

Chapter 11: Mucoadhesive polymers and permeation enhancers in nose-to-brain targeting

Shankar P. Chavhan¹, Pragati V. Patil¹, Shruti S. Yende¹, Hemant H. Gangurde¹, Nitin V. Devhadrao¹

¹*Abasaheb Kakade College of B Pharmacy Bodhegaon Tal. Shevgaon Dist. Ahilyanagar*

Abstract: Mucoadhesive polymers and permeation enhancers are integral components in the design of effective nose-to-brain drug delivery systems. The intranasal route offers a non-invasive alternative for targeting the central nervous system (CNS), enabling direct drug transport to the brain through the olfactory and trigeminal neural pathways while bypassing the blood–brain barrier. Mucoadhesive polymers enhance formulation performance by prolonging residence time within the nasal cavity, reducing mucociliary clearance, and promoting intimate contact with the nasal epithelium, thereby improving drug absorption and bioavailability. Concurrently, permeation enhancers facilitate trans-epithelial transport by transiently and reversibly modifying the nasal epithelial barrier, enhancing paracellular or transcellular drug permeation without causing significant mucosal damage. The synergistic incorporation of these functional excipients optimizes drug delivery efficiency, enhances therapeutic outcomes, minimizes systemic exposure, and improves patient compliance. Consequently, their application represents a promising and strategically significant approach for the targeted treatment of various neurological disorders via nose-to-brain delivery systems.

Keywords: Nose-to-brain delivery, Mucoadhesive polymers, Permeation enhancers, Olfactory pathway, Blood-brain barrier, CNS disorders.

1. Introduction

The effective pharmacotherapy of neurological disorders has historically been impeded by the blood–brain barrier (BBB), a formidable physiological checkpoint that restricts the entry of most therapeutic agents into the central nervous system (CNS). Structurally, the BBB is composed of endothelial cells joined by tight junctions and supported by a neurovascular unit comprising astrocytes, pericytes, and a basement membrane matrix. This architecture strictly limits paracellular diffusion, permitting selective transcellular transport primarily for small, lipophilic molecules [1]. Consequently, a vast array of

hydrophilic drugs, peptides, proteins, and gene-based therapeutics fail to achieve therapeutic concentrations in brain tissue when administered via systemic routes.

The concept of nose-to-brain delivery challenges the traditional paradigm that systemic circulation is the sole gateway to the CNS. Instead, it exploits the unique anatomical continuity between the nasal mucosa and the brain. The olfactory nerve, which mediates the sense of smell, provides a direct conduit from the nasal cavity to the olfactory bulb. Furthermore, branches of the trigeminal nerve innervate significant portions of the nasal epithelium and project to deeper brain regions, offering additional pathways for transport.

Following intranasal administration, therapeutic agents can access the central nervous system through multiple distinct and complementary mechanisms. One of the primary pathways involves extracellular diffusion along perineural spaces, where drug molecules migrate through channels surrounding olfactory and trigeminal nerve fibers to reach the brain. In addition, intracellular uptake followed by axonal transport represents another route, wherein drugs are internalized by neuronal cells and transported along axons toward the central nervous system, although this process is relatively slower.

Paracellular transport across the nasal epithelium also contributes to drug absorption, particularly when tight junctions between epithelial cells are transiently modulated, allowing molecules to pass between cells. Furthermore, transcellular diffusion across epithelial membranes enables lipophilic drugs to permeate directly through the cells of the nasal mucosa. Together, these mechanisms facilitate efficient nose-to-brain delivery and underscore the potential of the intranasal route as a non-invasive strategy for central nervous system targeting.

1.1 Nasal Anatomy and Physiological Barriers to Delivery

The nasal cavity functions as a complex physiological interface, orchestrating respiration, humidification, filtration, and olfaction. From the perspective of drug delivery, this dynamic organ presents a unique dichotomy of therapeutic opportunities and physiological barriers. Anatomically, the cavity is segmented into three distinct zones: the vestibular, respiratory, and olfactory regions.

The vestibular region, lined with stratified squamous epithelium, serves primarily as the initial filtration site for inhaled air. The respiratory region, which comprises the largest surface area, is lined with ciliated pseudostratified columnar epithelium. While its rich vascularity facilitates systemic absorption, this region is also the site of mucociliary clearance—a primary defense mechanism. The coordinated beating of cilia continuously transports mucus toward the nasopharynx, effectively clearing foreign particulates within approximately 15–20 minutes [3]. Although protective, this rapid clearance significantly limits the residence time of administered formulations, posing a major

challenge for drug absorption. Of particular significance for CNS targeting is the olfactory region, located in the superior posterior nasal cavity. Despite comprising only 5–10% of the total surface area, it provides a critical portal for direct nose-to-brain transport. Here, olfactory receptor neurons extend dendrites into the mucus layer and project axons through the cribriform plate directly into the olfactory bulb, creating a unique anatomical conduit to the central nervous system. At the cellular level, the nasal epithelium constitutes a selective barrier maintained by tight junction complexes (including claudins and occludins), adherens junctions, and lipid bilayer membranes. This architecture imposes distinct physicochemical constraints: hydrophilic therapeutics are primarily restricted by the integrity of tight junctions, whereas lipophilic compounds may encounter solubility limitations within the aqueous mucus layer. The complexity of nasal transport pathways is illustrated in Fig. 11.1, which depicts neuronal routes, epithelial transport mechanisms, and systemic absorption pathways.

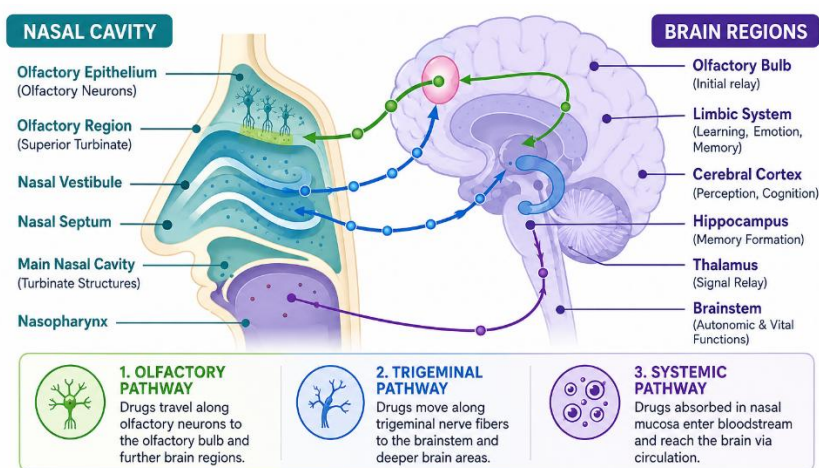


Fig. 11.1: Anatomical regions of the nasal cavity and neuronal pathways facilitating direct nose-to-brain drug transport.

1.2 Physiological and Biochemical Barriers to Intranasal Delivery

Despite the existence of direct anatomical conduits between the nasal cavity and the central nervous system, the efficiency of nose-to-brain delivery is significantly compromised by a series of physiological and biochemical barriers.

1.2.1 Mucociliary Clearance and Kinetic Challenges

The mucociliary apparatus represents a formidable kinetic barrier to absorption. The rapid turnover of the mucus layer significantly restricts the residence time of administered formulations at the absorption site. Therapeutics unable to withstand or circumvent this clearance mechanism are rapidly translocated to the nasopharynx and

subsequently swallowed, subjecting them to gastrointestinal degradation and systemic elimination rather than the intended CNS uptake.

1.2.2 Enzymatic Activity and Metabolic Barriers

Beyond physical clearance, the nasal mucosa presents a biochemical barrier characterized by a diverse array of metabolic enzymes. The epithelium expresses high levels of cytochrome P450 isoforms, aminopeptidases, and proteases, creating an enzymatic milieu that actively degrades xenobiotics. This metabolic activity poses a significant threat to the stability of peptide-based and protein therapeutics, often precipitating premature degradation and substantially reducing bioavailability before transport can occur.

1.2.3 Deposition and Targeting Limitations

Achieving precise deposition within the olfactory region is further complicated by nasal geometry and airflow dynamics. The olfactory cleft is located in the superior posterior nasal cavity, a region that is anatomically difficult to access. Conventional nasal delivery devices predominantly deposit cargo in the respiratory region or the nasal valve, failing to reach the olfactory epithelium in sufficient quantities to drive direct transport to the brain.

1.2.4 Epithelial Permeability Constraints

At the cellular level, the paracellular transport of hydrophilic macromolecules is severely restricted by the integrity of intercellular tight junctions. These protein complexes create a seal that limits the diffusion of polar compounds and high-molecular-weight biologics. Consequently, the transport of such agents often requires the use of permeation enhancers or specialized carrier systems to modulate junctional integrity or facilitate transcellular passage

The major physiological barriers are summarized in Table 11.1.

Table 11.1: Major Barriers Affecting Nose-to-Brain Drug Delivery

Barrier	Mechanistic Basis	Impact on Delivery	References
Mucociliary clearance	Ciliary movement and mucus flow	Reduced residence time	[3]
Enzymatic degradation	Nasal proteases and metabolic enzymes	Drug instability	[4]
Tight junction integrity	Claudin–occludin complexes	Limited paracellular transport	[5]

Limited olfactory surface	Small anatomical region	Reduced targeting efficiency	[2]
---------------------------	-------------------------	------------------------------	-----

2. Mucoadhesive Polymers in Nose-to-Brain Drug Delivery

2.1 Mechanistic Basis of Mucoadhesion in Nasal Delivery

Mucoadhesion represents a complex physicochemical phenomenon characterized by the interfacial interaction between synthetic or natural polymers and the mucosal glycoprotein network. This process is initiated by polymer hydration and swelling, which facilitates intimate contact with the mucus layer, followed by the interpenetration of polymer chains into the mucin mesh and the subsequent establishment of intermolecular forces. Several theoretical frameworks have been proposed to elucidate the mechanisms governing these interactions:

- **Electronic Theory:** Posits that adhesion arises from electron transfer across the polymer-mucin interface, resulting in the formation of an electrical double layer and electrostatic attraction.
- **Diffusion Theory:** Suggests that mucoadhesion is driven by the interdiffusion and entanglement of polymer chains with mucin glycoproteins, a process dependent on molecular weight and chain flexibility.
- **Adsorption Theory:** Emphasizes the role of secondary chemical interactions, including hydrogen bonding and van der Waals forces, in stabilizing the adhesive interface.
- **Covalent Bonding Theory:** Proposes that certain functionalized polymers, particularly thiolated derivatives, form stable disulfide bridges with cysteine-rich subdomains of mucin, significantly enhancing retention time.

Among mucoadhesive agents, cationic polymers such as chitosan have demonstrated exceptional efficacy. Their positive charge density facilitates strong electrostatic interactions with the negatively charged sialic acid residues of mucin. Furthermore, chitosan exhibits a dual functionality: beyond its adhesive properties, it has been shown to transiently modulate tight junction proteins, thereby enhancing paracellular permeability and facilitating the transport of hydrophilic therapeutics [6]. The stages of mucoadhesion are illustrated in Fig. 11.2.

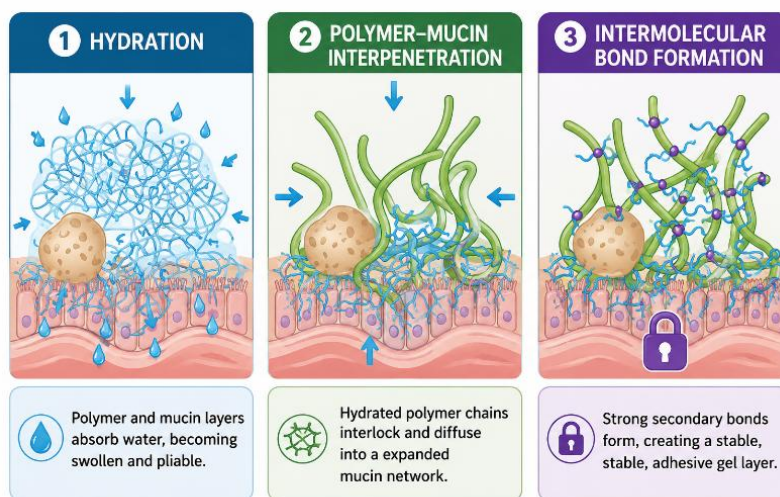


Fig. 11. 2: Sequential stages of mucoadhesion: hydration, polymer–mucin interpenetration, and intermolecular bond formation

2.2 Classification and Properties of Mucoadhesive Polymers

In nasal drug delivery, mucoadhesive polymers are generally classified based on their origin and chemical properties. Each class offers distinct advantages for overcoming mucosal barriers.

2.2.1 Natural Polymers: Biopolymers such as chitosan, alginate, and gelatin are widely favored for their excellent biocompatibility and biodegradability. Chitosan is particularly notable because its cationic nature allows it to interact strongly with the negatively charged mucosal surface. Beyond simple adhesion, it also has the unique ability to transiently open tight junctions between epithelial cells, thereby enhancing the absorption of hydrophilic drugs.

2.2.2 Synthetic Polymers: Synthetic options like Carbopol and other polyacrylic acid derivatives are valued for their robust mucoadhesive strength. These polymers function primarily through hydrogen bonding and their ability to significantly increase formulation viscosity. Their tunable rheological properties make them ideal for designing controlled-release systems that stay in place longer.

2.2.3 Thiolated Polymers: A more advanced class involves thiolated polymers, or "thiomers." These are modified polymers that can form covalent disulfide bonds with cysteine-rich subdomains in the mucus layer. This chemical cross-linking provides superior adhesion strength and significantly prolongs residence time compared to polymers that rely solely on non-covalent interactions [7].

A comparative overview is provided in Table 11.2.

Table 11.2: Classification and Functional Characteristics of Mucoadhesive Polymers

Polymer Type	Example	Mechanism of Adhesion	Additional Benefits	References
Natural	Chitosan	Electrostatic interaction	Tight junction modulation	[6]
Synthetic	Carbopol	Hydrogen bonding	Controlled viscosity	[6]
Thiolated	Thiolated chitosan	Disulfide bond formation	Prolonged retention	[7]

2.3 Functional Role of Mucoadhesive Polymers

In nasal formulations, the incorporation of mucoadhesive polymers serves a critical physiological function beyond simple adhesion. By significantly extending the residence time of the formulation on the mucosal surface, these polymers maintain a steep concentration gradient at the absorption site, which is the primary driving force for passive diffusion. Furthermore, the polymer matrix can act as a protective shield, reducing the exposure of labile drugs to luminal enzymes and facilitating sustained release kinetics.

Advanced delivery systems have leveraged these properties to great effect. For instance, surface-modified nanoparticles utilize mucoadhesive coatings to enhance cellular uptake and prevent premature clearance. Similarly, thermoresponsive *in situ* gels combine mucoadhesion with temperature-triggered gelation, creating a depot system that resists mucociliary clearance. Ultimately, these strategies address the most fundamental limitation of intranasal delivery: the insufficient contact time between the drug and the absorptive epithelium.

3. Permeation Enhancers in Nose-to-Brain Delivery

While mucoadhesive strategies effectively counteract rapid clearance, they do not fully resolve the challenge of the nasal epithelial barrier itself. For many therapeutics—especially hydrophilic compounds, peptides, proteins, and nucleic acids—the epithelium remains a formidable gatekeeper. To overcome this, permeation enhancers are frequently incorporated into formulations to transiently and reversibly modulate barrier properties, thereby facilitating transport into systemic circulation or directly to the CNS.

The nasal epithelium relies on tightly packed cells and complex junctional structures to maintain tissue integrity and exclude environmental toxins. However, this protective architecture also restricts the passage of therapeutic molecules. The challenge in developing effective enhancers lies in the delicate balance between efficacy and safety;

an ideal agent must increase permeability without causing irreversible epithelial damage, ciliary toxicity, or chronic inflammation.

3.1 Mechanisms of Permeation Enhancement

Permeation enhancers operate through several distinct, often synergistic mechanisms to facilitate drug transport:

- **Tight Junction Modulation:** One of the most established mechanisms involves the reversible opening of tight junctions, which regulate paracellular transport. Certain enhancers function by chelating extracellular calcium ions, which are essential for maintaining the integrity of junctional proteins. This calcium depletion leads to a transient loosening of the junctions, allowing hydrophilic drugs and macromolecules to pass through the paracellular space.
- **Membrane Fluidity Alteration:** Other enhancers, such as surfactants and fatty acids, target the lipid bilayer of the cell membrane. by inserting themselves into the phospholipid domains, they disrupt the ordered structure of the membrane, increasing its fluidity and reducing resistance. This mechanism primarily facilitates the transcellular diffusion of lipophilic drugs.
- **Enzymatic Inhibition:** Beyond structural modulation, some enhancers act by inhibiting the proteolytic enzymes present in the nasal mucosa. By reducing the activity of peptidases and proteases, these agents protect peptide and protein drugs from premature degradation, thereby preserving their bioactivity during the absorption window.

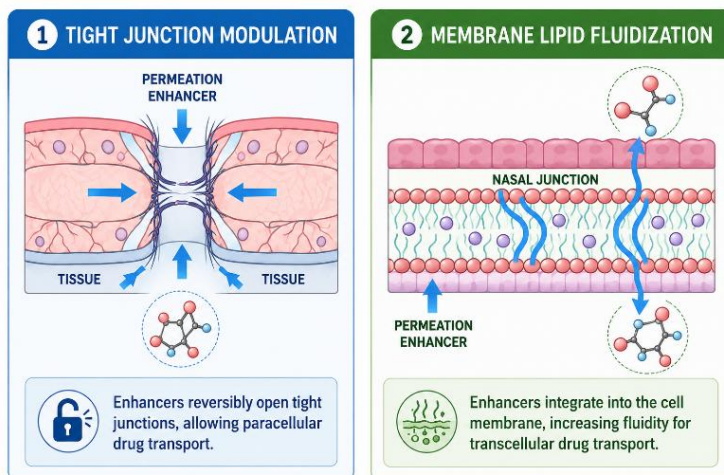


Fig. 11.3: Mechanisms of permeation enhancement in the nasal epithelium, including tight junction modulation and membrane lipid fluidisation.

Crucially, the safety profile of these agents is inherently dose-dependent. While low concentrations may induce subtle, reversible changes in permeability, higher concentrations carry the risk of significant epithelial toxicity. Consequently, optimizing the concentration of permeation enhancers is a pivotal step in formulation development to ensure therapeutic efficacy without compromising mucosal health.

The primary mechanisms of epithelial modulation are illustrated in Fig. 11.3, which depicts both paracellular and transcellular enhancement pathways.

3.2 Classification of Permeation Enhancers

Permeation enhancers utilized in nasal formulations are generally categorized by their chemical structure and mechanism of action. Each class offers distinct advantages for overcoming specific mucosal barriers.

3.2.1 Surfactants: Surfactants represent one of the earliest and most extensively studied classes of enhancers for nasal delivery. By reducing surface tension and interacting directly with the epithelial membrane, these agents facilitate drug diffusion across the mucosal barrier. Among them, nonionic surfactants are often preferred for clinical applications due to their favorable safety profile and lower irritation potential compared to ionic variants, which, despite their efficacy, require rigorous concentration control to avoid mucosal toxicity.

3.2.2 Fatty Acids and Derivatives: Fatty acids, particularly medium-chain derivatives, constitute another critical category of enhancers. These compounds function primarily by disrupting the ordered lipid packing within the cell membrane, thereby increasing epithelial permeability. Their action is typically rapid and reversible, making them well-suited for applications requiring transient modulation of the barrier function without long-term structural compromise.

3.2.3 Chelating Agents: Chelators such as ethylenediaminetetraacetic acid (EDTA) enhance permeability through a distinct mechanism: the sequestration of extracellular calcium ions. Since calcium is essential for the stability of tight junction proteins, its removal leads to a temporary opening of the paracellular pathway. This approach is particularly effective for the delivery of hydrophilic macromolecules; however, the concentration of chelating agents must be carefully optimized, as excessive calcium depletion can jeopardize epithelial integrity.

3.2.4 Cyclodextrins: While primarily employed as solubilizing agents, cyclodextrins also play a significant, albeit indirect, role in permeation enhancement. By encapsulating poorly soluble drugs within their hydrophobic cavities to form inclusion complexes, cyclodextrins effectively increase the concentration of dissolved drug available at the epithelial surface, thereby driving absorption through the concentration gradient. A

comparative overview of commonly used permeation enhancers and their mechanisms is presented in Table 11.3.

3.3 Safety and Toxicological Considerations

The safety profile of permeation enhancers remains a paramount concern, particularly for formulations intended for chronic administration. Given the nasal mucosa's essential role as a primary defence barrier, repeated exposure to aggressive enhancing agents carries the risk of functional impairment. Consequently, safety evaluations focus on several critical parameters: the reversibility of barrier modulation, the preservation of ciliary beat frequency, the absence of histopathological damage, and the lack of a sustained inflammatory response.

Preclinical assessment typically employs a tiered approach, integrating *in vitro* epithelial models, *ex vivo* nasal tissue studies, and *in vivo* animal experiments to fully characterize mucosal tolerance. For CNS therapies requiring long-term dosing, extended exposure studies are indispensable. Regulatory bodies emphasize that any strategy to enhance permeability must not compromise the mucosa's defensive integrity or increase susceptibility to local infection.

4. Synergistic Effects of Mucoadhesive Polymers and Permeation Enhancers

The concurrent use of mucoadhesive polymers and permeation enhancers represents a rational, synergistic strategy to overcome the multiple physiological barriers inherent in nose-to-brain delivery. While mucoadhesive polymers function primarily to extend residence time and maintain a high local concentration gradient, permeation enhancers actively facilitate transport across the epithelial barrier. Together, these complementary mechanisms significantly amplify the efficiency of drug delivery to the central nervous system.

4.1 Formulation Strategies and Design Considerations

Rational formulation design necessitates the careful selection of polymer–enhancer combinations tailored to the physicochemical properties of the drug and the specific therapeutic objectives. For instance, hydrophilic macromolecules generally benefit from polymers that ensure robust adhesion coupled with enhancers that modulate paracellular pathways. Conversely, lipophilic drugs may require enhancers that modify membrane fluidity, combined with polymers that provide moderate bioadhesion.

Optimizing the concentration ratio of these components is critical. Excessive viscosity can impede drug diffusion from the formulation, while high concentrations of enhancers may provoke mucosal irritation. Formulation scientists must therefore strike a delicate balance between retention time, release kinetics, and permeability enhancement.

Advanced delivery platforms—such as mucoadhesive nanoparticles, polymeric micelles, and thermoresponsive *in situ* gelling systems—increasingly incorporate both components. These sophisticated systems are designed to provide controlled drug release, prolonged mucosal retention, and enhanced epithelial interaction, thereby maximizing therapeutic efficacy while minimizing potential toxicity.

The complementary roles of mucoadhesion and permeation enhancement are illustrated in Fig. 11.4.

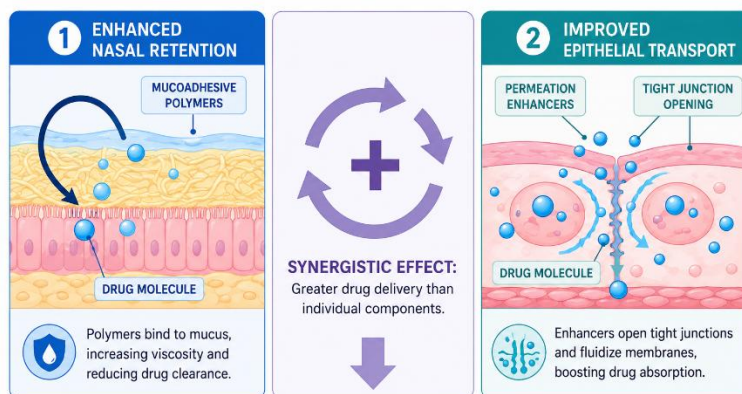


Fig. 11.4: Synergistic interaction of mucoadhesive polymers and permeation enhancers in enhancing nasal retention and epithelial drug transport.

4.2 Impact on Drug Delivery Efficiency

The synergistic application of mucoadhesive polymers and permeation enhancers significantly amplifies drug bioavailability within the brain. By prolonging residence time at the absorption site, mucoadhesive systems extend the duration of drug uptake, while permeation enhancers increase the fraction of the dose that successfully traverses the epithelial barrier. This dual mechanism often permits a reduction in the total administered dose, thereby minimizing systemic exposure and mitigating potential adverse effects. Such improvements are particularly critical for potent CNS-active drugs and biologics that possess narrow therapeutic windows.

4.3 Case Studies and Emerging Applications

Numerous studies have validated the efficacy of combined mucoadhesive–enhancer systems for the central delivery of small molecules, peptides, and proteins. For instance, intranasal benzodiazepine formulations have demonstrated rapid seizure control, attributed to their accelerated CNS penetration. Similarly, peptide-based therapies—including intranasal insulin and oxytocin—have exhibited enhanced central effects when

formulated with these synergistic components. Emerging research into nucleic acid delivery further suggests that similar strategies may soon enable non-invasive gene therapy for a spectrum of neurological disorders.

5. Therapeutic Applications of Nose-to-Brain Drug Delivery Systems

The clinical relevance of nose-to-brain delivery extends across a broad spectrum of neurological and psychiatric conditions, offering a promising alternative to conventional systemic administration.

5.1 Neurodegenerative Disorders Neurodegenerative diseases, characterized by progressive neuronal loss, have historically been difficult to treat due to poor CNS drug penetration. Intranasal delivery provides a direct conduit for neuroprotective agents, growth factors, and therapeutic peptides. In Alzheimer’s disease, the intranasal administration of insulin and other neurotrophic factors is being actively explored for its potential to enhance cognitive function and attenuate neuroinflammation. Similarly, therapies for Parkinson’s disease aim to deliver dopaminergic agents and neuroprotective molecules directly to the affected brain regions. For multiple sclerosis, an autoimmune demyelinating disorder, intranasal immunomodulatory therapies offer a novel approach, although clinical translation remains in the early stages.

5.2 Psychiatric Disorders Psychiatric conditions such as depression, anxiety disorders, and schizophrenia necessitate rapid and effective CNS drug delivery. Intranasal administration offers a distinct advantage over oral therapy, providing a faster onset of action while potentially reducing systemic side effects. Intranasal formulations of fast-acting antidepressants and anxiolytics are currently under investigation for acute symptom management. In the context of schizophrenia, nasal delivery of antipsychotics aims to improve central targeting efficacy while minimizing peripheral adverse events.

5.3 Other CNS Conditions

Table 11.4: Therapeutic Applications of Nose-to-Brain Drug Delivery

Condition	Therapeutic Agent	Delivery Strategy	Clinical Benefit
Alzheimer’s disease	Insulin	Mucoadhesive gel	Cognitive improvement
Parkinson’s disease	Dopamine agonists	Nanoparticles	Enhanced CNS targeting
Epilepsy	Benzodiazepines	Nasal spray	Rapid seizure control

Beyond neurodegeneration and psychiatry, additional therapeutic applications include the intranasal delivery of chemotherapeutic agents for brain tumors, the emergency treatment of epilepsy, and central analgesic delivery for pain management. In each of these scenarios, the ability to bypass the blood–brain barrier provides a significant therapeutic advantage, potentially transforming standard of care.

A summary of representative therapeutic applications is provided in Table 10.4.

6. Future Perspectives and Challenges

Despite significant advances in formulation science, biomaterials engineering, and intranasal device technology, the full clinical potential of nose-to-brain drug delivery remains largely unrealized. While preclinical studies consistently demonstrate enhanced brain targeting and improved pharmacodynamic responses, the translation of these findings into routine clinical practice has been slow. The complexity of nasal physiology, interindividual anatomical variability, safety concerns associated with chronic epithelial modulation, and persistent regulatory uncertainties continue to pose substantial barriers to progress.

Future advancements in this field will depend heavily on interdisciplinary collaboration among pharmaceutical scientists, neuroscientists, clinicians, biomedical engineers, and regulatory authorities. The integration of smart biomaterials, precision nanotechnology, computational modeling, and personalized medicine approaches represents the next transformative phase in nose-to-brain delivery research.

6.1 Emerging Technologies

6.1.1. Stimuli-Responsive and Smart Polymer Systems One of the most promising areas of advancement lies in the development of stimuli-responsive polymeric systems. Unlike conventional mucoadhesive polymers that provide passive retention, "smart" polymers are capable of dynamically responding to physiological cues within the nasal cavity. These materials can undergo significant changes in viscosity, swelling behavior, drug release rate, or structural conformation in response to specific stimuli such as temperature, pH, ionic strength, or enzymatic activity.

Thermoresponsive polymers, for instance, are engineered to remain in a low-viscosity liquid state during administration but undergo a rapid sol-gel transition at physiological nasal temperatures. This phase transformation enhances retention at the olfactory epithelium while maintaining patient comfort during dosing. Future systems are being designed to exhibit more precise gelation thresholds and tunable mechanical strength, allowing for better adaptation to individual mucosal conditions.

Similarly, pH-responsive systems are particularly relevant in pathological states such as rhinitis or sinus inflammation, where the local pH may deviate from physiological norms. Polymers capable of modulating drug release kinetics in response to these alterations could enable disease-adaptive therapy. Furthermore, enzyme-responsive materials that release their payload upon exposure to specific nasal or inflammatory enzymes offer the potential for highly controlled, site-specific therapeutic action.

6.1.2 Ligand-Modified and Targeted Nanocarriers: Nanotechnology continues to redefine the scope of intranasal brain delivery. While first-generation nanoparticles focused on protection and permeability, the next generation of nanocarriers aims to achieve molecular precision. Surface modification with ligands capable of binding to specific neuronal or epithelial receptors offers the possibility of receptor-mediated endocytosis and enhanced intracellular transport. Ligands currently under investigation include peptides, antibodies, aptamers, and small molecules that recognize receptors expressed in the olfactory epithelium or neuronal membranes. Such active targeting strategies may increase drug uptake through specific endocytic pathways while minimizing off-target absorption in the respiratory region. Another promising direction involves dual-functional nanoparticles that combine mucoadhesive properties with mucus-penetrating capabilities. Emerging surface engineering strategies allow these nanoparticles to transiently interact with mucus for retention while maintaining sufficient mobility to penetrate the mucus layer and reach the underlying epithelium.

6.1.3 Gene Therapy and Nucleic Acid Delivery: The intranasal route is increasingly being explored for the delivery of biologics, including mRNA therapeutics, small interfering RNA (siRNA), and CRISPR-based gene editing tools. Because large, negatively charged nucleic acids cannot cross the blood–brain barrier efficiently after systemic administration, nose-to-brain delivery provides a non-invasive alternative for treating genetic neurological disorders. However, ensuring nucleic acid stability, avoiding immune activation, and achieving efficient intracellular delivery remain significant technical hurdles. Advances in lipid nanoparticles, polymeric complexes, and biodegradable nanogels are expected to improve the feasibility of nasal gene therapy in the coming decade.

6.1.4 Artificial Intelligence and Computational Modeling: The integration of artificial intelligence (AI) and machine learning into formulation design is an emerging trend with significant potential. Predictive modeling of nasal deposition patterns, mucus interaction kinetics, and drug transport dynamics can accelerate formulation optimization while reducing the experimental burden. Computational fluid dynamics (CFD) models of nasal airflow are already being employed to refine spray device design and predict deposition in the upper nasal cavity. AI-guided design of polymer combinations and nanoparticle surface properties may further enable the precision engineering of nose-to-brain systems tailored to specific drugs and therapeutic targets.

6.2 Regulatory and Translational Challenges

6.2.1 Safety and Long-Term Toxicity: A principal obstacle to clinical translation is the requirement for rigorous safety evaluation. Many permeation enhancers function by transiently disrupting epithelial tight junctions or modifying membrane integrity. Although these effects are often reversible in short-term studies, the long-term

consequences of repeated administration remain incompletely understood. Chronic use of nasal formulations—particularly for neurodegenerative diseases requiring lifelong therapy—necessitates a comprehensive evaluation of histopathological alterations, effects on mucociliary clearance, local inflammatory responses, and potential neurotoxicity. Demonstrating reversible and non-cumulative epithelial modulation is essential for regulatory approval.

6.2.2 Standardization of Preclinical Models: Another significant challenge lies in the lack of standardized preclinical evaluation models. Animal nasal anatomy differs significantly from human anatomy, particularly regarding the proportion of olfactory surface area and airflow patterns. Consequently, brain-targeting efficiency observed in rodent models often does not directly translate to humans. The development of predictive *in vitro* nasal epithelial models, *ex vivo* human tissue platforms, and advanced imaging techniques will be critical for bridging this translational gap.

6.2.3 Device–Formulation Compatibility: Regulatory agencies increasingly view nasal products as combination products consisting of both the formulation and the delivery device. Variability in spray pattern, droplet size distribution, and actuation force can significantly influence deposition location and therapeutic performance. Ensuring consistency in dose delivery, device robustness, and reproducibility across large production batches remains a major manufacturing challenge. Additionally, the scale-up of nanoparticle-based systems must maintain particle size distribution and drug loading efficiency without compromising sterility or stability.

6.3 Personalized Medicine and Future Outlook

6.3.1 Patient-Specific Anatomical Considerations: The nasal cavity exhibits significant anatomical variability among individuals due to age, sex, ethnicity, and disease conditions. Factors such as septal deviation, turbinate hypertrophy, and mucosal inflammation can all affect deposition patterns and absorption efficiency. Future nose-to-brain systems may incorporate patient-specific deposition mapping using imaging technologies or computational modeling to tailor dosing strategies to individual anatomy.

6.3.2 Precision Dosing and Biomarker-Guided Therapy: The integration of diagnostic biomarkers with intranasal therapeutics offers the potential for true precision medicine. For example, patients with early-stage neurodegenerative disease identified through imaging or molecular markers could receive targeted intranasal biologics designed to slow disease progression. Adjustable dosing regimens based on pharmacogenomic profiles or disease severity may further optimize therapeutic outcomes while minimizing adverse effects.

6.3.3. Global Health and Accessibility: The non-invasive nature of intranasal administration makes it particularly attractive for emergency interventions and outpatient management. Portable, user-friendly devices may facilitate rapid treatment in epilepsy, acute anxiety attacks, or migraine. However, ensuring affordability, scalability, and regulatory harmonization across countries will be essential for the widespread adoption of these life-changing therapies.

7. References

- [1] Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(5):459-480.
- [2] Alzheimer's Disease International. World Alzheimer Report 2021: journey through the diagnosis of dementia. London: Alzheimer's Disease International; 2021.
- [3] Gooch CL, Pracht E, Borenstein AR. The burden of neurological disease in the United States: a summary report and call to action. *Ann Neurol.* 2017;81(4):479-484.
- [4] Daneman R, Prat A. The blood-brain barrier. *Cold Spring Harb Perspect Biol.* 2015;7(1):a020412.
- [5] Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis.* 2010;37(1):13-25.
- [6] Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx.* 2005;2(1):3-14.
- [7] Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev.* 2012;64(7):614-628.
- [8] Dhuria SV, Hanson LR, Frey WH II. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *J Pharm Sci.* 2010;99(4):1654-1673.
- [9] Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. *Int J Pharm.* 2009;379(1):146-157.
- [10] Crucho CIC, Barros MT. Polymeric nanoparticles: a study on the preparation variables and characterization methods. *Mater Sci Eng C Mater Biol Appl.* 2017;80:771-784.
- [11] Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. *Angew Chem Int Ed Engl.* 2009;48(30):5418-5429.
- [12] Illum L. Nasal drug delivery possibilities, problems and solutions. *J Control Release.* 2003;87(1-3):187-198.
- [13] Gizurason S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. *Curr Drug Deliv.* 2012;9(6):566-582.
- [14] Leopold DA, Hummel T, Schwob JE, Hong SC, Knecht M, Kobal G. Anterior distribution of human olfactory epithelium. *Laryngoscope.* 2000;110(3 Pt 1):417-421.
- [15] Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. *Life Sci.* 2018;195:44-52.
- [16] Merkus FWHM, Verhoef JC, Schipper NGM, Martin E. Nasal mucociliary clearance as a factor in nasal drug delivery. *Adv Drug Deliv Rev.* 1998;29(1-2):13-38.
- [17] Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: physicochemical and therapeutic aspects. *Int J Pharm.* 2007;337(1-2):1-24.
- [18] Thorne RG, Pronk GJ, Padmanabhan V, Frey WH II. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience.* 2004;127(2):481-496.
- [19] Johnson NJ, Hanson LR, Frey WH. Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. *Mol Pharm.* 2010;7(3):884-893.

- [20] Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Res Bull.* 2018;143:155-170.
- [21] Grassin-Delyle S, Buenestado A, Naline E, Faisy C, Blouquit-Laye S, Couderc LJ, et al. Intranasal drug delivery: an efficient and non-invasive route for systemic administration. *Pharmacol Ther.* 2012;134(3):366-379.
- [22] Ways TM, Lau WM, Khutoryanskiy VV. Chitosan and its derivatives for application in mucoadhesive drug delivery systems. *Polymers (Basel).* 2018;10(3):267.
- [23] Sonvico F, Clementino A, Buttini F, Colombo G, Pescina S, Guterres SS, et al. Surface-modified nanocarriers for nose-to-brain delivery: from bioadhesion to targeting. *Pharmaceutics.* 2018;10(1):34.
- [24] Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. *J Control Release.* 2012;161(2):505-522.
- [25] Neamtu I, Rusu AG, Diaconu A, Nita LE, Chiriac AP. Basic concepts and recent advances in nanogels as carriers for medical applications. *Drug Deliv.* 2017;24(1):539-557.
- [26] Agrawal M, Saraf S, Saraf S, Antimisariis SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. *J Control Release.* 2018;281:139-177.
- [27] Hanson LR, Frey WH. Intranasal delivery bypasses the blood-brain barrier. *BMC Neurosci.* 2008;9(Suppl 3):S5.
- [28] Lochhead JJ, Wolak DJ, Pizzo ME, Thorne RG. Rapid transport within trigeminal pathways. *J Neurosci.* 2015;35(2):518-530.
- [29] Illum L. Nasal drug delivery—recent developments. *J Control Release.* 2012;161(2):254-263.
- [30] Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. *Drug Discov Today.* 2002;7(18):967-975.
- [31] Merkus P, Guchelaar HJ, Bosch DA, Merkus FWHM. Direct access of drugs to the brain. *Neurosci Biobehav Rev.* 2003;27(1-2):91-103.
- [32] Gizurarson S. The effect of cilia and mucus on nasal drug delivery. *Int J Pharm.* 2015;478(2):497-506.
- [33] Illum L, Farraj NF, Davis SS. Nasal administration of gentamicin. *J Pharm Pharmacol.* 1988;40(6):457-458.
- [34] Al-Ghananeem AM, Saeed H, Florence R, et al. Intranasal drug delivery of didanosine. *Int J Pharm.* 2010;391(1-2):215-222.
- [35] Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery. *Curr Opin Solid State Mater Sci.* 2002;6(4):319-327.
- [36] Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood-brain barrier. *J Control Release.* 2012;161(2):264-273.
- [37] Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery. *Drug Discov Today.* 2009;14(23-24):1156-1165.
- [38] Djupesland PG, Skretting A. Wind-induced nasal deposition studies. *J Aerosol Med Pulm Drug Deliv.* 2012;25(2):93-100.
- [39] Djupesland PG. Nasal drug delivery devices and clinical performance. *Ther Deliv.* 2012;3(9):1127-1136.
- [40] Ugwoke MI, Agu RU, Kinget R. Nasal mucoadhesive delivery of macromolecules. *J Control Release.* 2005;102(1):197-205.
- [41] Patel MM, Patel BM. Crossing the blood-brain barrier via intranasal route. *CNS Drugs.* 2017;31(2):109-133.
- [42] Kanazawa T, Akiyama F, Kakizaki S, et al. Intranasal delivery of nanoparticles to the brain. *Int J Pharm.* 2013;446(1-2):10-17.
- [43] Illum L. Nasal delivery of biologics. *Drug Discov Today.* 2007;12(11-12):451-454.

- [44] Renner DB, Svitak AL, Gallus NJ, et al. Intranasal administration of insulin. *Pharm Res.* 2012;29(1):194-205.
- [45] Chapman CD, Frey WH, Craft S, et al. Intranasal insulin in Alzheimer's disease. *J Alzheimers Dis.* 2013;33(2):555-566.
- [46] Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy. *Arch Neurol.* 2012;69(1):29-38.
- [47] Pawar PS, Ahire SM, Shewale VV, Jadhav S, Mahajan SK. Nanotechnology in herbal medicines: a review. *J Hosp Pharmacy.* 2025;20(1 Suppl 3):1-9.
- [48] Alagusundaram M, Chengaiah B, et al. Nasal drug delivery system—overview. *Int J Res Pharm Sci.* 2010;1(4):454-465.
- [49] Ugwoke MI, Agu RU, Verbeke N. Nasal drug delivery—recent developments. *Pharm Dev Technol.* 2005;10(1):1-19.
- [50] Bernkop-Schnürch A, Hornof M, Zoidl T. Thiolated polymers. *Int J Pharm.* 2003;260(2):229-237.
- [51] Wang YY, Lai SK, Suk JS, et al. Nanoparticles in mucus. *Proc Natl Acad Sci U S A.* 2008;105(43):16455-16460.
- [52] Sonvico F, Clementino A, Buttini F, et al. Surface-modified nanoparticles. *J Control Release.* 2018;274:106-130.
- [53] Mittal D, Ali A, Md S, et al. Insights into direct nose-to-brain delivery. *J Control Release.* 2014;191:73-86.
- [54] Illum L, Watts P, Fisher AN, et al. Intranasal delivery of morphine. *J Pharmacol Exp Ther.* 2002;301(1):391-400.
- [55] Hallschmid M, Benedict C, Schultes B, et al. Intranasal insulin and cognition. *Diabetes.* 2004;53(1):192-198.
- [56] Lochhead JJ, Yang J, Ronaldson PT, Davis TP. Structure of the blood-brain barrier. *Pharm Res.* 2020;37(10):1-28.
- [57] Patel RB, Patel MR, Bhatt KK, Patel BG. Formulation aspects of nasal delivery. *Drug Dev Ind Pharm.* 2008;34(10):1084-1100.
- [58] Singh V, Sharma PK, et al. Nasal delivery of neurotherapeutics. *Asian J Pharm Sci.* 2016;11(2):267-275.
- [59] Erdő F, Bors LA, Farkas D, et al. Evaluation of intranasal delivery. *Drug Discov Today.* 2018;23(2):496-507.
- [60] Djupesland PG, Messina JC, Mahmoud RA. Breath-powered nasal delivery. *J Aerosol Med Pulm Drug Deliv.* 2014;27(6):394-402.
- [61] Pawar SP, Ahire MS, Shewale VV, Jadhav S, Mahajan KS, Sonawane DD. Silver nanoparticles: A comprehensive review on synthesis, properties and applications. *Research Journal of Pharmaceutical Dosage Forms and Technology.* 2025;17(4):279-85.
- [62] Jadhav SP, Ahire SM, Chitte NR, Pawar PS, Sonawane I, Shewale V. Crossing the Blood–Brain Barrier: Challenges, Strategies and Emerging Technologies. *Asian Journal of Research in Pharmaceutical Sciences.* 2026 Jul;16(3):234-42.
- [63] Battaglia L, Gallarate M. Lipid nanoparticles in brain diseases. *Adv Drug Deliv Rev.* 2012;64(5):456-467.
- [64] Salem II, Duzgunes N. Efficacy of liposomal delivery. *Adv Drug Deliv Rev.* 2003;55(5):609-625.
- [65] Kamei N, Takeda-Morishita M. Brain delivery of biologics. *Pharmaceutics.* 2015;7(4):409-429.
- [66] Illum L. Nasal drug delivery: new developments. *Int J Pharm.* 2012;429(1-2):1-2.
- [67] Ugwoke MI, Agu RU. Nasal drug delivery challenges. *Expert Opin Drug Deliv.* 2005;2(2):223-231.
- [68] Jansson B, Björk E. Nasal absorption enhancement. *J Pharm Pharmacol.* 2002;54(9):1237-1246.

- [69] Abdulkarim M, Sharma PK. Nasal in situ gels. *J Drug Deliv Sci Technol.* 2020;55:101398.
- [70] Mistry A, Illum L. Epithelial permeability enhancers for nasal drug delivery. *J Pharm Sci.* 2009;98(11):4274-4292.
- [71] Ahire SM, Pawar PS, Mahajan SK. Guillain-Barre Syndrome: A Review. *Research Journal of Pharmacology and Pharmacodynamics.* 2026 Apr 24;18(2):159-64.
- [72] Badhan RK, Kaur M. Brain targeting via nasal route: a review. *Drug Deliv Transl Res.* 2015;5(5):518-533.
- [73] Tzeyung AS, Md S, et al. Nose-to-brain delivery of antipsychotics. *Eur J Pharm Sci.* 2019;128:86-96.
- [74] Patel MM, Patel BM. Nasal nanocarriers in CNS disorders. *CNS Neurol Disord Drug Targets.* 2016;15(2):241-254.
- [75] Agrawal M, Saraf S. Nanocarrier-based nasal delivery. *Int J Pharm.* 2020;586:119538.
- [76] Erdő F, Hashimoto N, Karvaly G, et al. Nasal drug transport models. *Pharmaceutics.* 2021;13(2):1-24.
- [77] Djupesland PG. Nasal drug delivery devices: future directions. *Ther Deliv.* 2013;4(8):1021-1034.