

# An Overview on Nose to Brain Drug Delivery

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**Abstract:** *Nose-to-brain drug delivery is an emerging non-invasive approach that enables direct transport of therapeutic agents from the nasal cavity to the central nervous system (CNS), bypassing the blood–brain barrier (BBB). This route has gained significant attention for the treatment of neurological disorders such as Alzheimer’s disease, Parkinson’s disease, epilepsy, brain tumors, and psychiatric conditions. Drugs administered intranasally can reach the brain through olfactory and trigeminal neural pathways, resulting in rapid onset of action, improved bioavailability, reduced systemic side effects, and enhanced patient compliance. Various formulation strategies including nanoparticles, nanoemulsions, liposomes, hydrogels, and micellar systems have been developed to improve drug stability, mucoadhesion, permeability, and targeted brain delivery. Despite its promising advantages, challenges such as limited drug absorption area, mucociliary clearance, enzymatic degradation, and formulation stability remain significant barriers to clinical translation. Advances in nanotechnology, biomaterials, and device engineering are expected to overcome these limitations and expand the therapeutic potential of intranasal drug delivery systems. Overall, nose-to-brain drug delivery represents a promising frontier in neuropharmaceutical research, offering an efficient and patient-friendly alternative for delivering drugs directly to the brain while minimizing systemic exposure.*

**Keywords:** Nose-to-brain delivery, Intranasal drug delivery, Blood–brain barrier, Central nervous system, Olfactory pathway, Trigeminal pathway, Nanoparticles, Neurotherapeutics, Mucoadhesive systems, Brain targeting, Nanocarriers, Drug delivery systems, Neurodegenerative disorders, Bioavailability, CNS drug delivery

## I. INTRODUCTION

The delivery of drugs to the brain remains one of the greatest challenges in pharmaceutical and biomedical research due to the presence of the blood–brain barrier (BBB), a highly selective physiological barrier that restricts the entry of most therapeutic agents into the central nervous system (CNS). Conventional routes of drug administration such as oral and intravenous delivery often fail to achieve adequate drug concentrations in the brain because of poor permeability across the BBB, enzymatic degradation, and systemic side effects. Therefore, the development of alternative and effective brain-targeting strategies has become an important area of research.

Nose-to-brain drug delivery is a novel and non-invasive approach that enables direct transport of drugs from the nasal cavity to the brain through the olfactory and trigeminal nerve pathways, thereby bypassing the BBB. The nasal cavity offers several advantages for drug delivery, including a large surface area, rich vascularization, rapid absorption, avoidance of first-pass metabolism, and ease of administration. This route allows both local and systemic drug delivery and has shown considerable potential for targeting CNS disorders.

Intranasal administration has gained increasing attention for the treatment of neurological and neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, epilepsy, migraine, schizophrenia, depression, and brain tumors. Various categories of therapeutic agents including peptides, proteins, vaccines, hormones, and small molecules have been explored for intranasal brain targeting. In recent years, advanced drug delivery systems such as nanoparticles, liposomes, nanoemulsions, hydrogels, and mucoadhesive formulations have been developed to enhance drug permeation, retention time, and targeting efficiency in the nasal cavity.



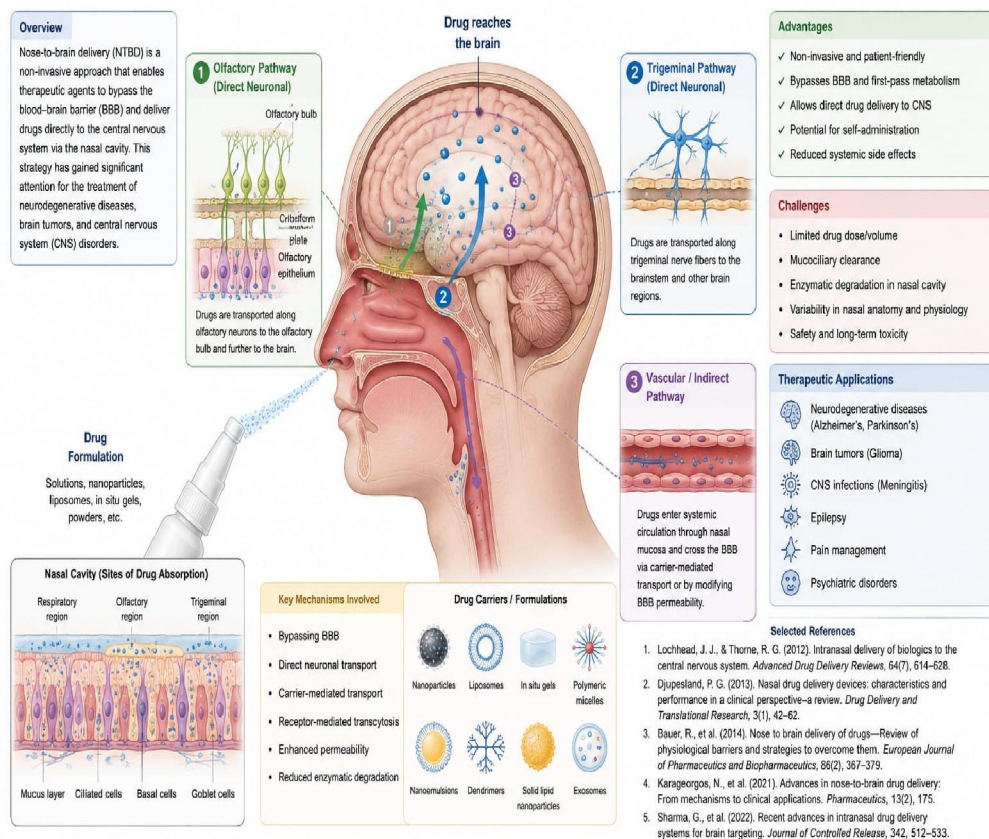
Despite its promising advantages, nose-to-brain drug delivery also faces several limitations including mucociliary clearance, limited dosing volume, enzymatic degradation within the nasal cavity, and variability in drug absorption. Continuous research in formulation development, nanotechnology, and nasal delivery devices is helping to overcome these challenges and improve therapeutic outcomes.

Overall, nose-to-brain drug delivery represents a promising strategy for effective CNS targeting and has the potential to revolutionize the treatment of brain-related disorders by providing safer, faster, and more efficient drug delivery to the brain.

### Anatomy and Physiology of Nasal Cavity in Nose-to-Brain Drug Delivery

## Nose-to-Brain Drug Delivery: Pathways, Mechanisms and Advances

REVIEW PAPER



The nasal cavity plays a crucial role in nose-to-brain drug delivery because of its unique anatomical structure, rich blood supply, and direct connection with the central nervous system (CNS). Understanding the anatomy and physiology of the nasal cavity is essential for developing effective intranasal drug delivery systems.

### Anatomy of the Nasal Cavity

The nasal cavity is divided into two symmetrical halves by the nasal septum and extends from the nostrils to the nasopharynx. It has a total surface area of approximately 150–200 cm<sup>2</sup> due to the presence of folds known as turbinates or nasal conchae. The nasal cavity is broadly divided into three functional regions:



### 1. Vestibular Region-

The vestibular region is the front part of the nasal cavity located just inside the nostrils. It is lined with stratified squamous epithelium and contains hairs called vibrissae that help filter dust particles and foreign materials. This region has limited importance in drug absorption because of its small surface area and low permeability.

### 2. Respiratory Region-

The respiratory region is the largest part of the nasal cavity and is highly vascularized. It is lined with pseudostratified ciliated columnar epithelium containing goblet cells that secrete mucus. This region is mainly responsible for systemic drug absorption because of:

- Large surface area
- Rich blood supply
- High permeability

The respiratory mucosa helps warm, humidify, and filter inhaled air. Most intranasally administered drugs are absorbed through this region.

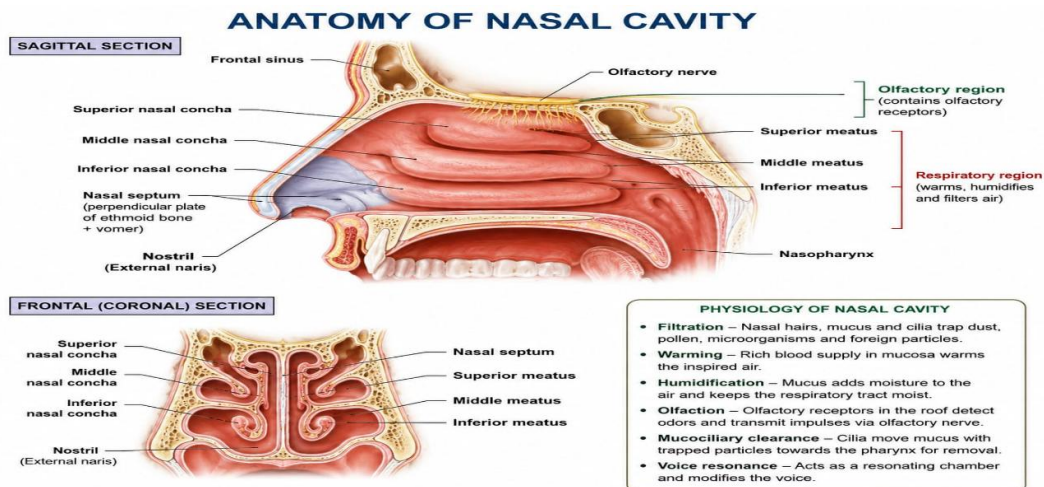
### 3. Olfactory Region

The olfactory region is located at the roof of the nasal cavity and covers approximately 5–10% of the total nasal surface area. It contains olfactory receptor neurons that directly connect the nasal cavity to the olfactory bulb of the brain. This region is highly important for nose-to-brain drug delivery because drugs can bypass the blood–brain barrier (BBB) and directly enter the CNS through olfactory neurons.

### Physiology of the Nasal Cavity

#### Nasal Mucosa-

The nasal mucosa consists of epithelial cells, mucus-producing goblet cells, and cilia. The mucus layer protects the nasal cavity by trapping pathogens and particles, while cilia continuously move mucus toward the nasopharynx through a process called mucociliary clearance.



#### Mucociliary Clearance-

Mucociliary clearance is a defense mechanism that removes foreign particles and excess mucus from the nasal cavity. Although it protects the body, it can reduce drug residence time and decrease drug absorption. Therefore, mucoadhesive formulations are often used to prolong nasal retention.



### **Blood Supply-**

The nasal cavity has an extensive vascular network supplied by branches of the carotid arteries. This rich blood supply enables rapid drug absorption into systemic circulation and supports fast onset of action.

### **Neural Pathways for Brain Delivery**

**Olfactory Pathway** Drugs absorbed through the olfactory epithelium can directly reach the olfactory bulb and different regions of the brain. This pathway is one of the major routes for direct nose-to-brain transport.

### **Trigeminal Nerve Pathway-**

The trigeminal nerve innervates both the respiratory and olfactory regions of the nasal cavity. Drugs can travel along trigeminal nerve branches to reach the brainstem and spinal cord.

### **Importance of Nasal Anatomy in Drug Delivery**

The unique structural and physiological features of the nasal cavity make it an attractive route for CNS drug delivery. Key advantages include:

- Direct access to the brain
- Rapid absorption
- Avoidance of first-pass metabolism
- Non-invasive administration
- Improved patient compliance

### **Mechanism of Nose-to-Brain Drug Delivery**

Nose-to-brain drug delivery is a specialized pathway through which drugs administered into the nasal cavity directly reach the brain and central nervous system (CNS), bypassing the blood-brain barrier (BBB). This transport occurs mainly through neural pathways associated with the olfactory and trigeminal nerves. The mechanism involves both intracellular and extracellular transport processes that enable rapid and targeted delivery of therapeutic agents to the brain.

### **Pathways of Nose-to-Brain Drug Delivery**

**1. Olfactory Pathway** The olfactory pathway is the primary and most important route for direct brain delivery. The olfactory region is located at the roof of the nasal cavity and contains olfactory receptor neurons connected directly to the olfactory bulb of the brain.

#### **Mechanism:**

Drug molecules deposited in the olfactory region cross the olfactory epithelium. The drugs are transported along olfactory neurons to the olfactory bulb. From the olfactory bulb, drugs distribute to different brain regions.

#### **Transport Mechanisms:**

##### **a) Intracellular Transport**

Drugs enter olfactory neurons through endocytosis or pinocytosis. They are transported inside neuronal cells by axonal transport. This process is relatively slow and may take several hours.

##### **b) Extracellular (Paracellular) Transport**

Drugs move through spaces between epithelial cells.



They reach the cerebrospinal fluid (CSF) and brain tissues rapidly.  
This pathway provides faster drug transport than intracellular movement.

**Importance:**

Direct access to CNS  
Bypasses BBB  
Suitable for peptides, proteins, and nanoparticles

**2. Trigeminal Nerve Pathway**

The trigeminal nerve innervates both the respiratory and olfactory regions of the nasal cavity. It provides another important route for drug transport to the brain.

**Mechanism:**

Drugs absorbed through nasal mucosa enter trigeminal nerve endings.  
The drug is transported to the brainstem and spinal cord.  
From there, distribution occurs to different CNS regions.

**Significance:**

Supports delivery to deeper brain structures  
Useful for rapid CNS targeting  
Enhances overall brain uptake

**3. Systemic Pathway**

Some portion of intranasally administered drugs may be absorbed into systemic circulation through the highly vascularized respiratory epithelium.

**Mechanism:**

Drug enters blood vessels in the nasal cavity.  
It reaches systemic circulation.  
A fraction of the drug may cross the BBB and enter the brain.

**Limitations:**

Reduced targeting efficiency  
Possibility of systemic side effects  
BBB still limits many drug

**Drug Delivery Systems and Formulations**

Drug delivery systems and formulations play a vital role in improving the efficiency of nose-to-brain drug delivery. Conventional formulations often face challenges such as poor drug absorption, rapid mucociliary clearance, enzymatic degradation, and limited residence time in the nasal cavity. To overcome these limitations, advanced drug delivery systems have been developed to enhance drug stability, permeability, retention time, and targeted delivery to the brain.

**Objectives of Advanced Nasal Formulations**

The major goals of formulation development in nose-to-brain delivery include:

Enhancing drug absorption across nasal mucosa  
Increasing residence time in the nasal cavity  
Protecting drugs from enzymatic degradation  
Improving drug stability and bioavailability  
Achieving targeted and controlled brain delivery  
Reducing systemic side effects



## **Types of Drug Delivery Systems**

### **1. Nanoparticles-**

Nanoparticles are colloidal carrier systems with particle sizes generally ranging from 1–1000 nm. They are widely used in nose-to-brain delivery because they can cross biological barriers and provide sustained drug release.

#### **Advantages:**

- Improved drug permeability
- Enhanced brain targeting
- Protection of drug from degradation
- Controlled and sustained release
- Increased bioavailability

#### **Types:**

- Polymeric nanoparticles
- Solid lipid nanoparticles (SLNs)
- Nanostructured lipid carriers (NLCs)

#### **Applications-**

Used for delivery of drugs in Alzheimer's disease, Parkinson's disease, and brain tumors.

### **2. Liposomes-**

Liposomes are spherical vesicles composed of phospholipid bilayers capable of encapsulating both hydrophilic and lipophilic drugs.

#### **Advantages:**

- Biocompatibility and biodegradability
- Reduced toxicity
- Improved drug penetration
- Sustained release properties

#### **Role in Nose-to-Brain Delivery:**

Liposomes enhance transport of drugs across the nasal mucosa and improve brain uptake.

### **3. Nanoemulsions**

Nanoemulsions are thermodynamically stable dispersions of oil and water stabilized by surfactants, with droplet sizes in the nanometer range.

#### **Advantages:**

- Improved solubility of poorly soluble drugs
- Rapid absorption
- Enhanced permeability
- Better drug distribution in CNS

#### **Applications:**

Useful for lipophilic CNS drugs and neuroprotective agents.

### **4. Hydrogels**

Hydrogels are three-dimensional polymeric networks capable of absorbing large amounts of water.



**Advantages:**

- Prolonged nasal residence time
- Controlled drug release
- Improved mucoadhesion
- Enhanced patient compliance

**In Situ Hydrogels:**

These formulations remain liquid during administration and convert into gel upon contact with nasal conditions such as temperature or pH changes.

**5. Microspheres**

Microspheres are small spherical particles prepared from natural or synthetic polymers.

**Advantages:**

- Controlled drug release
- Increased contact time with nasal mucosa
- Better drug stability
- Improved absorption

**Common Polymers:**

- Chitosan
- Gelatin
- Albumin

**6. Mucoadhesive Drug Delivery Systems**

Mucoadhesive formulations contain polymers that adhere to nasal mucosa and prolong drug residence time.

**Common Mucoadhesive Polymers:**

- Chitosan
- Carbopol
- Hydroxypropyl methylcellulose (HPMC)
- Sodium alginate

**Advantages:**

- Reduced mucociliary clearance
- Enhanced drug absorption
- Improved bioavailability

**7. Nasal Sprays and Drops**

These are the most commonly used conventional nasal formulations.

**Advantages:**

- Easy administration
- Rapid onset of action
- Patient-friendly

**Limitations:**

- Short residence time
- Poor targeting efficiency

**8. Nanostructured Lipid Carriers (NLCs)**

NLCs are advanced lipid-based carriers made from solid and liquid lipids.



**Advantages:**

Higher drug loading capacity  
Improved stability  
Sustained release

Better brain targeting efficiency

**Evaluation of Nasal Formulations**

Important evaluation parameters include:

Particle size analysis  
Drug entrapment efficiency  
Mucoadhesion studies  
In vitro drug release studies  
Nasal permeation studies  
Stability studies  
Brain uptake studies

**Recent Advances in Formulation Strategies**

Recent research focuses on:

Targeted nanoparticles  
Surface-modified carriers  
Stimuli-responsive hydrogels  
Multifunctional nanocarriers  
Combination delivery systems

These innovations aim to improve drug targeting accuracy and therapeutic outcomes.

**Evaluation Parameters of Nose-to-Brain Drug Delivery Systems**

Evaluation parameters are essential for determining the quality, safety, stability, and effectiveness of nose-to-brain drug delivery systems. Proper evaluation helps in optimizing formulations for enhanced nasal absorption, brain targeting, and therapeutic efficacy. Different physicochemical, biological, and pharmacokinetic parameters are assessed during formulation development.

**1. Particle Size and Particle Size Distribution-**

Particle size is an important parameter, especially for nanosystems such as nanoparticles, liposomes, and nanoemulsions.

**Importance:**

Influences drug absorption and permeability  
Affects nasal residence time  
Determines brain targeting efficiency  
Impacts stability of formulation

**Methods:**

Dynamic light scattering (DLS)  
Laser diffraction  
Electron microscopy

**Ideal Range:**

Generally, nanoparticles ranging from 10–200 nm are preferred for efficient brain targeting.

**2. Zeta Potential**

Zeta potential indicates the surface charge of particles and predicts formulation stability.

**Importance:**

Determines particle aggregation



Influences mucoadhesion  
Affects stability and interaction with nasal mucosa

**Interpretation:**

High positive or negative zeta potential values indicate better stability.

**3. Drug Entrapment Efficiency**

Entrapment efficiency measures the percentage of drug incorporated within the carrier system.

**Importance:**

Indicates formulation efficiency  
Determines drug loading capacity  
Influences sustained drug release

**Formula:**

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount of Entrapped Drug}}{\text{Total Drug Added}} \times 100$$

**4. Drug Loading Capacity**

Drug loading capacity represents the amount of drug present within the delivery system relative to total carrier weight.

**Importance:**

Determines dose efficiency  
Helps reduce administration frequency

**5. In Vitro Drug Release Studies**

These studies evaluate the pattern and rate of drug release from the formulation.

**Importance:**

Determines sustained or controlled release behavior  
Predicts in vivo performance

**Methods:**

Dialysis membrane method  
Franz diffusion cell

**6. Mucoadhesion Studies**

Mucoadhesion studies evaluate the ability of formulations to adhere to nasal mucosa.

**Importance:**

Increases nasal residence time  
Enhances drug absorption  
Reduces mucociliary clearance

**Evaluation Methods:**

Texture analyzer  
Wash-off method  
Mucoadhesive strength measurement

**7. Nasal Permeation Studies**

These studies assess the ability of drugs to cross nasal mucosa.

**Importance:**

Determines permeability efficiency  
Predicts brain uptake potential



**Methods:**

Excised animal nasal mucosa  
Diffusion chambers

**8. Viscosity Measurement**

Viscosity affects formulation flow properties and retention within the nasal cavity.

**Importance:**

Influences ease of administration  
Affects drug release and residence time

**Instrument:**

Brookfield viscometer

**9. pH Determination**

The pH of nasal formulations should be compatible with nasal mucosa.

**Importance:**

Prevents nasal irritation  
Maintains drug stability  
Enhances patient comfort

**Ideal Nasal pH:**

Approximately 4.5–6.5

**10. Osmolarity Measurement**

Osmolarity should be isotonic or near isotonic with nasal fluids.

**Importance:**

Prevents mucosal damage  
Avoids irritation and discomfort

**11. Stability Studies**

Stability studies determine the physical and chemical stability of formulations under different conditions.

**Parameters Evaluated:**

Particle size changes  
Drug degradation  
pH variation  
Appearance

**Guidelines:**

Performed according to ICH stability guidelines.

**12. Histopathological Studies**

These studies examine the effect of formulations on nasal tissues.

**Importance:**

Detects tissue damage or irritation  
Evaluates formulation safety

**Method:**

Microscopic examination of nasal mucosa after treatment.



### **13. Nasal Toxicity Studies**

Nasal toxicity studies assess local toxic effects caused by the formulation.

#### **Parameters:**

Irritation  
Inflammation  
Ciliary damage

### **14. Pharmacokinetic Studies**

Pharmacokinetic evaluation measures drug concentration in plasma and brain over time.

#### **Importance:**

Determines bioavailability  
Assesses brain targeting efficiency  
Compares different formulations

#### **Parameters:**

C<sub>max</sub>  
T<sub>max</sub>  
Area under curve (AUC)  
Half-life (t<sub>1/2</sub>)

### **15. Brain Uptake Studies**

These studies evaluate the extent of drug delivery to the brain.

#### **Importance:**

Confirms successful nose-to-brain transport  
Measures targeting efficiency

#### **Methods:**

Animal studies  
Imaging techniques  
Biodistribution studies

### **16. In Vivo Studies**

In vivo studies are conducted using animal models to evaluate therapeutic efficacy and safety.

#### **Importance:**

Assesses actual brain delivery  
Evaluates pharmacological response

#### **Common Animal Models:**

Rats  
Mice  
Rabbits

#### **Result-**

The present review on nose-to-brain drug delivery demonstrates that intranasal administration is a promising and effective approach for delivering therapeutic agents directly to the central nervous system (CNS). This route successfully bypasses the blood-brain barrier (BBB), which is one of the major obstacles in conventional brain drug delivery. Various studies reported improved brain targeting, enhanced bioavailability, rapid onset of action, and reduced systemic side effects through intranasal formulations.



Advanced drug delivery systems such as nanoparticles, liposomes, nanoemulsions, hydrogels, microspheres, and mucoadhesive formulations showed significant improvement in drug absorption, nasal residence time, and brain uptake efficiency. Nanotechnology-based carriers particularly demonstrated enhanced permeation across the nasal mucosa and protection of drugs from enzymatic degradation.

Evaluation studies indicated that optimized formulations possessed suitable particle size, high entrapment efficiency, controlled drug release, good mucoadhesive properties, and acceptable stability profiles. Pharmacokinetic and brain uptake studies confirmed increased drug concentration in brain tissues following intranasal administration compared to conventional delivery methods.

## II. CONCLUSION

Nose-to-brain drug delivery has emerged as a promising and innovative approach for the direct delivery of therapeutic agents to the central nervous system (CNS). This route effectively bypasses the blood–brain barrier (BBB), which is a major limitation in conventional brain drug delivery systems. Intranasal administration offers several advantages such as non-invasive delivery, rapid onset of action, improved bioavailability, reduced systemic side effects, and enhanced patient compliance.

The unique anatomy and physiology of the nasal cavity, particularly the olfactory and trigeminal neural pathways, facilitate direct transport of drugs from the nasal cavity to the brain. Advanced drug delivery systems including nanoparticles, liposomes, nanoemulsions, hydrogels, microspheres, and mucoadhesive formulations have significantly improved drug targeting efficiency, stability, and nasal residence time. Various evaluation studies and experimental findings have demonstrated successful brain targeting and enhanced therapeutic efficacy for the treatment of neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, brain tumors, migraine, and psychiatric disorders. Despite these advantages, certain challenges such as mucociliary clearance, enzymatic degradation, limited drug dosing, and formulation stability still need to be addressed. Continuous advancements in nanotechnology, biomaterials, and formulation strategies are expected to overcome existing limitations and further improve the effectiveness of intranasal brain delivery systems. Therefore, nose-to-brain drug delivery represents a highly potential and rapidly developing field that may revolutionize the future treatment of CNS disorders through safe, targeted, and patient-friendly drug delivery approaches.

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