, trigeminal routes, or CSF-mediated distribution is also influenced by other variables such as molecular weight, ionization, and hydrodynamic size. To ensure optimal targeting of the intended nose-to-brain pathway, these physicochemical limitations must be taken into account during formulation design (12).

Influence of formulation and delivery device characteristics

One of the main factors influencing whether transport pathways are triggered is the location of deposition inside the nasal cavity. Viscosity, mucoadhesive strength, droplet size, particle size, and the use of permeation enhancers are formulation factors that have a major impact on whether medications enter the olfactory area or remain within the respiratory epithelium. Similarly, the effectiveness of upper nasal deposition is strongly influenced by delivery device characteristics, including spray plume geometry, actuation dynamics, and nozzle orientation. These parameters determine how efficiently a formulation reaches specific regions of the nasal cavity and, consequently, whether drug transport preferentially engages olfactory or trigeminal nerve–associated pathways. Careful optimization of both formulation properties and device design therefore enables selective targeting of nose-to-brain transport mechanisms, which can enhance CNS bioavailability and improve therapeutic outcomes (32).

Integrated role of multiple mechanisms in CNS Delivery

The transportation of drugs from the nose to the brain ultimately depends on the coordinated interaction of extracellular perivascular and CSF-driven processes, trigeminal pathways, and olfactory neuronal transport. Together, these complementary pathways (Figure 2) enable intranasal treatments to quickly and non-invasively reach the CNS by avoiding the blood–brain barrier. The confluence of several pathways highlights the therapeutic promise of the intranasal route for treating neurological illnesses that would normally require invasive or systemic treatments, in addition to improving the speed and breadth of medication distribution inside the brain. Because of the convergence of these channels, nose-to-brain transport has emerged as a key area of interest for contemporary CNS drug delivery research (33).

Advantages and limitations of nose-to-brain drug delivery

The following are the advantages of nose-to-brain drug delivery: due to direct access to CNS pathways, intranasal administration provides a route for therapeutics to reach the brain through olfactory and trigeminal interfaces, reducing dependence on BBB permeability (11, 31). Rapid therapeutic onset is possible due to the high vascularity of the nasal epithelium and proximity to neuronal pathways, which support fast absorption and quick CNS action (34). Intranasal administration allows delivery of biologic and macromolecular therapeutics — such as proteins, peptides, or nucleic acids — directly to the brain, thereby bypassing the BBB and enabling CNS targeting of agents that would otherwise be excluded by systemic delivery (35). It is non-invasive and user-friendly. This route supports patient self-administration and improves compliance, especially for chronic neurological conditions (11).

This route of administration also has a few limitations, such as a short residence time, where efficient mucociliary activity rapidly removes deposited formulations, limiting the duration available for absorption (36). Restricted dosing volume is also observed as the nasal cavity can only retain small fluid volumes, which constrains dosing for many therapeutic agents (29). Enzymatic instability occurs as enzymes in nasal tissues—especially peptidases—can degrade vulnerable drugs, particularly peptides and proteins (36). Anatomical and physiological variability among individuals represents an additional source of inconsistency in intranasal drug delivery. Differences in nasal cavity geometry, epithelial integrity, and mucosal condition can

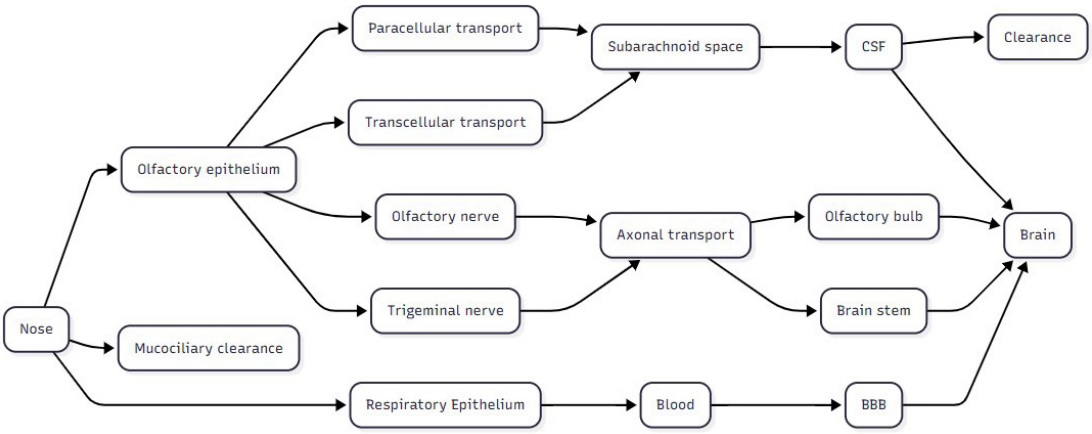

Figure 2. Schematic representation of intranasal drug delivery routes to the brain
CSF: cerebrospinal fluid; BBB: blood-brain barrier

alter airflow dynamics and regional deposition, leading to variability in drug absorption. Disease-related changes, including inflammation or compromised mucosal health, may further disrupt barrier properties and residence time, thereby affecting the reproducibility of therapeutic outcomes following intranasal administration (37).

Formulation strategies for nose-to-brain delivery

The development of formulation strategies for nose-to-brain drug delivery has been driven by the need to balance efficient brain targeting with the inherent constraints of the nasal environment. Intranasal formulations must contend with rapid mucociliary clearance, restricted administration volumes, local enzymatic activity, and the challenge of achieving sufficient drug exposure at olfactory and trigeminal interfaces without excessive systemic absorption. As a result, formulation design has shifted from simple liquid preparations toward systems that can modulate residence time and absorption behavior within the nasal cavity. These include mucoadhesive and in situ gelling formulations, particulate and lipid-based carriers, and solid nasal dosage forms, each selected to address specific delivery limitations rather than serve as universal solutions. Such approaches aim to improve formulation stability and mucosal interaction while enabling controlled transport of small molecules and more complex therapeutics to the brain, thereby supporting more consistent and targeted intranasal delivery.

Mucoadhesive systems

Because of their ability to extend the residence period of formulations within the nasal canal, mucoadhesive systems continue to be essential for intranasal-to-brain medication delivery (38). For example, the cationic polymer chitosan binds firmly to the negatively charged mucin in the nasal epithelium, increasing absorption and decreasing mucociliary clearance (39). This improved residency facilitates drug distribution to the olfactory and trigeminal areas, which are essential for nose-to-brain transport, and promotes both paracellular and transcellular transport routes (40). Additionally, preclinical research has demonstrated that mucoadhesive nano-aggregates (such as chitosan-based nanoparticles) enhance the brain transport of anti-tuberculosis medications, exhibiting greater effectiveness and safety in mice when compared to oral formulations (41). However, formulation design must also consider reversibility, local tolerability, and safety since excessive muco-adhesion may change mucus rheology or impede mucociliary function (40).

In situ gels

Stimuli-responsive polymers are used in *in situ* gelling systems for nasal delivery. These polymers stay liquid during administration but quickly solidify into a gel in the nasal cavity, creating a depot that extends retention and permits prolonged drug release (41). For intranasal use, thermo-responsive formulations utilizing poloxamer (such as Poloxamer 407) in conjunction with mucoadhesive ingredients like HPMC or chitosan have been effectively created (40). For instance, in rat pharmacokinetic investigations, a risperidone-loaded thermosensitive intranasal gel showed a sol–gel transition around 34-37 ˚C and produced around 5.4-fold greater brain AUC compared with oral treatment, indicating its potential for improved brain targeting (40). However, maintaining the chemical stability of the therapeutic payload inside the gel network, guaranteeing uniform drug distribution during sol-to-gel conversion, and managing gelation kinetics to avoid premature gelation in the delivery device are still major formulation issues (29, 42). Other methylcellulose (MC) designs have also been optimized: in research on the Parkinson's medication piribedil, in situ MC gels considerably enhanced nasal retention, decreased mucociliary clearance, and raised brain AUC when compared to traditional suspensions (43). Thermoreversible gels (such as those based on Pluronic F-127 and HPMC) have increased residence time and have been shown to boost brain bioavailability while preserving mucosal safety in animal experiments in sheep and rats (40).

Nano- and microparticles

Nanoparticles and microparticles may encapsulate labile medications (such as peptides and small molecules), shield them from degradation, and be engineered for targeted delivery, offering a potent platform for intranasal-to-brain administration. Particle size, surface charge, hydrophobicity, and functional ligands (such as transferrin, lactoferrin, or cell-penetrating peptides) are critical design elements that directly influence how particles interact with the nasal mucosa, cross the epithelial barrier, and traverse neuronal or perivascular pathways. Although excellent brain biodistribution has been demonstrated in animal models using polymeric nanoparticles (such as PLGA), lipid-based carriers, and tailored microparticles, translating these findings to humans is challenging because of anatomical variations across species and differences in dosing geometries. Additionally, these particles may be engineered to limit systemic exposure, modify release kinetics (pulsatile or sustained), and incorporate targeting or diagnostic moieties to enable theranostic applications (44).

The comparison of different formulation strategies for nose-to-brain delivery is given in Table 1.

Nanotechnology in nose-to-brain delivery

Nanotechnology has been increasingly applied to nose-to-brain drug delivery as a means of addressing the biological constraints that restrict efficient access of therapeutics to the CNS. The use of nanoscale carriers allows modulation of drug stability and residence time within the nasal cavity, while also supporting transport through olfactory and trigeminal pathways. A broad range of nanosystems—including polymer-based particles, lipid formulations, dendritic structures, nanogels, and surface-engineered carriers—has been investigated for their ability to regulate drug release, influence cellular uptake, and interact with the nasal mucosa. Through these properties, nanotechnology broadens the scope of compounds amenable to intranasal administration. It contributes to improved brain exposure, reduced peripheral distribution, and enhanced therapeutic performance in the context of neurological disease. By shielding sensitive payloads, increasing residence duration on the nasal mucosa, and promoting neuronal uptake via olfactory and trigeminal routes, nanotechnology offers adaptable platforms that significantly increase the transfer of therapeutic drugs from the nasal cavity to the brain (45).

Table 1. Comparison of formulation strategies for nose-to-brain delivery

Formulation Type	Mechanism	Advantages	Limitations	Clinical status	References
Simple solutions/suspensions	Passive diffusion	Low cost, simple, familiar formulation	Rapid mucociliary clearance (15-20 min); low brain bioavailability	Approved (e.g., sumatriptan)	(1, 2, 6, 23)
Mucoadhesive systems	Adhesion to mucin; prolonged nasal residence	Extended retention (hours vs minutes); improved absorption	Potential mucosal irritation; may alter mucus rheology	Preclinical/early clinical	(38-40)
In situ gels	Sol-gel transition (temperature/pH/ion-responsive)	Easy administration; sustained drug release	Gelation kinetics difficult to control; drug distribution uniformity	Preclinical (risperidone, piribedil)	(42, 43)
Nanoemulsions	Enhanced solubility and permeability	High drug loading; small droplet size	Stability concerns; potential surfactant toxicity	Preclinical	(35)
Polymeric nanoparticles	Encapsulation; controlled release	Protection of labile drugs; tunable release kinetics	Batch-to-batch variability; scale-up challenges	Preclinical (paroxetine, miR-132)	(47-49)
Solid lipid nanoparticles (SLNs)	Lipid matrix; enhanced transcellular uptake	Biocompatible; protects sensitive drugs	Drug expulsion during storage; lipid polymorphism	Preclinical	(44, 46)
Nanostructured lipid carriers (NLCs)	Mixed solid/liquid lipids	Higher drug loading; better stability than SLNs	Scale-up reproducibility; long-term stability	Preclinical	(44, 46)
Dendrimers	Highly branched; multivalent surface	High loading capacity; surface functionality	Toxicity (high-generation cationic dendrimers)	Preclinical	(52, 54)

PLGA: poly lactic glycolic acid; HPMC: hydroxypropyl methylcellulose; CNS: central nervous system; BBB: blood-brain barrier

Polymeric nanoparticles (PNs), solid lipid nanoparticles (SLNs), dendrimers/nanogels, and surface-modified carriers are among numerous nanoparticle systems that exhibit great promise for intranasal-to-brain transport (44).

Liposomes and niosomes

Considering that they can encapsulate both hydrophilic and lipophilic medications, shield sensitive cargo from enzymatic degradation, and fuse with cellular membranes to improve uptake, lipid vesicles like liposomes and niosomes are especially appealing for intranasal administration. Liposomal and niosomal formulations administered via the nasal route have shown higher brain accumulation of small molecules, peptides, and other therapeutic substances in several preclinical trials. Deposition in the olfactory region and retention in target neuronal regions are further enhanced by optimizing surface features, such as PEGylation (to promote mucus penetration) or ligand conjugation (for receptor targeting). However, there are challenges in translating to clinical use: large-scale production, vesicle sterilization, long-term stability, and possible toxicity or immunogenicity must all be carefully considered (46).

Polymeric nanoparticles

Polymeric nanoparticle systems, such as those based on PLGA or PEG, as well as dendrimer architectures, have been explored for nose-to-brain drug delivery because their size, surface properties, and drug-release characteristics can be deliberately adjusted. In preclinical studies, modification of these carriers with mucoadhesive components or targeting ligands, including peptides and antibodies, has been associated with improved interaction with the olfactory epithelium and enhanced distribution of drugs within selected brain regions (44). Altering the physicochemical properties (size, surface charge, hydrophobicity), which can be optimized to improve mucoadhesion, permeability, and drug release kinetics, biodegradable polymeric nanoparticles made of materials like poly (lactic-co-glycolic acid) (PLGA), chitosan, polycaprolactone, and other FDA-approved polymers are especially appealing for nose-to-brain delivery (47). For instance, chitosan-coated PLGA nanoparticles promote paracellular transport by improving mucosal adherence and partially opening tight junctions in the nasal epithelium. In one particular study, paroxetine-loaded PLGA nanoparticles coated with chitosan (PAR-CS-PLGA NPs) demonstrated a particle size of approximately 181 nm, a high entrapment efficiency of approximately 87.5%, and sustained release for up to 72 hours; when administered intranasally in mice, they significantly increased drug concentration in the brain and showed improved behavioral outcomes in depression models (48). In a different design, miR-132 was delivered via PEG-PLA (polyethylene glycol–polylactic acid) core–shell nanoparticles, which provided defense against mucociliary clearance and degradation while exhibiting neuroprotective effects *in vivo* (49).

Solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers (NLCs)

The lipid matrix of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) is made of physiological, biocompatible lipids, which lowers toxicity and improves patient safety (50). Compared with traditional SLNs, NLCs are a more recent lipid carrier that includes both liquid and solid lipids to create a less ordered crystalline structure that helps prevent drug ejection during storage and allows for greater drug loading (39). In light of their advantageous size, biocompatibility, and release kinetics, intranasally administered SLNs and NLCs show improved brain delivery in various CNS disease models, including Parkinson's and Alzheimer's (50). Mechanistic studies indicate that nanostructured lipid carriers (NLCs) often provide improved drug-loading capacity and formulation stability compared with solid lipid nanoparticles (SLNs). However, despite these experimental advantages, challenges related to long-term physical stability, batch-to-batch reproducibility, and scalability of manufacturing processes remain significant barriers to successful clinical translation (51). SLNs and related nanostructured lipid carriers (NLCs) offer high drug loading and controlled release appropriate for intranasal delivery by combining the stability of a solid core with the biocompatibility of lipids (52). These lipid-based carriers can enhance transcellular absorption and shield labile medications from enzymatic breakdown in the nasal cavity. Due to increased mucosal penetration and improved retention, intranasally administered SLNs have shown higher brain accumulation in preclinical models than free

drug (44). However, formulation issues such as consistent targeting across species, drug ejection over time, and lipid polymorphism continue to pose difficulties for their clinical translation (52).

Dendrimers and nanogels

For nasal-to-brain applications, dendrimers—highly branching, monodisperse macromolecules—and nanogels—cross-linked polymer networks—offer additional benefits because of their high loading capacity, surface functionality, and stimuli-responsive nature. Higher-generation dendrimers, particularly those bearing cationic surface charges, may induce cellular toxicity, necessitating strategies such as surface neutralization or shielding to balance efficacy with biocompatibility. Although these nanocarriers demonstrate considerable promise at the experimental level, their clinical translation will depend on robust evidence of scalable manufacturing, acceptable safety profiles, and a clear therapeutic advantage over established formulation approaches (44). Therapeutic drugs and targeted moieties can conjugate on their multivalent surface, and temperature- or pH-sensitive nanogels can create in situ gels in the nasal cavity, prolonging residence time and decreasing removal. For example, some dendrimers with optimal surface chemistry and size have produced effective absorption via the olfactory mucosa, delivering macromolecules and small compounds to the CNS with less systemic exposure (53). However, careful design with respect to generation, surface groups, and degradability is required because of possible problems with dendrimer toxicity, long-term biopersistence, and immunogenicity (54).

Surface modification and targeting ligands

Enhancing transport over nasal barriers, extending retention, and increasing brain targeting all depend on surface engineering of nanoparticles. PEGylation to reduce opsonization and non-specific interactions, coating with mucoadhesive polymers (such as chitosan or hyaluronic acid), and conjugation of targeting ligands (such as transferrin, lactoferrin, or cell-penetrating peptides) that promote receptor-mediated uptake are some strategies (53, 55). For instance, transferrin-decorated chitosan nanoparticles (~110-150 nm) demonstrated improved transport to glioblastoma cells in a transwell model and enhanced uptake in nasal epithelial cells *in vitro*, demonstrating the potential of ligand-functionalized NPs for improved nose-to-brain delivery (56). However, optimal surface alterations necessitate striking a balance: charged or reactive surfaces may cause mucosal irritation or immunological responses. In contrast, extremely mucoadhesive surfaces may prevent deeper penetration into the olfactory area (53).

The comparison of nanoparticle types and key preclinical outcomes is given in Table 2 and Figure 3.

Smart drug delivery systems

Smart drug delivery systems are therapeutic platforms engineered to regulate drug release in response to defined internal or external stimuli. These systems rely on materials that respond to physiological conditions, such as changes in pH, temperature, enzymatic activity, and redox environment, as well as externally applied triggers, enabling spatial and temporal control over drug release. The development of these platforms draws on advances in nanotechnology, biomaterials, and molecular engineering to improve drug localization and reduce unintended systemic exposure. By enabling more precise modulation of drug delivery, smart systems have the potential to enhance therapeutic effectiveness while limiting off-target effects, particularly in applications requiring controlled, site-specific drug action (48). Their adaptability allows for

Table 2. Comparison of nanoparticle types and key preclinical outcomes

Nanoparticle type	Particle size (nm)	Encapsulation efficiency (%)	Drug release profile	Key preclinical findings	References
Curcumin-loaded PLGA nanoparticles	~200	~80	Sustained	Demonstrated efficient cellular uptake via caveolae-mediated endocytosis and enhanced CNS delivery	(21)
Solid Lipid Nanoparticles (SLNs)	50-400	60-90	Variable	Increased brain accumulation and mucosal penetration compared with free drug formulations	(44)
Nanostructured Lipid Carriers (NLCs)	50-500	70-95	Sustained	Improved drug loading capacity, stability, and brain delivery in Parkinson's and Alzheimer's disease models	(44)
Liposomal formulations	80-250	60-90	Sustained	Enhanced protection of encapsulated drugs from enzymatic degradation and increased brain accumulation following intranasal administration	(46)
Niosomal formulations	100-300	65-92	Sustained	Improved drug stability and prolonged residence time in the nasal cavity, resulting in enhanced brain targeting	(46)
Chitosan-coated PLGA nanoparticles (Paroxetine)	~181	~87.5	Sustained (up to 72 hr)	Significantly increased brain drug concentration, ~5.4-fold higher brain AUC than oral administration, and improved antidepressant activity in mice	(45)
PEG–PLA nanoparticles (miR-132)	~120	NR	Sustained	Protected miR-132 from degradation and mucociliary clearance; demonstrated neuroprotective effects *in vivo*	(47)
Transferrin-modified chitosan nanoparticles	110-150	Moderate-High	Controlled release	Enhanced uptake by nasal epithelial cells and improved brain transport through receptor-mediated mechanisms	(53)
Dendrimer-based nanocarriers	10-100	Variable	Controlled release	Improved transport of macromolecules across olfactory mucosa with reduced systemic exposure	(54)

PLGA: poly lactic glycolic acid; SLN: solid lipid nanoparticle; NLC: nanostructured lipid carrier; PEG: polyethylene glycol; PLA: polylactic acid; CNS: central nervous system; AUC: area under the curve; NR: not reported

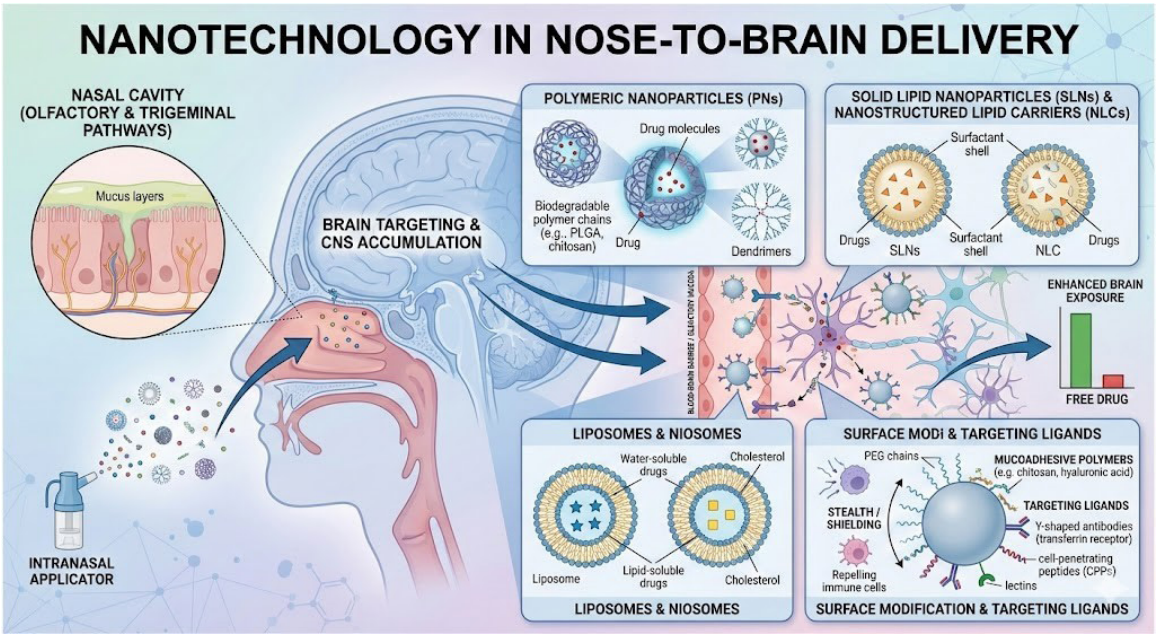

Figure 3. Nanotechnology to nose-to-brain delivery
PNs: polymeric nanoparticles; PLGA: polylactic glycolic acid; SLNs: solid lipid nanoparticles; NLCs: nanostructured lipid carriers; PEG: polyethylene glycol; CPPs: cell-penetrating peptides; CNS: central nervous system

optimized pharmacokinetics, reduced dosing frequency, and enhanced patient adherence, making them a promising strategy for managing complex and chronic diseases. As research progresses, smart drug delivery systems continue to evolve toward greater biocompatibility, tunability, and clinical applicability (48).

Stimuli-responsive formulations (pH, temperature, enzyme)

To increase residence time and promote controlled deposition in olfactory and respiratory regions, stimuli-responsive formulations take advantage of changes in the local chemical or physical environment to initiate sol–gel transition, drug release, or structural rearrangement at the nasal mucosa (56, 57). Poloxamers, methylcellulose derivatives, or thermosensitive copolymers are examples of polymers used in thermoresponsive in-situ gelling systems that are liquid at room temperature but quickly gel at nasal mucosal temperature, decreasing mucociliary clearance and permitting sustained release into perineural pathways to the brain (56, 58). To improve local retention and shield labile cargo from enzymatic degradation, pH-sensitive polymers that experience ionization or network collapse in response to the mildly acidic to neutral nasal milieu have been used to specifically trigger drug liberation or mucoadhesive strengthening upon nasal administration (57, 59). When paired with mucoadhesive matrices, enzyme-responsive carriers—designed to break down in the presence of nasal proteases or glycosidases—allow for localized release of peptides and proteins with temporal control and decreased systemic exposure. These carriers have demonstrated promise in preclinical nose-to-brain applications (57, 60).

Targeted and controlled release systems

Targeted nose-to-brain systems enhance brain accumulation and decrease peripheral distribution by combining biological targeting (ligands, antibodies, peptides) with physicochemical control (size, charge, hydrophobicity) to promote receptor-mediated transcytosis across the nasal epithelium or neuronal uptake via olfactory/trigeminal pathways (55, 61). In both *in vitro* and *in vivo* models, surface functionalization techniques like ligand conjugation (e.g., transferrin, lactoferrin), adsorption of cell-penetrating peptides, or temporary coating with mucoadhesive polysaccharides have enhanced epithelial uptake and parenchymal delivery; however, each payload must balance mucoadhesion (for residence) and mucopenetration (for access to olfactory regions)(55, 62). PLGA nanoparticles, lipid-based depots, and crosslinked nanogels are examples of controlled-release matrices that enable adjustable release kinetics that match pharmacokinetics with pharmacodynamic windows necessary for CNS targets and have produced better pharmacological results in animal models of neurodegeneration and psychiatric disorders (61, 63).

Biodegradable and sustained-release carriers

Many sustained-release nasal carriers are made of biodegradable polymers like PLGA, polycaprolactone, and naturally derived biopolymers (like chitosan and hyaluronic acid) because they combine established safety profiles with predictable hydrolytic degradation, allowing for extended drug exposure in the nasal cavity and gradual transport into the brain (63, 64). Compared with traditional solutions or suspensions, biopolymer-based nanoparticles and *in situ* gelling depots have been shown to protect peptides and nucleic acids from nasal enzymes while continuously releasing therapeutic concentrations over hours to days; several recent preclinical studies report improved brain AUC and pharmacodynamic efficacy for drugs delivered via these systems (60, 63). Controlling release burst, reproducible large-scale manufacturing, long-term mucosal tolerability, and carefully choosing polymer molecular weight and end-group chemistry to adjust degradation rates without causing local inflammation are translation challenges for biodegradable sustained-release systems (64).

Nasal drug delivery devices

Conventional nasal sprays

Conventional nasal sprays continue to be the most popular intranasal delivery method because they are easy to use, affordable, and self-administrable. When used properly, they create a small droplet plume that distributes medication throughout the anterior and middle nasal cavities (65). However, standard spray pumps typically deliver only small volumes (100-200 µl per actuation), which limits dose escalation for poorly permeable drugs (66, 67). They also frequently suffer from variable dose delivery and user-dependent factors (spray angle, inhalation, head position) that significantly affect deposition pattern and drug bioavailability. To improve regional targeting (e.g., olfactory area) and minimize lower airway deposition, formulation parameters (viscosity, surface tension, osmolarity) and device nozzle geometry are crucial design variables since they both affect droplet size distribution and spray plume dynamics (67, 68).

Metered-dose inhalers (MDIs) and pressurized systems adapted for nasal use

Metered-dose inhaler (MDI) technology and pressurized aerosol systems have been evaluated and adapted for intranasal applications where precise metering and rapid droplet/aerosol generation are required; these systems deliver precise unit doses and reduce variability related to manual actuation, despite being traditionally associated with pulmonary delivery (69). MDIs formulate low-viscosity solutions or suspensions for quick mucosal wetting and absorption by using propellants and specially designed actuator orifices to control droplet size; nevertheless, formulation stability (suspension homogeneity, propellant-drug compatibility) and environmental considerations (propellant selection) must be taken into account for nasal adaptations (69, 70). If the plume and particle/droplet size are matched to the target region, pressurized devices may achieve deeper or more uniform intranasal dispersion than liquid sprays; nonetheless, patient technique and coordination are still crucial performance factors (70).

Breath-powered and bi-directional delivery devices

Breath-powered (bidirectional) delivery devices strengthen deposition to higher posterior nasal regions, including the olfactory cleft, and minimize lung exposure by using the patient's exhalation to propel the medication into the nasal cavity while also sealing the soft palate to minimize pulmonary entry (71). Bidirectional breath-powered systems can improve deposition to deeper nasal sites, increase local drug uptake, and reduce variability seen with conventional sprays, according to clinical and imaging studies. These benefits have been used in acute therapies like intranasal sumatriptan and other emergency medications (71, 72). The successful outcome of breath-powered systems in directing aerosol to target locations and limiting undesirable clearance or throat deposition is influenced by device design variables like delivery pressure, one-way valves, sealing geometry, and plume characteristics (73).

Smart delivery systems and wearable technologies

To facilitate controlled dosing, adherence monitoring, and customized delivery regimens, smart nasal delivery systems use sensors, microelectronics, actuation control, and connectivity. These platforms offer superior administration consistency and the capacity to connect dosing to physiological signals or digital therapeutics (74). Examples include devices that track usage for remote adherence monitoring, monitor actuation force or inhalation flow, and provide feedback to optimize head position or timing. These features can be particularly helpful for chronic CNS indications where repeated, precisely timed intranasal dosing is crucial (75). To offer programmed, sustained, or on-demand intranasal dosing, wearable and automated pump systems are being investigated. Although early prototypes and pilot trials demonstrate feasibility, regulatory, usability, and long-term mucosal safety data are required before general clinical use (59, 74). In the Danga *et al.* (2025) paroxetine hydrochloride nasal gel study, the authors explicitly referred to the use of a metered-dose pump as the delivery device for administering the nasal gel formulation (e.g., twice daily dosing via actuations through the pump) — linking the formulation to a device-mediated administration component that aligns with smart delivery device functions such as controlled dosing and actuation monitoring (76).

The comparison of nasal delivery device types is given in Table 3 and Figure 4.

Discussion

Unlike earlier descriptive reviews that primarily compile existing literature, the present review offers several distinctive contributions. First, we provide a critical comparison of the four major transport pathways—olfactory, trigeminal, perivascular, and CSF-mediated—evaluating their relative contributions, time courses, and dependence on drug physicochemical properties. Second, we explicitly address translational failures and inconsistencies between preclinical and clinical studies, rather than focusing solely on successful outcomes. Third, we include structured comparative tables that allow readers to directly assess the advantages, limitations, and clinical readiness of different formulation strategies, nanoparticle systems, and delivery devices. Fourth, we discuss regulatory challenges specific to nose-to-brain combination products, a topic often omitted in narrative reviews. Fifth, we integrate recent literature (2023-2025) with foundational studies to present both historical context and current advances.

A critical evaluation of the literature reveals that the relative importance of each transport pathway depends heavily on experimental conditions. The olfactory pathway provides the most direct route to the brain, with extracellular perineural diffusion delivering drugs to the olfactory bulb within minutes. However, the olfactory epithelium occupies only 3-5% of the human nasal cavity, severely limiting its practical capacity. The trigeminal pathway, while slower for some molecules, innervates a much larger surface area, including the respiratory epithelium, making it more relevant for conventional nasal sprays that do not specifically target the olfactory region. Perivascular and CSF pathways offer the fastest distribution to widespread brain regions (5-30 min), but drug dilution in CSF reduces local concentrations at specific targets. Importantly, most preclinical studies use rodents, where the olfactory epithelium covers approximately 50% of the nasal cavity. This anatomical difference means that olfactory pathway transport may be substantially overestimated in animal models compared to

Table 3. Comparison of nasal delivery device types

Device type	Deposition region	Droplet/Particle size	Advantages	Limitations	Clinical example	References
Conventional spray pump	Anterior/middle nasal cavity	30-100 µm	Low cost; self-administered; familiar	Variable deposition; user-dependent; poor olfactory targeting	Most nasal sprays	(65- 68)
Metered-dose inhaler (MDI)	Variable (device-dependent)	10-50 µm	Precise dose; consistent delivery	Propellant issues; patient coordination required	Some migraine therapies	(69)
Breath-powered (bi-directional)	Upper/posterior (olfactory cleft)	30-80 µm	Improved olfactory deposition; seals soft palate; reduced lung exposure	Higher cost; patient training needed	Sumatriptan (Onzetra Xsail)	(70- 72)
Smart/wearable systems	Targeted (programmable)	Variable	Controlled dosing; adherence monitoring; personalized delivery	Early development; regulatory uncertainty; cost	Investigational	(73-76)

humans. Formulation scientists should therefore consider trigeminal and perivascular pathways as equally important targets, particularly for clinical translation.

Despite numerous preclinical studies reporting successful nose-to-brain delivery, clinical translation has been disappointing for many candidates. Several factors explain this gap. First, as noted above, rodent nasal anatomy differs substantially from human anatomy, and the olfactory target area is much smaller in humans. Second, most animal studies use forced dosing protocols with animals restrained in a supine position, which does not mimic real-world patient use. Third, preclinical studies often measure brain drug concentrations at single time points after a single dose, whereas clinical efficacy requires sustained therapeutic levels over longer periods. Fourth, many published studies report brain accumulation but do not demonstrate functional improvement or target engagement in disease models. For example, intranasal insulin showed promising results in rodent models of Alzheimer's disease and in small human Phase II trials, but larger Phase III studies failed to meet primary endpoints. Similarly, intranasal oxytocin for autism spectrum disorder has yielded inconsistent results across multiple trials, with outcomes highly dependent on dosing protocol, patient selection, and administration technique. These examples highlight that successful nose-to-brain delivery in animals does not guarantee clinical efficacy, and more rigorous, translationally relevant models are needed.

Nose-to-brain products often combine a drug formulation with a specific delivery device, thereby qualifying as combination products under most regulatory frameworks. However, regulatory guidance for such products remains underdeveloped. The U.S. Food and Drug Administration has not issued specific guidance documents for nose-to-brain combination products, creating uncertainty regarding required preclinical and clinical data packages. Key unanswered questions include: What level of device characterization is sufficient? How should formulation-device interactions be evaluated? What bioequivalence standards apply for generic versions of nasal CNS products? In the European Union, the European Medicines Agency has provided guidance on nasal products in general, but not specifically on nose-to-brain delivery. This regulatory uncertainty poses a barrier to clinical development, as companies may be unsure what studies are needed for approval. Additionally, because device performance (spray pattern, droplet size, plume geometry) significantly affects regional deposition in the nasal cavity, even minor changes in device design could alter brain bioavailability. Regulatory agencies have not yet established standards for demonstrating equivalence when device components are

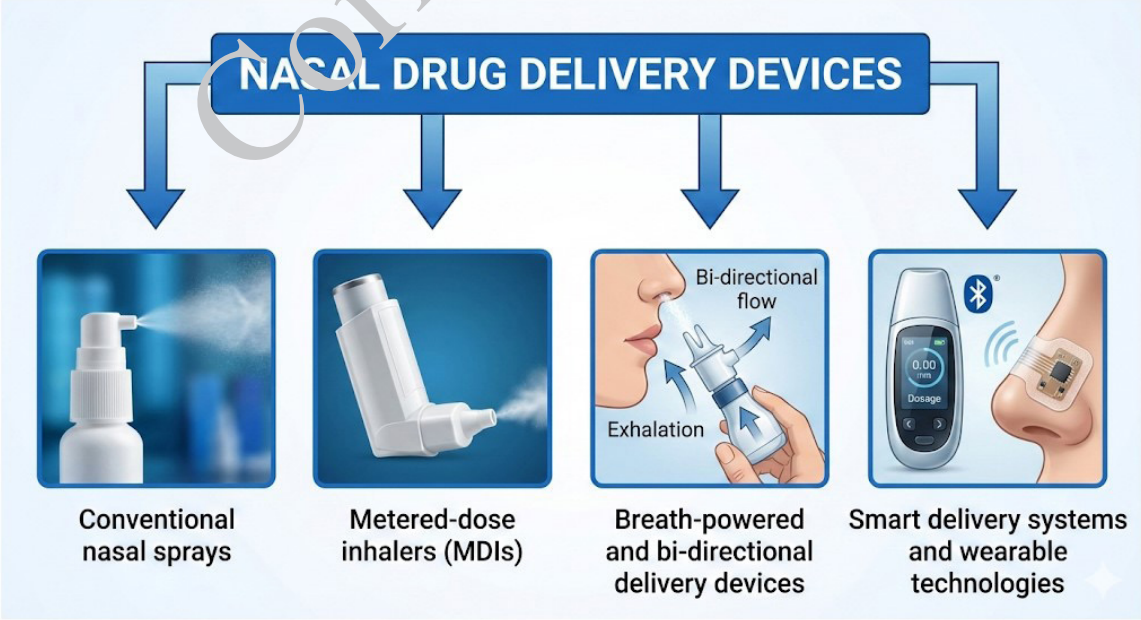

Figure 4. Nasal drug delivery devices
MDIs: metered-dose inhalers

modified. Addressing these regulatory gaps will require coordinated efforts between researchers, industry, and regulatory bodies to develop product-specific guidance that accounts for the unique challenges of nose-to-brain delivery.

The findings from this review show that intranasal delivery offers a practical way to bypass the BBB using olfactory and trigeminal nerve pathways. Several key points emerge from the literature.

Conclusion

Intranasal delivery can effectively transport drugs to the CNS by bypassing the BBB through olfactory and trigeminal pathways. Formulation advances — including mucoadhesive systems, in situ gelling matrices, polymeric and lipid-based nanoparticles, and surface-engineered carriers—have improved drug retention, permeability, and brain targeting in preclinical models. However, clinical translation faces real challenges. These include major anatomical differences between rodents and humans, inconsistent results from human trials, a lack of clear regulatory guidance for device-formulation combinations, and limited data on long-term mucosal safety. Future progress will depend on several developments. First, researchers need better comparative studies of transport mechanisms rather than assuming all pathways work equally well for all drugs. Second, standardized testing frameworks should be developed to allow comparisons across studies. Third, quantitative imaging methods could help measure actual drug doses reaching the brain in humans. Fourth, regulatory agencies need to provide clearer pathways for approving nose-to-brain products. With these advances, nose-to-brain delivery can become a valuable clinical tool for treating neurodegenerative, neuropsychiatric, and acute CNS disorders.

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Authors' Contributions

KSVVSS S contributed to resourcing and drafting; RD K was involved in conceptualization, supervision, manuscript review, and editing.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Declaration

During the preparation of this work, the authors used artificial intelligence tools for language polishing (Quillbot) and figure conceptualization. All content, including text, data interpretation, and final figures, has been reviewed and edited by the authors, who take full responsibility for the content of the publication.

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