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A REVIEW ON INTRANASAL DRUG DELIVERY TO THE BRAIN

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ABSTRACT

Intranasal drug delivery has been recognized as a non-invasive and efficient route for targeting the central nervous system (CNS) and has received considerable attention. The blood–brain barrier (BBB) is one of the main challenges in neurotherapeutics as it limits the access of most pharmacological agents to the brain. The intranasal route offers a unique alternative for the direct transport of drugs through the olfactory and trigeminal pathways, circumventing the BBB. This review discusses the structural and physiological features of the nasal cavity that favor drug absorption and the mechanisms of nose-to-brain transport, including intracellular and extracellular pathways. Apart from the fundamentals, this article covers various intranasal formulations such as liquid sprays, semisolids (gels, ointments) and solid systems (microparticles, nanoparticles) and the role of bioadhesive polymers, penetration enhancers, solubilizers and antioxidants in improving the drug stability and absorption. Special emphasis is placed on the therapeutic potential of intranasal delivery in neurological and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, epilepsy, and migraine, where traditional drug administration often fails to achieve effective concentrations in the brain. Although mucociliary clearance, enzymatic degradation and inter-individual variability present challenges, advances in nanotechnology, polymer science and device development are helping to overcome these limitations.

KEYWORDS: Intranasal drug delivery, Blood–brain barrier, Nose-to-brain transport, Nanoparticles, Neurological disorders.

INTRODUCTION

CNS drugs are often associated with high failure rates and much longer times for development, mainly due to problems in the transportation of drugs across the blood-brain barrier (BBB). Generally, only small, lipophilic molecules with a molecular weight less than 400 Da can cross the BBB, while most large proteins and genetic materials cannot, unless they are facilitated by an active transport mechanism.[1] Conventional delivery methods for CNS drugs, such as oral and

intravenous routes, are limited by many critical drawbacks. The BBB is a serious obstacle for drug penetration into the central nervous system, while metabolic degradation and first-pass hepatic effects reduce systemic bioavailability. Non-specific distribution often leads to off-target toxicity. Clinical efficacy and patient adherence are further restricted by poor CNS permeability, short half-life, narrow therapeutic windows, and frequent dosing requirements. Such challenges highlight the need for more effective and specific CNS drug delivery systems. Unlike conventional routes such as oral or intravenous administration, intranasal drug delivery enables drug absorption through the nasal mucosa, with direct access to systemic circulation, avoiding first-pass metabolism in the liver and gastrointestinal tract, and offers a promising approach to circumventing the BBB. This improves the bioavailability of drugs.[2,3]

A wide-range of therapeutics, such as peptides, proteins, gene vectors and stem cells, have been successfully delivered through IN administration to small animal brains and have shown efficacy in treating CNS diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, autism spectrum disorders, seizures, drug addiction, eating disorders, and stroke.[3] There are different factors responsible for crossing the blood brain barrier like binding of the drug to a transporter, opening and closing of ion channels, lipophilicity, enzymatic degradation of drug, higher molecular weight of drug and the presence of functional groups. These are the factors which determine the blood brain barrier permeability of any drug.[4]

Anatomy and Physiology of Nasal Cavity

The nasal cavity is the space inside your nose made up of bones, tissues, blood vessels, and nerves. Its main jobs are warm and moisten the air you breathe and to protect the body by stopping harmful germs from entering.[5]

The nasal cavity is the uppermost part of the respiratory tract. It connects with the outside environment through the front openings called nares and with the nasopharynx through the back openings called choanae. This space is divided into two parts by the septum and is supported by both bone and cartilage. Each nasal cavity has a roof, floor, inner wall (medial wall), and outer wall (lateral wall). Inside each cavity, there are three main sections: the nasal vestibule, the respiratory area, and the olfactory area.

Around the nasal cavities are air-filled spaces lined with mucosa, called sinuses. These include the frontal sinuses (upper front), ethmoid sinuses (upper), paired maxillary sinuses (side), and sphenoid sinuses (back). All the paranasal sinuses, except the sphenoid sinus, are connected to the nasal cavity through small ducts that open into areas on the side wall. The sphenoid sinus connects to the back roof of the nasal cavity. Understanding the structure of the nasal cavity is important for knowing its functions.[6]

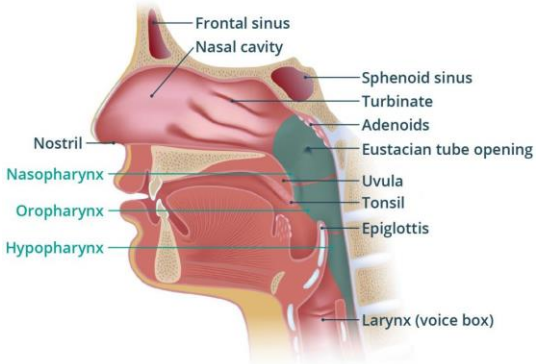

Fig. 1: The structure of the nasal cavity.[7]

Nasal Vestibule

The nasal vestibule is the first part of the nasal cavity, located just behind the nostrils (anterior nares). Its front half is lined with keratinized squamous epithelium and contains coarse hairs (vibrissae) that trap inhaled particles. The back half is lined with respiratory epithelium—pseudostratified ciliated columnar cells.[8]

Respiratory Region

The respiratory region serves to moisten, warm, purify, defend, and remove particulate matter. Lined with respiratory epithelium and mucus-secreting cells, it constitutes the largest portion of the nasal cavity. As inhaled air passes through this region, it is brought to body temperature and achieves nearly complete humidity. This process is facilitated by the rich neurovascular network. The nasal airflow is modulated by altering the blood volume within the erectile tissue of the inferior turbinate and the anterior nasal septum. Under normal circumstances, sympathetic stimulation via the superior cervical ganglia maintains these structures in a decongested state. Any particles that bypass the nasal vestibule become ensnared within the mucus layer of the nasal cavity. When this occurs, the mucociliary clearance mechanism removes these trapped materials. The ciliated pseudostratified columnar epithelium propels them at approximately one centimeter per minute toward the nasopharynx for subsequent elimination. The nasal mucus acts as a protective shield against inhaled microorganisms. Key defensive components within the mucus include immunoglobulin A, lysozyme, and lactoferrin, which collectively inhibit pathogen invasion.[8,9]

Olfactory Region

Olfaction (sense of smell) depends on airflow through either the orthonasal route (inhaling through the nose) or the retronasal route (airflow from the mouth to the nose) to carry odor molecules up to the olfactory epithelium at the top of the nasal cavity. When these odors molecules get trapped in the mucus, they bind to special proteins called odorant-binding proteins, which help gather and dissolve them. These molecules then attach to olfactory receptors on tiny hair-like structures (cilia). The receptors send specific signals through the cribriform plate to connect with neurons in the olfactory bulb. From there, signals travel via the olfactory nerve (cranial nerve I) to secondary neurons for advanced processing before reaching the brain. One unique feature of olfactory receptors is that each receptor cell can detect only one specific type of odor molecule— and these cells cannot regenerate once lost.[8,9]

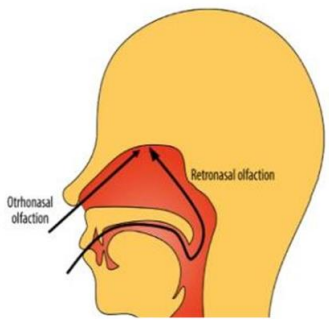

Fig. 2: Olfactory Region.

Blood supply

The nasal cavity has a rich network of blood vessel that helps in warming and moistening the air we breathe. These vessels also allow the nasal lining (mucosa) to expand or shrink depending on signals from the sympathetic nerves. The arteries that supply the nose mainly come from two sources — the internal carotid artery (ICA) and the external carotid artery (ECA).[6]

Internal Carotid Artery (ICA)

From the ICA, the ophthalmic artery is the key vessel supplying the nasal area. This artery gives rise to:
Anterior ethmoidal artery – provides blood to the side wall of the nasal cavity and the nasal septum.

Posterior ethmoidal artery – supplies the upper turbinate and part of the septum. Dorsal nasal artery – supplies the bridge (dorsal part) of the external nose.

External Carotid Artery (ECA)

The ECA forms two important arteries: the maxillary artery and the facial artery. These further branch into smaller vessels to nourish different parts of the nasal region.

Maxillary Artery
Descending palatine artery – travels through the pterygopalatine fossa and palatine canal, dividing into the greater and lesser palatine arteries. The greater palatine artery moves forward along the palate and enters the nasal cavity through the incisive canal, supplying the septum and nasal floor.

Sphenopalatine artery – enters the nasal cavity via the sphenopalatine foramen (just behind the middle turbinate). It divides into:

Posterior lateral nasal branches – supply the middle and lower turbinate.
Posterior septal branch – supplies the back portion of the septum.

Facial Artery: The facial artery branches into:
Superior labial artery – gives off alar and septal branches to supply the nostril wings and the septum.
Lateral nasal artery – supplies the nostril wings and nasal vestibule.
Angular artery – supplies the tip, bridge, and side wall of the external nose.[6]

Lymphatic system

A lymphatic pathway connects the nasal cavity to the brain through perineural spaces around the olfactory nerves in the cribriform plate. This olfactory/nasal lymphatic route drains cerebrospinal fluid (CSF) and interstitial fluid (ISF) from the brain to cervical lymph nodes, helps clear waste, regulates brain fluid balance, and allows immune cell migration.[11]

Its efficiency declines with age and is influenced by genetics, sleep patterns, and posture—factors linked to neurological disorders such as neurodegenerative, vascular, and inflammatory diseases. Therapeutically, this route offers a way to bypass the blood– brain barrier (BBB), enabling intranasal delivery of peptides, genetic materials, and other drugs directly to the CSF and brain tissue, maintaining effective concentrations while reducing systemic side effects.[11,12]

Nasal mucociliary clearance

The mucociliary system can be divided into two fundamentals units - The mucus and the cilia. Both are studied extensively for chemical composition and ultrastructure respectively. The clinicians are more interested of both the mucociliary clearance.[13]

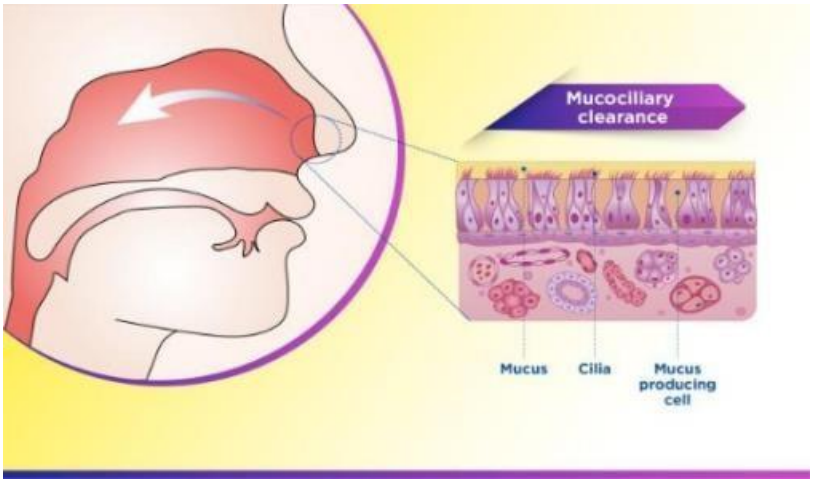

Fig. 3: Nasal mucociliary system.

Blood-Brain-Barrier: A Major Challenge

Neurons in the CNS send messages using both electrical and chemical signals, and this requires strict control of the ion balance around synapses and axons for proper function. This need for stability is believed to have driven the evolution of protective systems like the blood–brain barrier (BBB). In mammals, including humans, the BBB is formed by the endothelial cells lining brain capillaries. Another protective layer is the blood–cerebrospinal fluid barrier (BCSFB), formed by the epithelial cells of the choroid plexus, which produce cerebrospinal fluid (CSF). Interstitial fluid (ISF) in the brain partly comes from the BBB and can mix with CSF at certain sites, with ISF contributing 10–60% of CSF volume. A third interface is the arachnoid epithelium beneath the dura mater, which seals the CNS from the rest of the body's fluids. Although it acts as a barrier, its small surface area and lack of blood vessels limit its exchange role. All these barriers work through tight cell junctions (physical), specialized transport systems, and metabolic enzymes, and their function can change in health or disease.[15]

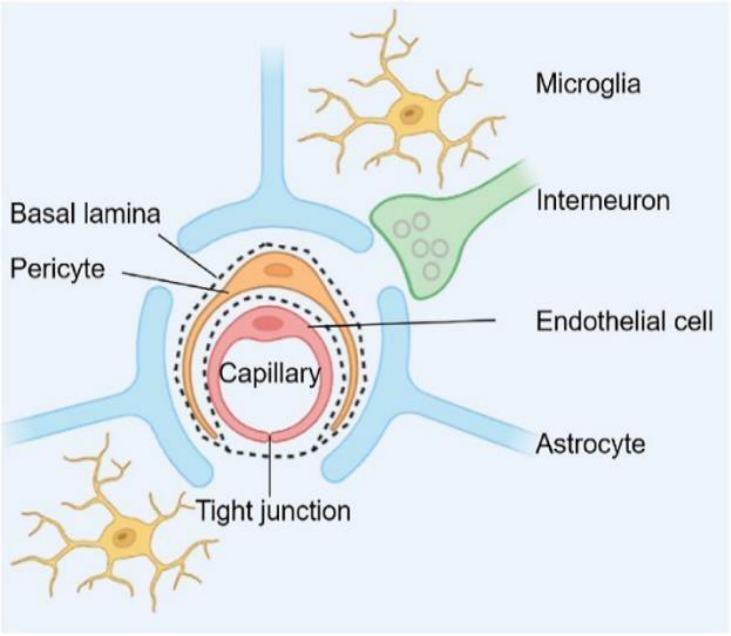

Fig. 4: Blood-Brain-Barrier.

The failure of several neurotherapeutic drug in CNS treatment is largely due to poor delivery to brain tissue. Effective transport to the brain is still a major hurdle, even in the presence of rich cerebral blood circulation.[16] The nasal–brain delivery pathway enables localized drug transport to the brain, mainly via the olfactory route. Interest has grown in the nasal–brain lymphatic system for delivering anticancer agents, but challenges like low drug permeability, nasal mucosal barriers, and mucociliary clearance limit its effectiveness. Nanocarriers and mucoadhesive agents are being explored to overcome these issues, though few drugs are clinically approved due to limited research and understanding of the mechanism.[17,18] More than 98% of CNS active drugs not able to cross the barrier because of its physiochemical properties do not match the criteria for the entry of molecules into the CNS. Lipophilic molecules, the drug that has a partition coefficient (Log P) between 1.5–2.7 and with the molecular weight less than 600 Dalton (Da) may be permeable to the BBB.[19]

Mechanisms of Nose -to-Brain Drug Transport

To understand intranasal-to-CNS drug delivery systems, it's important to first know the different routes and how they work, as these influence formulation choice, drug properties, safety, and effectiveness. Drugs can reach the brain through either the olfactory or trigeminal nerves, but the olfactory route is better studied. Because of its unique epithelial structure, blood supply, and shorter nerve length, the olfactory pathway generally allows faster and more efficient drug absorption into the CNS with less entry into the systemic circulation. In this discussion, focus will be on the olfactory nerve unless noted otherwise.[20] The transport mechanism involves three different way such as an olfactory pathway, Trigeminal pathway and systemic pathway.

Olfactory Pathway

The olfactory nerve pathway is the most extensively studied mechanism for intranasal drug delivery to the brain. Drugs absorbed by the olfactory epithelium are transported along olfactory nerve fibers, bypassing the BBB and directly reaching the cerebral cortex, hippocampus, and other brain regions. This provides a crucial foundation for the treatment of CNS diseases such as stroke, epilepsy and traumatic brain injury.[21,22] The olfactory pathway supports the treatment of not only small molecule but also peptide, protein and macromolecules that are otherwise restricted by the BBB, achieving rapid absorption and high brain concentration.[23]

After reaching the olfactory mucosa, drugs can enter the CNS via two main routes: (1) Intracellular transport – drugs are taken up by olfactory receptor neurons through clathrin-mediated endocytosis, then moved along axons to the olfactory bulb, where they are released; this is a slow process, taking hours to days. (2) Extracellular transport – a faster route involving passive movement across epithelial membranes or tight junctions into the extracellular space of olfactory nerve bundles, followed by bulk flow to the olfactory bulb and diffusion into cerebrospinal fluid, allowing broad brain distribution.[24,25]

Nanocarriers move efficiently through the olfactory pathway due to their affinity for lipid-rich tissues, while hydrophilic drugs may depend on carrier proteins. Particles between 50–200 nm, especially those under 150 nm, are considered optimal for nasal- to-brain transport. Liposomes below 150 nm have shown improved brain uptake and extended release for up to 96 h, boosting bioavailability over conventional forms. Nanoemulsions (~20–200 nm) can raise brain permeation by about 1.68-fold, while solid lipid nanoparticles (~129 nm) and nanostructured lipid carriers (~191 nm) provide sustained release and higher brain targeting, often outperforming intravenous delivery in AUC values. Overall, nanoparticles in this size range promote strong mucosal adhesion, better passage via olfactory and

trigeminal routes, and fewer systemic effects, making them highly suitable for CNS drug delivery through the nasal route.[26]

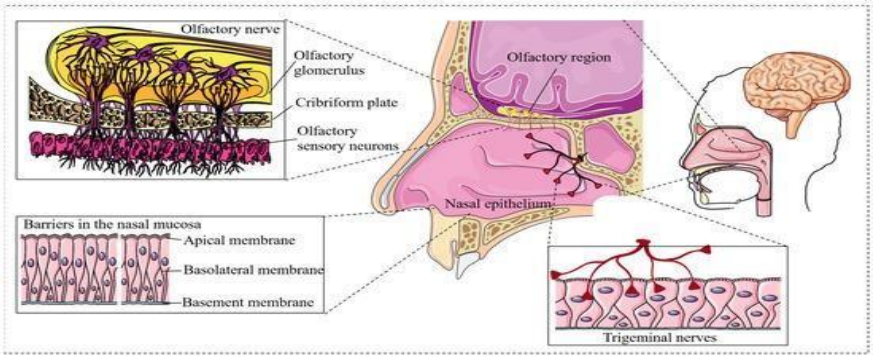

Fig. 5: Olfactory nerve pathway.

Trigeminal Nerve Pathway

Alongside the olfactory pathway, the trigeminal nerve provides another non-invasive route for direct drug transport to the brain. Originating from the pons and branching into the ophthalmic, maxillary, and mandibular divisions, it innervates the nasal respiratory mucosa and projects to brainstem and thalamic regions. Drugs absorbed through the nasal epithelium can interact with sensory neurons of the trigeminal nerve, where mechanisms may involve TRP channel activation (e.g., TRPV1), receptor-mediated endocytosis, and dynein-driven retrograde axonal transport. Delivery occurs via both intra-axonal transport and extracellular diffusion, independent of the olfactory route.

A key difference lies in the target site: while the olfactory nerve delivers drugs to the olfactory bulb, the trigeminal pathway directs them to the pons, leading to slower cerebrospinal fluid distribution due to the longer distance to CNS targets. Despite slower intracellular transport, this pathway still enables drugs to reach deep brain structures and offers a viable anatomical basis for intranasal CNS delivery. Further research is needed to determine the exact contribution of this route and refine formulations for optimal use.[27]

Transduction Transcellular and Paracellular Pathways in Intranasal Drug Delivery

Apart from traveling through the main nerve pathways, drugs can also move along the tiny fluid-filled spaces surrounding the olfactory and trigeminal nerves. These spaces act like extra channels, allowing the drug to pass either between cells (paracellular transport) or through cells (transcellular transport) to reach the brain. This helps the drug go deeper into brain regions and supports the neural transport routes.

Paracellular transport happens when drugs slip between the gaps of epithelial cells into the perineural space, and then enter the subarachnoid space via cerebrospinal fluid (CSF). The movement of CSF, driven by arterial pulsations, spreads the drug through the brain's glymphatic (perivascular) system — a network similar to lymphatic drainage. Special tight junction proteins like claudin-4, claudin-5, occludin, and ZO-1 keep this pathway regulated. Drugs such as insulin and interferon-β have successfully used this route to reach the CNS.

Transcellular transport involves drugs crossing directly through cells using different uptake systems — including clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, carrier-mediated active transport, and efflux pumps. Small molecules (e.g., peptides, nanoparticles) often enter via clathrin-coated vesicles, while

lipophilic drugs like paclitaxel in liposomes mainly use caveolae-mediated transport. Larger molecules, such as proteins and exosomes, usually enter cells through macropinocytosis.[28]

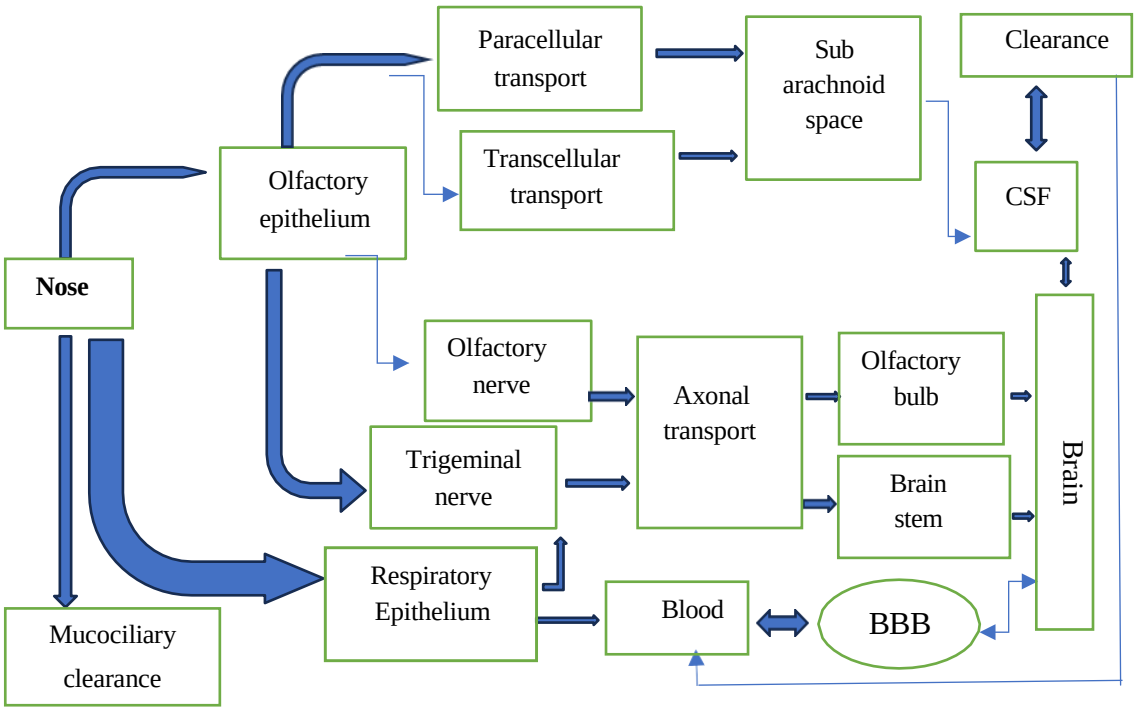

Fig. 6: Transduction Transcellular and Paracellular Pathways in Intranasal Drug Delivery.

Role of Neural Connection

The olfactory and trigeminal nerves form direct anatomical links between the nasal cavity and the brain. These nerves act like "highways" that bypass the blood–brain barrier, allowing drugs to travel straight into the central nervous system (CNS).

Olfactory pathway – The olfactory nerve endings in the nasal olfactory epithelium pick up the drug molecules, which then move along axons to the olfactory bulb and further into brain regions such as the cortex, hippocampus, and amygdala.

Trigeminal pathway – The trigeminal nerve branches in the respiratory epithelium carry drugs to the brainstem and thalamic regions, influencing both sensory and motor brain centers. These routes provide fast and targeted delivery of drugs to CNS tissues without significant systemic circulation exposure, which can reduce side effects. They are especially useful for neurotherapeutics like peptides, proteins, neuroprotective agents, and nanoparticles.[29]

Advantages of Intranasal Drug Delivery

1. Better Bioavailability

Intranasal delivery provides higher bioavailability compared to oral medicines, as it avoids liver metabolism (first-pass effect). This means the drug reaches its target more quickly and effectively.

2. Fast Action

The nose has a rich blood supply and large surface area, allowing medicines to be absorbed quickly. This ensures rapid relief, which is useful in emergencies such as migraine, allergies, or severe pain.

3. Non-Invasive & Comfortable

This method removes the need for injections, making treatment easier for patients, especially children or people afraid of needles. It improves comfort and compliance.

4. Direct Brain Delivery

The nasal route can bypass the blood-brain barrier, allowing drugs to reach the brain directly. This is helpful for neurological and psychiatric disorders, where drug delivery is otherwise difficult.

5. Helpful in Children & Elderly

Young and old patients often face problems swallowing tablets. Intranasal administration is simple, safe, and reduces risks like choking.

6. Targeted Local Therapy

This route can also deliver medicines directly to the nose and sinuses, useful for conditions like rhinitis, sinusitis, and nasal infections.

7. Alternative for Vaccines

Intranasal vaccines can trigger local immunity in the nose (first site of pathogen entry) and are more patient-friendly compared to injections, especially for needle-phobic individuals.[29]

Limitations of Intranasal Drug Delivery System

1. The permissible administration volume in the nasal cavity is limited, usually ranging between 25–200 µl (though sometimes cited up to 1000 µl).
2. Large molecular weight drugs (above ~1 kDa) cannot be effectively delivered through this pathway.
3. Rapid mucociliary clearance significantly reduces the retention time of drugs inside the nasal cavity.
4. Conditions like nasal blockage, cold, or allergic rhinitis can negatively affect drug absorption.
5. Once the drug is instilled intranasally, withdrawal or removal is not possible.
6. Certain therapeutic compounds may induce local irritation or discomfort in the nasal mucosa.
7. Chronic or frequent intranasal use can potentially cause structural or functional damage to the nasal lining.
8. The dosage volume capacity is highly restricted compared to other routes of administration.
9. There is still a limited understanding of transport mechanisms and the availability of reliable experimental models is inadequate.
10. The use of absorption enhancers may lead to systemic side effects or toxicity.
11. Compared to the gastrointestinal tract, the nasal route offers a smaller absorptive surface area, which can limit drug uptake.[31,32]

Pharmaceutical Formulation Based on Nasal Delivery System

The pattern of drug deposition within the nasal cavity, as well as the specific area where the formulation settles, largely depends on the type of formulation and the design of the delivery device. Various intranasal dosage forms and their role in transporting therapeutic agents to the central nervous system are highlighted in this section.

Liquid dosage forms

1. Nasal Spray

Nasal sprays are available as both solutions and suspensions, delivered in precise volumes (about 25–200 µl) using metered-dose pumps and actuators. They consist of the active drug, either dissolved or dispersed, along with excipients such as preservatives, viscosity enhancers, emulsifiers, or buffering agents. These formulations are packaged in non-pressurized dispensers that can be designed for single or multiple doses.[33,34] The spray mechanism—comprising the nozzle, orifice, and pump components—ensures uniform and reproducible delivery by dispersing the formulation into fine droplets using mechanical force. Since the container, closure, pump, and protective packaging together form the complete dosage unit, their design directly influences stability, dosing accuracy, and overall performance. Nasal sprays can be used for both local action within the nasal cavity and systemic or CNS delivery.[35]

2. Nasal Drop

Nasal drop are one of the most simple and convenient delivery system among all formulation. The main disadvantage of this system is the lack of dose precision. It has been reported that nasal drops deposit it human serum albumin in the nostrils more efficiently than nasal spray.[36]

Nasal emulsion, Microemulsion and nanoparticle

Intranasal emulsions and nanoparticles have not been investigated as widely as other liquid-based nasal delivery approaches. Emulsion formulations provide certain benefits for localized administration, primarily because of their thickness/viscous nature. One of the key drawbacks is limited user acceptability. The formulation challenges mainly include maintaining the stability of emulsions and achieving accurate dose delivery.[37]

Semisolid dosage forms

Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.

3. Nasal Gel

Nasal gels are viscous solutions or suspensions with increased thickness. The benefits of using a nasal gel include minimizing post- nasal drip due to their high viscosity, lowering the effect of unpleasant taste because of reduced swallowing, decreasing anterior leakage of the formulation, lessening irritation by incorporating soothing or emollient agents and enabling targeted delivery to the nasal mucosa for enhanced absorption. Vitamin B12 and apomorphine gels have been effectively utilized to attain the required therapeutic levels through intranasal administration.[38]

Solid dosage forms

Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa.

4. Nasal powder

Powder-based dosage forms can be considered when solution or suspension formulations are not feasible, primarily because of poor drug stability. The key benefits of nasal powder formulations include the absence of preservatives and improved stability of the active ingredient within the product. Nevertheless, the appropriateness of a powder system

depends on factors such as solubility, particle size, aerodynamic behavior and the potential nasal irritation caused by the drug and/or excipients. Another advantage of this approach is the possibility of localized drug delivery; however, challenges such as mucosal irritation and achieving accurate metered dosing remain concerns for formulation scientists and device developers working with powder-based systems.[39]

Enhancer Used in Nasal Formulation

Nasal Formulation use a variety of excipient types. The following excipient are frequently used and added.[40,41]

1. Bioadhesive polymer

A bioadhesive polymer is a compound that can stick or attach itself to biological surfaces using interfacial forces, and it remains attached for a long time. When this attachment occurs specifically with the mucus membrane, the polymer is called a mucoadhesive. At the molecular level, mucoadhesion happens due to different types of attractive interactions like:

Van der Waals forces Electrostatic interactions Hydrogen bonding

Hydrophobic interactions

The strength of bioadhesion depends on:

Nature of the polymer, pH of the medium, Swelling ability of polymer, Physiological factors such as mucin turnover and disease conditions.

2. Gelling agent

Gelling agents are used in nasal formulations to increase viscosity, prevent leakage, and prolong residence time by resisting mucociliary clearance. Commonly used polymers include poloxamer, chitosan, ethyl cellulose, pectin, xylulose, Carbopol (pH- responsive), and guar gum (ion-responsive).

These polymers undergo sol-gel transition when exposed to physiological conditions like temperature, pH, ions, or enzymes. This means the formulation can be administered easily in sol form, and once inside the nasal cavity, it converts into a gel of suitable viscosity, ensuring better retention.

3. Penetration enhancer

Improve drug absorption.

Types: Solvents, alkyl methylsulfoxides, pyrrolidones, azones (e.g., 1- dodecylazacycloheptan-2-one), surfactants, buffers.

Small dose (25–200 μL, avg. 100 μL) → nasal secretions can change pH → buffers are added to maintain pH and drug absorption.

4. Solubilizer

In nasal formulations, poor water solubility of drugs is a major limitation. To enhance solubility, co-solvents like glycols, small alcohol amounts, Transcutol, medium-chain glycerides, and Labrasol are used. Cyclodextrins (e.g., HP-β-CD) or surfactants with absorption enhancers can also help, but their nasal irritation risk must be considered.

5. Preservatives

Preservatives – Most nasal formulations are water-based, so preservatives are added to prevent microbial growth. Common examples include benzalkonium chloride, phenyl ethyl alcohol, parabens, EDTA, and benzyl alcohol.

6. Anti-oxidant

Added in small amounts to protect drugs from oxidation. Common examples: sodium bisulfite, sodium metabisulfite, BHT, and tocopherol. They usually don't irritate nasal mucosa or affect absorption, but their interaction with drugs, excipients, and packaging should be checked.

7. Humectant

In chronic or allergic conditions, nasal mucosa may become dry or form crusts. Some preservatives and antioxidants can also cause nasal irritation at higher levels. To avoid this, humectants are added, especially in gel-based formulations.

They keep the mucosa moist and reduce irritation, without affecting drug absorption. Common examples: glycerin, sorbitol, mannitol.

Factors Affecting Nasal Drug Absorption

Various factors affect bioavailability of nasally administered drugs as follow:[42]

1. Biological Factor

- Structural Features
- Biological changes

2. Physiological factor

- Blood supply and neuronal regulation
- Nasal secretion
- Mucociliary clearance and ciliary beat frequency
- Pathological condition
- Environment condition
- Membrane permeability

3. Physicochemical properties of drug

- Molecular weight
- Size
- Solubility
- Lipophilicity
- Pka and partition coefficient
- Chemical from of drug
- Polymorphism
- Chemical state
- Physical state

4. Physicochemical properties of formulation

- Physical from of formulation
- pH
- osmolarity
- viscosity

Biological factor

Structural feature: The nasal cavity is divided into five parts: nasal vestibule, atrium, respiratory region, olfactory area, and nasopharynx. The cell type, density, and structure in each part affect drug permeability. In some cases, absorption enhancers are added with drugs to improve penetration.[43]

Biochemical changes: Enzymatic Barrier – The nasal mucosa contains several enzymes like oxidative, conjugative, proteases, and peptidases that break down drugs, leading to a pseudo first-pass effect. Drugs such as decongestants, alcohol, nicotine, and cocaine are metabolized by the P450 monooxygenase system, while proteases/peptidases reduce the absorption of peptide drugs (e.g., insulin, calcitonin, LHRH, desmopressin). To prevent this, enzyme inhibitors like bacitracin, amastatin, boroleucin, and puromycin are used.

Physiological factor

Blood supply and neuronal regulation Nasal mucosa is a highly permeable surface. When parasympathetic activity increases blood flow, it causes congestion and enhances drug absorption. In contrast, sympathetic activity lowers blood flow, leading to relaxation and reduced absorption. Thus, higher drug permeability is mainly linked with parasympathetic stimulation.

Nasal secretions are produced by serous and seromucus glands in the anterior region, with daily secretion around 1.5–2 mL. Drug absorption through nasal mucosa is influenced by:

Viscosity of secretions – If mucus is too thick, cilia movement slows; if too thin, contact with cilia is reduced. Both affect mucociliary clearance and drug contact time with mucosa.

Drug solubility – For absorption, the drug must dissolve properly in nasal secretions. Hence, suitable physicochemical properties are essential.

Diurnal variation – Secretions follow circadian rhythm; at night, clearance decreases, altering drug absorption pH of nasal cavity – Normally 5.5–6.5 in adults and 5.0–7.0 in infants. Drug absorption is better when nasal pH is below the pKa, as more drug remains in the unionized form. Formulations should have pH 4.5–6.5 with good buffering for optimal uptake.[44]

Physicochemical properties of drug

Molecular weight and Size Drug absorption through the nasal route mainly depends on factors like molecular weight, size, hydrophilicity, and lipophilicity.

For large molecules (>1 kDa), the bioavailability is usually very low (about 0.5–5%) and can be predicted mostly from their molecular weight. For small drugs (<300 Da), their passage is not much influenced by physicochemical properties,

as they generally move through aqueous channels of the nasal membrane. For drugs around 300 Da, the permeation rate becomes highly sensitive to molecular properties, so even small changes can affect absorption.

Solubility The main factor that controls drug absorption through biological membranes is solubility. Since nasal fluids are mostly watery, the drug should dissolve well in water for better absorption.

Lipophilic drugs dissolve poorly in nasal secretions, so their absorption is limited.Water-soluble drugs generally get absorbed by passive diffusion, while lipophilic drugs may require active transport depending on how well they dissolve.[45]

Physicochemical form of formulation

Physical form of formulation The form of the nasal formulation affects drug absorption. In studies, liquid forms were found less effective than powders for insulin delivery in rabbits. Highly viscous (thick) formulations reduce systemic drug absorption. However, adding some viscosity agents in desmopressin formulations showed slightly longer effects, though overall bioavailability did not increase. A thicker formulation can help reduce nasal drip.

pH of formulation The absorption of drugs depends on their ionization, which is influenced by pH (pH-partition hypothesis). Therefore, nasal formulations should be adjusted to a proper pH. Correct pH helps avoid irritation, improves absorption, and prevents bacterial growth. The ideal pH range for nasal formulations is 4.5–6.5. Normally, nasal surface pH is about 7.39, while nasal secretions have a pH of 5.5–6.5 in adults and 5.0–6.7 in infants/children.

Osmolarity The tonicity of a nasal formulation has a strong effect on the nasal mucosa. Usually, isotonic formulations are preferred to avoid irritation. In animal studies, researchers tested the effect of sodium chloride concentration on the nasal absorption of secretin in rats. They found that absorption was highest at 0.462 M NaCl, but at this level the epithelial cells showed shrinkage. This shows that formulation tonicity directly influences drug absorption [46]

CNS Disorders Treated via Intranasal Route

Parkinson Disease

In recent years, nose-to-brain delivery has emerged as a promising approach to overcome limitations of oral and systemic therapies in PD. The intranasal route bypasses the blood–brain barrier, providing direct access to the CNS via the olfactory and trigeminal pathways. Preclinical and clinical studies have investigated several agents using this strategy:

Rotigotine nanoparticles delivered intranasally achieved higher brain bioavailability compared to intravenous dosing, improving dopaminergic signaling in PD models.

Selegiline, a MAO-B inhibitor with poor oral bioavailability, showed improved brain uptake and reduced motor deficits when given intranasally.

Insulin, known to modulate lipid metabolism and mitochondrial function, demonstrated neuroprotective effects and improvement in motor and cognitive outcomes after intranasal administration.

Glutathione, an endogenous antioxidant depleted in PD, reached the CNS safely via intranasal sprays and showed symptomatic benefits in clinical trials.

siRNA-loaded nanoparticles administered through the nasal route effectively reduced α-synuclein expression in experimental PD models, indicating potential for gene therapy approaches.

Alzheimer disease

The intranasal route has emerged as a promising alternative for drug delivery in AD, since it bypasses the blood–brain barrier and enables direct CNS targeting. Both preclinical and clinical studies have evaluated this approach using diverse therapeutic agents:

Insulin: Restores glucose metabolism, reduces tau phosphorylation and amyloid aggregation, and improves memory performance in animal models. Clinical trials report cognitive benefits, plaque reduction, and safety in patients with mild cognitive impairment and AD, though results are sometimes inconsistent due to device limitations.

Colivelin: A synthetic derivative of humanin that protects neurons; intranasal administration improved memory and spatial cognition in AD animal models.

Basic Fibroblast Growth Factor (bFGF): Enhanced memory performance when delivered intranasally in AD rat models.

Stem Cells and Secretome: Intranasal stem cell therapy decreased neuroinflammation, promoted neurogenesis, and reduced amyloid burden in preclinical models. Early-stage trials are ongoing in humans.

siRNA-based therapies: Intranasal siRNA targeting BACE1 or caspase-3 reduced amyloid deposition, neuroinflammation, and memory deficits in transgenic AD mice, showing potential for gene therapy.

Epilepsy

Emergency seizure treatment is often oral or intravenous, but these routes can be impractical during seizures. Intranasal delivery offers a rapid, patient-friendly alternative, suitable even in home settings. User-friendly unidose sprays are preferred for non-professionals, while MAD devices are used by healthcare workers.

Nose-to-Brain Delivery Drugs in Epilepsy

Lamotrigine: Nanocapsules/nanoparticles for intranasal use showed high brain- targeting in rodents.

Carbamazepine: Mucoadhesive nanoemulgel delayed seizures in mice compared to

IV. Neuropeptides: Intranasal nanoparticles of thyrotropin-releasing hormone reduced seizure severity in temporal lobe epilepsy models.

Benzodiazepines: Preclinical: Lorazepam nanostructured lipid carriers and clobazam microemulsion enhanced brain uptake and reduced seizures in animal models.

Clinical: FDA-approved midazolam (Nayzilam) and diazepam (Valtoco) nasal sprays, and EMA-approved midazolam (Nasolam), confirmed safe and effective for acute seizures.

Migraine

Migraine is a chronic episodic headache often accompanied by nausea and vomiting. Nose-to-brain delivery of triptane.

Sumatriptan: Solid lipid nanoparticles and nanoethosomal gels improved brain uptake and showed beneficial effects in animal migraine models.

Zolmitriptan: Pharmacokinetic studies in rodents confirmed faster and higher brain delivery intranasally compared to IV.

Approved Intranasal Therapies

Sumatriptan nasal spray: EMA-approved in 1996 (Imigran), FDA-approved in 2019 (Tosymra). Sumatriptan nasal powder (ONZETRA® Xsail®): Enhanced upper nasal cavity deposition and reduced nausea, though device use requires patient cooperation. Zolmitriptan nasal spray (Zomig®): EMA-approved in 2002, FDA-approved in 2003; showed faster relief (within 15 min) compared to tablets.[47]

Intranasal Formulation Reduce Side Effect

Epilepsy

Long-term AED (antiepileptic drugs) therapy causes serious side effects and poor adherence. FDA-approved intranasal diazepam and midazolam sprays show safe and effective seizure control, even in children and adolescents. Clinical trials confirm better quality of life and rapid seizure cessation compared to oral/IV routes. Novel approach: siRNA intranasal delivery targeting GluN1 subunit reduced excitatory neurotransmission and delayed seizures in animal models.[48]

Brain Cancer

Systemic chemotherapy often causes severe side effects. Intranasal perillyl alcohol (chemotherapeutic agent) is under Phase I/II clinical trials for glioblastoma multiforme (GBM).[49]

Multiple Sclerosis (MS)

Teriflunomide, an MS drug, causes liver toxicity with systemic use. Intranasal delivery in rats showed 2-fold higher brain accumulation vs. IV route, with no liver toxicity or hematological issues. Also being studied for anti-cancer potential via nasal route.[50]

Prospective Development in Intranasal CNS Therapy

In the coming years, nose-to-brain drug delivery is expected to grow rapidly with the help of new technologies. Nanotechnology-based carriers will become more advanced, allowing drugs to be delivered with higher accuracy and even tailored for individual patients. Biomimetic nanoparticles inspired by natural systems may improve safety and reduce immune reactions.[51] Precision medicine will help design treatments that match each patient's needs, while theranostic systems can combine therapy with real- time monitoring of treatment response. Smart, bioresponsive delivery systems are being developed to release drugs only when triggered by specific biological signals, ensuring timely action. New formulation strategies aim to improve stability, mucoadhesion, and drug-loading, leading to better retention and prolonged release in the nasal cavity.[52] Gene and RNA-based therapies delivered intranasally hold promise for precise interventions at the molecular level. In addition, novel biological agents that enhance transport across the nasal mucosa could further improve absorption and brain targeting.[53]

Altogether, these strategies may revolutionize nose-to-brain delivery, making treatments more precise, effective, and patient-friendly, while expanding options for neurological disorders.[54]

CONCLUSION

Intranasal drug delivery has emerged as a groundbreaking approach for bypassing the blood–brain barrier and directly targeting the brain. This route not only offers rapid onset of action and improved patient compliance but also minimizes systemic side effects compared to conventional methods. Recent advances in nanotechnology, bioadhesive polymers, and device innovations have further enhanced the efficiency of nose-to-brain transport. Despite promising outcomes, challenges such as limited drug permeability, enzymatic degradation, and variability in nasal physiology still need to be addressed. Future research should focus on optimizing formulation strategies, developing personalized delivery systems, and conducting large-scale clinical trials to validate safety and efficacy. With continued progress, intranasal delivery has the potential to become a game-changing strategy in CNS pharmacotherapy, opening new avenues for the treatment of complex neurological and neurodegenerative disorders.

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