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Advances in nose-to-brain drug delivery: A focus on nanocarriers for CNS disorders

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Abstract
Forest being the most important resosource for the welfare of humankind, provide many tangible and intangible benefits to human beings. In many countries, people are dependent on forests for various produces of which fuelwood is the main component. Fuelwood is the principal energy service provider to about 70% of the Indian population as it is extensively used for cooking and heating purposes. Lack of alternative sources of fuelwood makes the rural population mostly dependent on adjoining forest resources which ultimately results in the depletion of forest resources. The aim of present study was to examine the patterns of fuelwood consumption and their ecological implications in two villages namely village Chhani and village Lanchan of Bhaderwah forest division (J&K). The study was based on general survey and interview and it was observed that 12 plant species such as *Pinus wallichiana, Pinus roxburgii, Cedrus deodara, Quercus floribunda, Quercus leucotrichophora, Quercus semicarpifolia, Lyonia ovalifolia, Aesculus indica, Pyrus pashia, Indigofera species, Alnus nitida and Abies pindraw* were utilized as source of fuel wood in the study area. However, *C. deodara, Q. floribunda* and *P. wallichiana* were the most exploited fuel wood plant species. The preference for these species were due to ease of their availability and better fuel quality. Increase in fuel wood harvest caused intense forest degradation and biodiversity loss. The forests of the study area demand immediate attention in order to conserve the depleting forest structure. The policy makers must provide a sustainable solution to reduce the overexploitation of forest resources.

Keywords: Nose-to-brain delivery, blood-brain barrier, nanocarriers, CNS disorders, nanoparticles, mucoadhesion, targeted delivery

Introduction

Disorders of the central nervous system (CNS) affect progressive neurological functioning disorders worldwide resulting in socio-economic burdens [1]. One of the major reasons for the difficulties in the treatment of disorders of the central nervous system (CNS) is the presence of the blood-brain barrier (BBB), which is a biological barrier segregating the CNS from the systemic blood circulation [2]. The barrier can defend the CNS from the entry of viruses, bacteria, and toxic compounds. Although, in cases of disorders of the CNS, one of the major issues is the barrier's property of segregating the CNS froma most therapeutics. The advent of nanocarrier systems for drug delivery provides for the first time a new method of drug delivery focused on direct delivery to the CNS. This mechanism of delivery, referred to as "nose-to-brain delivery systems", provides for direct delivery of therapeutics to the CNS for treatment of neurological disorders resulting in a greater therapeutic effectiveness [3-5]. The direct delivery of therapeutics to the brain improves the bioavailability of the drug and therefore the therapeutic effectiveness. Direct delivery is also important in cases of neurological emergencies where rapid action of the therapeutic is a major requirement. A major factor in the use of the method is improved compliance, as the method is self-administered through the nares. However, there are still problems related to the delivery which need to be overcome in order to improve the method. The main challenges are rapid clearance of the [6], degradation, and absorption, drug permeability, drug irritancy, and improving drug stability and absorption are essential in achieving the desired outcomes.

In the last few decades, the incorporation of nanotechnology in the pharmaceutical sciences has broadened the horizons of drug delivery systems [6, 7]. These systems, which are less than 1000 nm in size, 1000-fold the benefits of traditional drug delivery systems, 1000-fold the surface area of the drug, 1000-fold the solubility, absorption, and stability of the drug. Micelles, liposomes, nanoemulsions, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and numerous other formations are used in drug delivery [8, 9]. These systems are also gaining importance in the delivery of drugs via the nasal cavity. They have the ability to overcome numerous difficulties related to IN administration. These systems considerably enhance the accumulation of the drug in the brain and increase the effectiveness of therapy by extending the nasal cavity residence time, solubility, absorption, and stability [10-13]. Other advanced nanocarrier systems are capable of optimizing delivery and minimizing the number of times a drug needs to be administered by providing sustained release. Moreover, nanocarriers can be designed to release drugs to specific regions of the brain, enabling focused therapy for various neurologic conditions.

2. Anatomy and Physiology of the Nasal Cavity Relevant to Drug Delivery

The nasal cavity is anatomically divided into three regions: vestibular, respiratory, and olfactory. The olfactory region, situated at the roof of the nasal cavity, provides a direct neural connection to the brain, facilitating drug transport to the CNS. The respiratory region, richly vascularized, allows systemic drug absorption. The mucociliary clearance mechanism, enzyme activity, and limited epithelial permeability present significant challenges for effective intranasal drug delivery (Figure 1). Nanocarrier systems are designed to overcome these barriers by improving mucoadhesion, enzymatic stability, and epithelial penetration [5, 9-14].

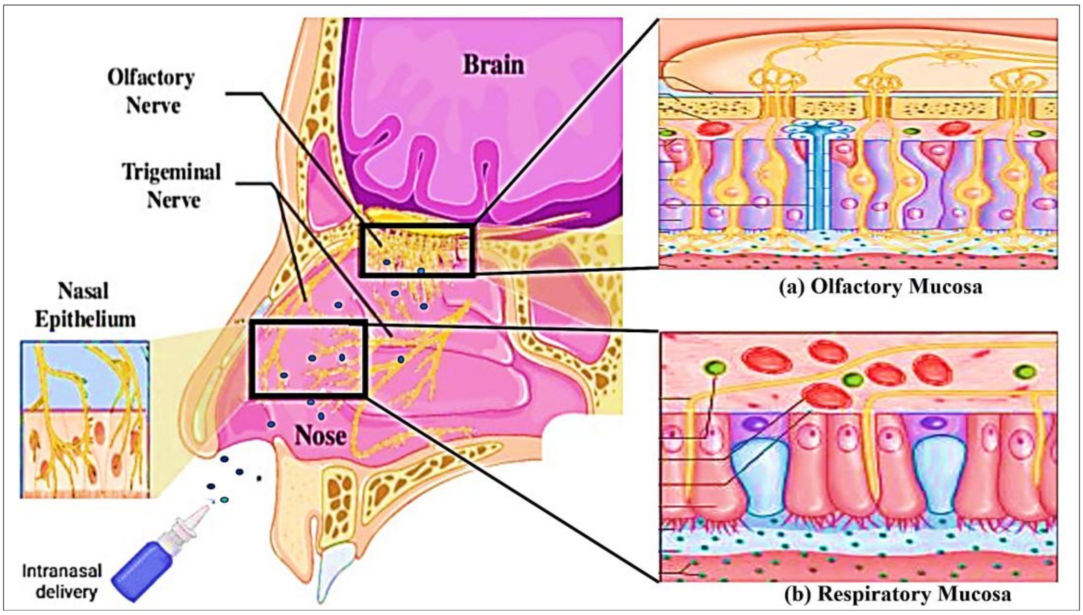


Fig 1: Diagram of nasal cavity highlighting olfactory and respiratory mucosa.

3. Pathways of Nose-to-Brain Transport

Figure 1 depicted the drugs administered intranasally can reach the brain via two main pathways:

3.1 Olfactory Pathway

The path of IN drug delivery. Along with the brain structures and bulbs, through the epithelium and neurons, the olfactory pathway leads to the brain. The olfactory region, located in the upper nasal cavity, is substantial for IN drug delivery even though it has less surface area. The olfactory epithelium contains neurons, supporting cells, basal cells, and gland cells from Bowman [12, 13]. The olfactory bulb extends to the piriform cortex, the amygdala, and the hypothalamus in a way that permits direct access to the brain. Once therapeutic modalities used to be administered through the nose, they continued to the olfactory mucosa. The olfactory mucosa has olfactory receptor neurons. The receptor neurons are responsible for transduction through their cilia and olfactory receptors, which is located at the end of the olfactory receptor neurons. Molecules access olfactory receptor neurons through the transcellular and paracellular pathways. Portions of the nasal epithelium, together with tight junctions, desmosomes, adherens junctions, and spaces between the epithelial cells, facilitate paracellular transport. The neuronal pathway is the determining step of the nose to brain route. Along the axon, drug moieties travel and cross the cribriform plate, following the nerve bundle to reach the olfactory bulb, which lies at the surface of the brain [15].

The therapeutic moiety can gain access to the cerebrospinal fluid (CSF) and the olfactory bulb via the olfactory nerves. Following this, the drug can pass through the CSF and enter the brain by interstitial fluid mixing. After a drug is administered nasally, olfactory transport ensures the drug reaches the brain within minutes. There are two opposite pathways to the brain via the olfactory neurone - the intraneuronal and the extra-neuronal pathway. The intraneuronal pathway is via the axons and it can take the active moiety hours to the days to reach the brain from different brain areas. In the extra-neuronal pathway, passive transport through the perineuronal spaces can take the active moiety directly to the brain in minutes. The olfactory nerves reach and innervate the more central and deeper structures of the brain, including the cortex, cerebrum, and cerebellum.

3.2 Trigeminal Pathway

The trigeminal nerve innervates the mucous membrane and connects to several centers in the central nervous system. The trigeminal nerve cell bodies are in the semilunar ganglion, and the nerve axons project to the pons and then to the medulla and the spinal cord. Some lateral branches go to the olfactory bulb, and some pass through the cribriform plate, forming an access route for drugs to reach the brain. The trigeminal nerve endings below the mucosal epithelium would not facilitate the movement of drugs. The trigeminal nerve pathway connects the base of the brain, medulla, and pons. The trigeminal nerve pathway allows for drugs to be transported directly to the brain through the olfactory system. The trigeminal nerve (fifth cranial nerve) is the largest cranial nerve and has three branches: the ophthalmic, maxillary, and mandibular. The ophthalmic and maxillary branches are primarily responsible for the trans-nasal route to brain access and directly innervate the nasal mucosa. Some of the trigeminal nerve branches terminate in the olfactory bulb.

The trigeminal nerve's ophthalmic branches innervate the dorsal part of the nasal mucosa and anterior part of the nose, but the maxillary branch innervates the turbinates of the nasal mucosa. After the compounds diffuse across the mucosa of the nasal cavity, they reach the trigeminal branches within the olfactory and respiratory regions, and from there, they reach the brain stem through the axonal route. Some of the trigeminal nerve branches that innervate the forebrain through the cribriform plate may also participate in the nasal cavity-deviced therapeutics. An example would be the rapid intra nasal delivery of insulin-like growth factor I that reached the brain via the trigeminal nerve pathway. The drugs or nanoparticles administered through the nasal cavity pass through the mucus as the first step in absorption. After the mucus, there are several mechanisms that facilitate transport through the mucosa. These include the paracellular route, transcellular route, carrier-mediated transport, receptor-mediated transport, and transcytosis. The paracellular route is defined as the transport of molecules between cells. The transcellular route involves the transport of the drug or other molecules across the cells. This may occur by carrier-mediated transport or endocytosis [13]. The adsorptive transcytosis mechanism within the transcellular route involves the transport of macromolecules.

Interaction between bloodstream ligands and cells surfaces occurs and in the case of proteins and other blood ligands and macromolecules, this mutual contact might result from electrostatic effects, whereby a positively charged macromolecular appendage engages a negatively charged membrane. Certain nanoparticles and specific agents can still permeate the membrane by means of transcytosis.

Table 1: Comparison of olfactory and trigeminal pathways in nose-to-brain delivery.

Parameter	Olfactory Pathway	Trigeminal Pathway
Location	Upper nasal cavity	Throughout nasal mucosa
Transport Speed	Fast	Moderate
Brain Regions Targeted	Olfactory bulb, frontal cortex	Brainstem, spinal cord
Drug Size Limitations	Small to moderate	Moderate to large

4. Nanocarrier Systems for Nose-to-Brain Drug Delivery

4.1 Polymeric Nanoparticles

Polymeric nanoparticles ideal for CNS delivery are made from biocompatible and biodegradable polymers like PLGA, chitosan, and PEG. These carriers enhance drug encapsulation efficiency, protect against enzymatic degradation, and offer sustained release profiles [11].

4.2 Liposomes

Liposomes are spherical vesicles with lipid bilayers capable of entrapping hydrophilic and lipophilic drugs. Surface-modified liposomes with targeting ligands or PEGylation can improve brain specificity and circulation time [14-16].

4.3 Nanoemulsions

These are dispersions of oil and water which are thermodynamically stable and are stabilized by surfactants. Their nanoscale droplet size enables improved mucosal permeation and brain uptake, especially for poorly water-soluble drugs.

4.4 Dendrimers

Dendrimers possess highly branched, tree-like structures that offer multiple binding sites for drug conjugation. Their tunable surface chemistry and high loading capacity make them effective for CNS drug delivery [11].

4.5 Spanlastics

Spanlastics are elastic vesicles composed of non-ionic surfactants and edge activators. Their deformability facilitates better penetration through nasal epithelium, enhancing drug targeting and bioavailability.

Table 2: Summary of nanocarriers used in N2B drug delivery [14-19].

Nanocarrier	Composition	Advantages	Applications
Polymeric NP	PLGA, Chitosan	Biocompatible, controlled release	Alzheimer's, Parkinson's
Liposomes	Phospholipids	Biodegradable, modifiable	Glioblastoma, epilepsy
Nanoemulsions	Oil, surfactants	High solubility, permeability	Depression, schizophrenia
Dendrimers	PAMAM, PPI	Multivalency, high loading	Neuroinflammation
Spanlastics	Span 60, Tween 80	Elasticity, deep penetration	Brain tumors

5. Applications in CNS Disorders

5.1 Alzheimer's Disease

Intranasal delivery of drugs like rivastigmine and donepezil via nanoparticles has shown improved memory and reduced amyloid-beta deposition in animal models. Curcumin-loaded dendrimers demonstrated anti-inflammatory and antioxidant effects [11].

5.2 Parkinson's Disease

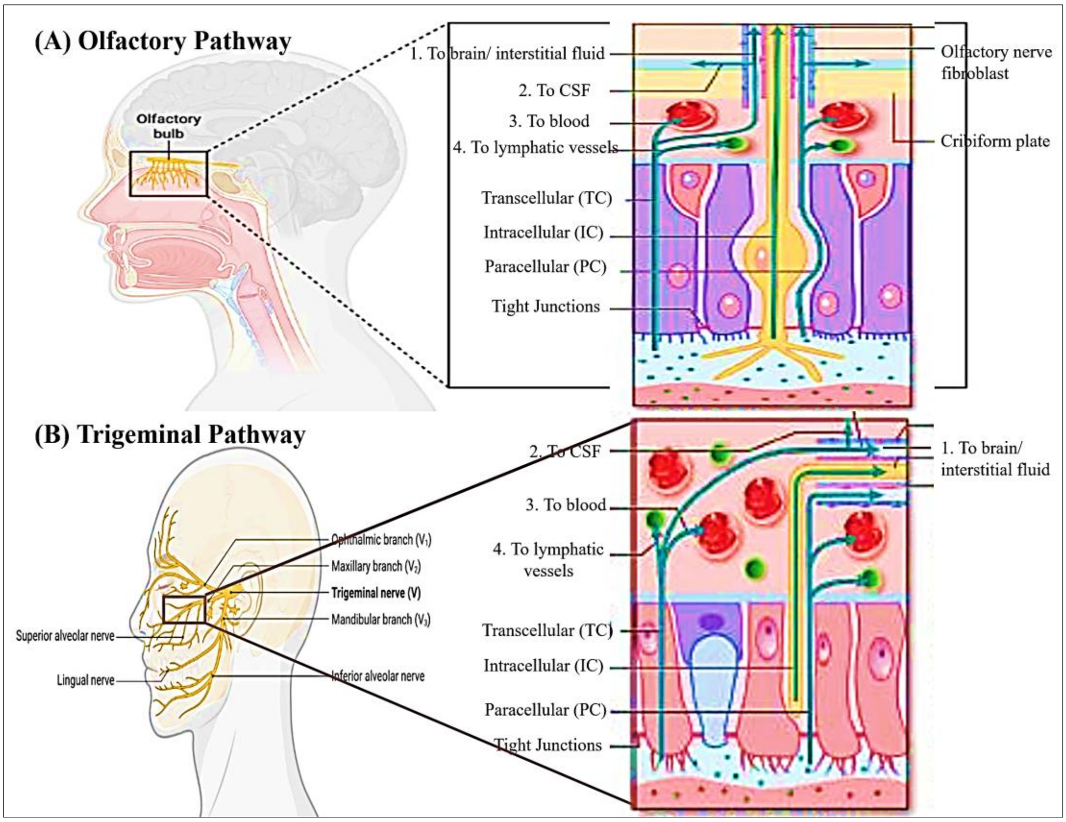
Dopamine and levodopa, when delivered via nanocarriers intranasally, bypass systemic metabolism and improve brain bioavailability. Chitosan-coated nanoparticles have shown enhanced uptake in substantia Nigra regions.

5.3 Epilepsy

Intranasal nanoemulsions of carbamazepine and valproic acid offer rapid onset and prolonged seizure suppression with reduced hepatic side effects.

5.4 Brain Tumors

Temozolomide-loaded liposomes and paclitaxel-spanlastics have demonstrated enhanced accumulation in glioma tissues via the nasal route, with minimized systemic toxicity.



Figas 2: Mechanism of drug transport via intranasal nanocarriers to the brain

6. Mechanisms of Nanocarrier Transport

This figure 2 illustrates the nasal-to-brain drug delivery pathways specifically, the olfactory (A) and trigeminal (B) routes that enable substances administered through the nasal cavity to reach the central nervous system (CNS).

6.1 Paracellular and Transcellular Transport Routes

Nanocarriers, such as nanoparticles and liposomes, employ both paracellular and transcellular mechanisms to traverse the nasal epithelium and ultimately reach the brain. In paracellular transport, nanocarriers or their cargo move between epithelial cells through tight junctions, facilitating the passage of hydrophilic and small-molecule drugs. Strategies to transiently open tight junctions (e.g., through surfactants or bioactive polymers like chitosan) further enhance paracellular permeation. Transcellular transport, conversely, involves the movement through the cell itself via endocytosis, transcytosis, or carrier-mediated mechanisms [14, 16-19]. Receptor-mediated endocytosis is especially beneficial for delivering larger macromolecules or targeted therapies, where nanocarriers functionalized with specific ligands or antibodies bind to complementary receptors on nasal epithelial cells and are internalized [19-21].

6.2 Axonal Transport via Olfactory and Trigeminal Nerves

The unique anatomical connectivity of the nasal cavity and brain allows direct neural access through olfactory and trigeminal pathways. Upon application, nanocarriers deposit in the olfactory epithelium at the roof of the nasal cavity. Here, two major mechanisms prevail:

- **Olfactory route:** Nanocarriers may be internalized by olfactory sensory neurons and carried via axonal transport—crossing the cribriform plate to the olfactory bulb, then diffusing to diverse brain regions, including the hippocampus and prefrontal cortex.
- **Trigeminal route:** Nanocarriers can interact with trigeminal nerve termini in the nasal mucosa (especially the maxillary and ophthalmic branches), which then transport the cargo to brainstem sites and, via central projections, potentially deeper into the CNS. The trigeminal route is thought to predominate for certain nanocarriers, especially those not readily accessing the olfactory region in humans.
- Performance along these routes is influenced by carrier size, surface charge, and formulation matrix, with smaller particles (<200 nm) typically demonstrating more efficient olfactory/axonal transport.

6.3 Surface Modifications: PEGylation and Ligand Attachment

The surface engineering of nanocarriers is crucial for optimizing brain targeting and systemic safety. PEGylation—attachment of polyethylene glycol (PEG) chains—confers "stealth" properties, reducing clearance by nasal mucosa and phagocytic cells while increasing nasal residence time and systemic bioavailability[11]. Additionally, attaching targeting ligands that recognize cell surface receptors (e.g., transferrin, lactoferrin, or antibodies against neural cell adhesion molecules) promotes active uptake by nasal or neural cells and enhances transcytosis across the blood-brain barrier (BBB). Such modifications have been shown to increase therapeutic brain concentrations and enable selective targeting of disease-relevant brain regions [11, 24].

Brain Region Targeting

Following successful nasal uptake and axonal/neural transport, nanocarriers show evidence of region-specific delivery. Studies demonstrate high initial concentrations in the olfactory bulb, with subsequent distribution to the hippocampus, cortex, thalamus, and deeper brain structures depending on carrier properties and transport mechanism. Surface functionalization with region-specific ligands or antigens may allow future nanocarrier systems to preferentially target sites implicated in diseases like Alzheimer's, Parkinson's, or brain tumors.

7. Formulation and Optimization Strategies

- **Particle Engineering: Functionalization, Size Tuning, Mucoadhesive Properties**
  Optimal particle design is essential for effective nose-to-brain delivery. Functionalization (surface coating/modification) controls stealth and targeting, while precise tuning of particle size (<200 nm for olfactory transport) and shape impacts penetration and neuronal uptake. Mucoadhesive polymers (e.g., chitosan, carbomers, HPMC) help nanocarriers adhere to the nasal mucosa and prolong residency, compensating for mucociliary clearance and improving absorption. These properties also facilitate sustained and controlled release of encapsulated drugs.
- **In Situ Gel (ISG) Systems**
  To further increase nasal residence time and absorption, in situ gel (ISG) systems have gained popularity. These formulations remain liquid at room temperature and undergo gelation upon contact with nasal mucosa (due to temperature or ionic triggers), creating a depot effect. When loaded with nanocarriers, ISGs synergistically combine mucoadhesion, reduced clearance, and enhanced delivery for brain targeting [19-21].
- **Quality-by-Design Approaches**
  The systematic Quality-by-Design (QbD) approach is now recommended for developing robust, reproducible nanocarrier systems. QbD involves identifying critical quality attributes (particle size, distribution, drug release kinetics, gel strength), optimizing formulation/process parameters, and validating performance through in vitro and in vivo assays. This framework ensures safety, efficacy, stability, and regulatory compliance of nasal nanocarrier formulations [14, 20].

Recent Innovations and Breakthroughs

Targeted Nanocarrier Systems for CNS Disorders

Recent advancements have led to disease-specific nanocarrier systems:

- **Alzheimer's disease:** Chitosan, PLGA, or lipid-based nanoparticles carrying anti-amyloid agents, donepezil, or galantamine, with improved brain targeting and cognitive function in preclinical models.
- **Parkinson's disease:** Nanogels and liposomes encapsulating dopamine, gene-editing CRISPR/Cas9 systems, or neuroprotective agents for neurorestorative interventions, showing preclinical promise in reducing neural degeneration.
- **Glioblastoma:** Polymeric micelles and nanocarriers loaded with temozolomide or gene therapies for direct tumor targeting, overcoming limitations of systemic chemotherapy [21].

Controlled and Sustained-Release Profiles

Incorporation of biocompatible polymers allows for tailored drug release kinetics, maintaining therapeutic concentrations in the brain over days to weeks, reducing dosing frequency, and mitigating side effects. Such sustained delivery is critical for chronic CNS conditions.

7. Clinical Trial Updates and Regulatory Perspectives

While numerous nanocarrier-based approaches have shown efficacy in animal models, human clinical trials remain limited. Formulations for Alzheimer's, Parkinson's, and CNS tumors are in early-phase trials, with regulatory agencies scrutinizing safety, manufacturing, and long-term toxicity. Some ISG-nanocarrier combinations have reached late preclinical milestones or compassionate use approvals in select regions [21, 22].

Safety, Toxicity, and Challenges

Potential Risks

1. **Nasal Mucosal Toxicity:** Prolonged contact with particulate systems, excipients, or bioadhesives may damage cilia, disrupt epithelial integrity, or provoke local inflammation. Certain surfactants or preservatives can exacerbate toxicity.
2. **Immunogenicity:** Both inherent carrier properties and surface modifications (e.g., PEG, chitosan) can stimulate immune responses, with potential for allergic reactions, antibody formation, or adverse neuroimmune events [11].
3. **Mucociliary Disruption:** Mucoadhesive polymers, while beneficial for retention, must be used at non-irritating concentrations, as they can impede mucociliary clearance and compromise nasal defense mechanisms [23].

Strategies to Minimize Adverse Effects

- Use of biocompatible, biodegradable, and non-immunogenic materials (e.g., chitosan, alginate, PLGA)
- Optimization of particle size and dose to minimize mucosal irritation
- Avoidance or minimization of toxic excipients and preservatives
- Preclinical and in vitro assessment of mucosal irritation, ciliary function, and local immune activation
- Long-term animal and eventual human studies for chronic toxicity evaluation.

8. Preclinical and Clinical Advancements

Preclinical studies in rodent models have shown successful delivery of various drugs via nanocarriers to the brain, with improved pharmacokinetics and pharmacodynamics. Clinical trials evaluating intranasal insulin and oxytocin for Alzheimer's and autism, respectively, have shown encouraging results.

Table 3: Summary of preclinical and clinical studies using nanocarriers for N2B delivery [24].

Study	Drug	Nanocarrier	Outcome
Preclinical	Rivastigmine	Chitosan NPs	Improved cognition in AD rats
Clinical	Insulin	PEGylated liposomes	Cognitive improvement in AD patients
Preclinical	Dopamine	PLGA NPs	Motor recovery in PD models

8. Challenges and Limitations

- **Formulation Stability:** Nanocarriers must remain stable in the nasal environment [22].
- **Mucoadhesion vs. Clearance:** Enhancing adhesion while resisting mucociliary clearance.
- **Scalability:** Difficulties in large-scale manufacturing and quality control.
- **Safety and Toxicity:** Long-term toxicity studies are needed [23].
- **Regulatory Hurdles:** Lack of harmonized guidelines for intranasal nanocarrier-based products [22].
- **Limited Drug Absorption and Bioavailability:** The nasal cavity offers a small surface area for drug absorption. Enzymatic degradation and mucociliary clearance can reduce drug availability before it reaches the brain [13].
- **Mucociliary Clearance**: Rapid clearance by the nasal mucosa limits the residence time of nanocarriers, reducing the window for absorption into the brain.
- **Variability in Nasal Physiology**: Inter-individual differences in nasal anatomy, mucus composition, and ciliary activity affect drug uptake and consistency of therapeutic outcomes [23].
- **Barrier Properties of Nasal Epithelium**: Tight junctions in the nasal epithelium restrict paracellular transport, especially for larger nanocarriers.
- **Particle Size and Surface Properties**: Optimizing nanoparticle size, charge, and hydrophobicity is critical but challenging, as these parameters significantly influence transport efficiency and safety [23-26].

9. Future Directions and Innovations

Future research should focus on:

- Development of multifunctional and stimuli-responsive nanocarriers.
- Integration with diagnostic agents for theranostic applications.
- Real-time tracking of drug transport via imaging techniques.
- Use of AI in formulation optimization and predictive modeling.
- Translational studies for regulatory approval and commercialization.

10. Conclusion

Nose-to-brain drug delivery, empowered by recent advances in nanocarrier technologies, offers a groundbreaking alternative for the treatment of central nervous system (CNS) disorders that have long been limited by the restrictive nature of the blood-brain barrier (BBB). By capitalizing on the unique anatomical features of the nasal cavity—specifically the olfactory and trigeminal pathways—nanocarriers such as polymeric nanoparticles, liposomes, nanoemulsions, dendrimers, and nanostructured lipid carriers enable direct and efficient transport of therapeutics to the brain, bypassing systemic circulation and first-pass metabolism.These nanoformulations are meticulously engineered to enhance drug solubility, mucoadhesion, and stability, while surface modifications like PEGylation and ligand attachment further improve brain targeting, optimize absorption, and extend retention time within the nasal mucosa and brain tissue.Recent innovations—including in situ gel systems and quality-by-design approaches—have substantially enhanced the performance, reproducibility, and safety profile of nose-to-brain nanomedicine platforms. Disease-specific applications, ranging from Alzheimer's and Parkinson's to glioblastoma and epilepsy, have demonstrated significant preclinical efficacy, with several formulations now advancing through the clinical trial pipeline. The versatility of these platforms allows not only for controlled and sustained drug release but also the potential for region-specific targeting within the brain, opening new frontiers in precision neuromedicine. However, challenges remain around biocompatibility, mucosal toxicity, immunogenicity, and the long-term effects of chronic administration, necessitating refined material selection, dose optimization, and rigorous preclinical and clinical testing.Looking ahead, the integration of advanced nanocarriers into intranasal platforms holds promise for revolutionizing the management of CNS disorders, offering rapid onset, improved bioavailability, reduced systemic side effects, and superior patient compliance. As ongoing research continues to address formulation, safety, and regulatory hurdles, nose-to-brain nanomedicine is poised to establish itself as a transformative paradigm for brain-targeted therapy, with the potential to significantly improve therapeutic outcomes and patient quality of life in neuropsychiatric and neurodegenerative diseases.

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12. Conflict of Interest

The authors declare no conflict of interest.

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