INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

# Nose-to-Brain Drug Delivery Systems for Central Nervous System Disorders: Mechanisms, Formulation Strategies, and Therapeutic Applications

**Paramveer Dutt, Charanpreet Singh, Jasmeen Kaur, Kiranjeet Kaur, Shivani Kumari***

*Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, India 140111*

ARTICLE INFO

Published: 5 Jun 2026
Keywords:
nose-to-brain delivery; blood–brain barrier; intranasal drug delivery; nanocarriers; olfactory pathway; central nervous system disorders; nanostructured lipid carriers; neurotherapeutics
DOI:
10.5281/zenodo.20567077

## ABSTRACT

Although central nervous system (CNS) disorders exert an increasing burden on global health, the blood–brain barrier (BBB), which prevents most drug classes from reaching sufficient brain concentrations by conventional systemic delivery methods still dramatically, limits pharmacological treatment. Therefore, the intranasal (nose-to-brain, N2B) route has provided a promising non-invasive option that takes advantage of the direct anatomical connectivity of olfactory and trigeminal nerve pathways to deliver drugs (including biologics) directly from the nasal mucosa to the brain. This review systematically analyses the mechanisms, formulation strategies, therapeutic applications and current status of clinical translation of N2B drug delivery systems. In this overview, we briefly discuss key nanocarrier platforms such as solid lipid nanoparticles, nanostructured lipid carriers (NLCs), polymeric nanoparticles, nanoemulsions, liposomes and mucoadhesive gels and exosome-based carriers with a special emphasis on how they improve mucoadhesion and protect drug payloads from enzymatic degradation while also enabling neuronal uptake. The summary, upon evaluation against preclinical and clinical evidence includes those therapeutic applications across Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma and psychiatric disorders.We survey recent domain advances in surface functionalisation, stimuli-responsive systems and engineered extracellular vesicles within the context of the expanding clinical landscape encompassing both approved intranasal agents and over 130 active trials. In vitro nasal models validated pharmacokinetic benchmarks and olfactory-targeting devices for accelerated clinical translation are prioritized.

***Corresponding Author:** Shivani Kumari
**Address:** *Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, India 140111*
**Email** ✉: shivanikumari75910@gmail.com

**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## INTRODUCTION

Diseases of the central nervous system are some of the most crippling and fastest growing risks to health worldwide. Abstract Hundreds of millions of individuals across the globe are affected by brain disorders, characterized by significant disability adjusted life years and include conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, depression, schizophrenia and primary brain tumors. Obstacles to drug entry into the CNS Although advances in CNS drug delivery have undergone decades of research and substantial pharmaceutical innovation, most prospective drug candidates still fail to attain sufficient brain concentrations following traditional oral or parenteral routes of administration. This failure is mainly due to the blood-brain barrier (BBB), which is a very specialized and carefully controlled structure made up of brain endothelial cells, pericytes, and the ends of astrocytes. Together, these components limit the movement of substances between cells and actively pump many treatment molecules back into the bloodstream.

Worldwide healthcare information shows that central nervous system (CNS) diseases account for about 6–8% of the direct and indirect costs to the global economy. Additionally, the number of neurodegenerative diseases has significantly risen as the global population ages [1]. Even with this trend, traditional treatments that use pills or injections are still greatly restricted by the blood-brain barrier (BBB).

Different methods to get past the blood-brain barrier (BBB) have been looked into, such as injecting directly into the brain's ventricles and using focused ultrasound to break down the BBB. However, these methods are mostly invasive, need special equipment, and come with a high chance of causing negative side effects. In contrast, using the intranasal method provides an easy and friendly option for patients. This approach lets medications avoid the blood-brain barrier by moving through the olfactory and trigeminal nerve pathways straight from the nose to the brain [2]. This method is good for daily use and has been proven in both early studies and clinical trials to send medicine straight to the brain. This helps raise the amount of drugs in the central nervous system while lowering the overall exposure to the body and reducing side effects [3].

However, using the intranasal route does come with some difficulties. Mucociliary clearance, the breakdown of substances by enzymes in the nasal lining, and the small amount of medication that can be placed in the nasal passage all limit how much medicine can reach the brain [4]. Nanocarrier-based formulations have become effective solutions to overcome these challenges. They improve how well drugs dissolve, shield them from being broken down by enzymes, extend the time they stay in the nose, and help them get taken up by the nerve cells in the nose [5]. This review gives a detailed and thoughtful look at how N2B drug delivery systems work, what they are made of, how they can be used for diseases, and their current status in clinical use for central nervous system (CNS) disorders.

## 2. LITERATURE REVIEW

### 2.1 Historical Development of Nose-to-Brain Drug Delivery

The idea of sending medicine straight to the brain through the nose has changed a lot in the last thirty years. In the early 1990s, researchers looked into how substances can move from the nose to the brain. They found that when they applied certain markers to the nose tissues of rodents, they could see these markers in the olfactory bulb and nearby areas of the brain just a few hours later, without

any significant amount showing up in the rest of the body [6]. These basic studies gave the first clear proof that the olfactory nerve pathway can act as a direct link between the outside world and the central nervous system, without needing to go through the blood-brain barrier (BBB). In the early 2000s, Illum and his team did important research that showed clear proof that both small molecules and larger molecules, like peptides and proteins, can get to the central nervous system (CNS) after being placed in the nose. This research sparked a lot of interest in studying how to create these formulations and the ways these substances are transported to deliver N2B [7].

By the middle of the 2000s, the area had grown to include delivery systems based on nanoparticles. The use of chitosan nanoparticles for delivering medicine through the nose was an important breakthrough. The positively charged chitosan particles connected with the negatively charged nasal lining, which helped them stay longer and significantly increased the amount of medicine absorbed by the smell-sensitive tissue in the nose [8]. Later on, lipid-based nanoparticles, especially solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), became effective tools for delivering both fat-loving and water-loving drugs for the central nervous system (CNS). They showed much better ability to target the brain compared to traditional nasal solutions in tests with mice before clinical trials [9]. These improvements happened at the same time as people began to realize there is a big need for better treatments for brain and nervous system disorders worldwide. This led to more money being put into developing drugs that can be taken through the nose, both in universities and in companies.

**Table no. 1**

| Year/Period | Key Development | Model/Drug | Significance |
|---|---|---|---|
| 1990s | Initial demonstration of olfactory transport | Tracers in rodents | Established anatomical connection between nasal cavity and brain |
| Early 2000s | Systematic studies on N2B delivery | Peptides, proteins | Proved macromolecules can reach CNS via nasal route |
| Mid-2000s | Introduction of mucoadhesive systems | Chitosan nanoparticles | Increased nasal residence time and absorption |
| 2010s | Emergence of nanocarriers | SLNs, NLCs, PLGA nanoparticles | Improved targeting efficiency and drug stability |
| 2020s | Bioinspired delivery systems | Exosomes, extracellular vesicles | Enhanced biocompatibility and CNS targeting |

## 2.2 The Blood–Brain Barrier as the Principal Obstacle

The BBB is a very specialized part of the brain's blood system. It includes tiny blood vessel cells in the brain that are linked together by tight connections made of proteins like claudins, occludins, and zonula occludens. It also has pericytes and the ends of astrocyte cells. All these parts work together to form an active barrier that allows some molecules to move from the bloodstream into the brain tissue while keeping others out [10]. The blood-brain barrier (BBB) successfully prevents over 98% of small-molecule drugs and nearly all large therapeutic molecules, such as peptides, proteins, antibodies, and nucleic acids, from reaching effective levels in the central nervous system (CNS) when given through regular systemic administration [11]. Also, there are drug transporters, especially P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), found on the surface of brain blood vessel cells that work to

push many drugs back into the blood. This action makes it harder for these drugs to enter the brain effectively [12].

Ways to get around the blood-brain barrier (BBB) have been looked into, such as changing chemicals to make them more fat-loving, using prodrugs, taking advantage of receptor-mediated transport, and using focused ultrasound to temporarily disrupt the barrier. These methods have had varying levels of success but often come with risks like overall body toxicity, unintended exposure to the central nervous system (CNS), or dangers related to the procedures [13]. The N2B method takes advantage of the special structure of the olfactory and trigeminal nerve pathways to deliver medications straight from the nasal lining to the brain tissue, completely avoiding the blood-brain barrier and the overall bloodstream [2].

### 2.3 Evolution of Nanocarrier Technologies for Nose-to-Brain Delivery

The progress of nanotechnology systems for N2B delivery has gone through multiple stages, each more advanced than the last. First-generation formulations included basic solutions and suspensions of medicine in water-based or fat-based carriers. Although these showed a basic idea of how N2B transport works, their effectiveness was limited by quick clearing of mucus, little absorption in the nose, and the drugs not dissolving well [14]. Second-generation methods brought in mucoadhesive polymers and in situ gelling systems to extend the time drugs stay in the nose. This led to significant improvements in how long the drug contacts the olfactory epithelium and how well it is absorbed [15]. Chitosan and its related forms have become the most commonly used sticky agents in medicines because they have a positive charge, break down naturally in the body, and can temporarily open tight connections between cells. This helps drugs move more easily between cells.

Third-generation nanocarrier systems, which include PLGA and PLA nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, liposomes, and dendrimers, have made significant improvements in how well they can hold drugs, release them in a controlled way, modify their surfaces, and protect sensitive substances from being broken down by enzymes [16, 17]. Changing the surface of nanoparticles with specific targeting molecules like wheat germ agglutinin (WGA), transferrin, lactoferrin, and cell-penetrating peptides (CPPs) helps these particles to focus on olfactory sensory neurons. This process allows them to enter the cells through receptor-mediated endocytosis and then move inside the neurons to reach the olfactory bulb [18]. Recently, there has been a lot of interest in bioinspired carriers, especially exosomes and other extracellular vesicles that come from mesenchymal stem cells or dendritic cells. These carriers are naturally compatible with the body and are accepted by the immune system, making them good options for delivering complex biomolecular materials. This includes things like microRNAs and therapeutic proteins, which can be sent directly to the central nervous system through the nose [19, 20].

**Table no. 2**

| Generation | System Type | Key Features | Limitations |
|---|---|---|---|
| **First** | Solutions/Suspensions | Simple formulation, easy administration | Rapid clearance, low bioavailability |
| **Second** | Mucoadhesive/In situ gels | Increased residence time, improved absorption | Limited drug loading |

| | | | |
|---|---|---|---|
| **Third** | Nanocarriers (SLNs, PLGA, liposomes) | Controlled release, protection from degradation | Complex formulation |
| **Fourth** | Bioinspired systems (exosomes) | High biocompatibility, targeted delivery | Scalability and cost issues |

### 2.4 Key Findings from Preclinical and Clinical Literature

A large amount of research before clinical trials has shown the benefits of using the N2B method for drug absorption and effects in various models of central nervous system diseases. Important pharmacokinetic measures that help evaluate how well N2B targets the brain include the drug targeting efficiency (DTE%) and drug transport percentage (DTP%). These measures look at the levels of the drug in the brain compared to the levels in the plasma when given through the nose versus through the veins. Additionally, they also consider the nose-to-brain direct transport percentage (DTP%). Many systematic reviews and meta-analyses have gathered and summarized the early research findings. They have consistently shown that intranasal formulations using nanocarriers lead to brain concentrations that are two to ten times higher than the same doses given through intravenous or oral routes in rodent studies [21]. The proof is especially strong for using lipid nanoparticles in models of Parkinson's disease, polymeric nanoparticles for Alzheimer's disease uses, and nano-emulsions in models of epilepsy [22].

In clinical terms, the area has progressed from initial ideas to getting official approval for various intranasal treatments for the central nervous system. In 2019, the FDA approved intranasal midazolam (Nayzilam) for quickly treating groups of seizures. Then, in 2020, intranasal diazepam (Valtoco) was also approved. These were the first intranasal medicines approved for treating epilepsy [23]. In 2019, the FDA approved intranasal esketamine (Spravato) for people who have depression that does not respond to other treatments. This made it the first approved nasal spray that works directly on the central nervous system [24]. Intranasal naloxone (Narcan) has received wide approval from regulatory bodies and is now commonly used in medical settings to reverse opioid overdoses [25]. Together, these approvals show that using the intranasal method is a good option for treating central nervous system (CNS) conditions. This success has encouraged more investment in a new group of intranasal drugs aimed at treating neurodegenerative diseases, mental health issues, and cancers affecting the CNS. As of 2024, there are over 130 ongoing clinical trials for intranasal neurotherapeutic treatments listed on ClinicalTrials.gov. These trials include studies from Phase I to Phase III [26].

### 2.5 Gaps in the Existing Literature and Rationale for This Review

Even though a lot of research has been published, there are still some significant gaps in the N2B literature. First, many early studies use rodent models, but their sense of smell structure is quite different from that of humans. In rats, the area responsible for smell makes up about 50% of their nasal surface, while in humans, it only accounts for about 2–10%. This means that we need to be very careful when applying early research results to real-life situations in humans [27]. Secondly, there are still no consistent ways to measure how well N2B drugs are transported in living organisms. Differences in how studies are designed, the dosing methods used, and the ways of analysing the results make it hard to compare findings from

different studies reliably. Third, there is not much information available about the long-term safety of using intranasal nanoparticles repeatedly. There are specific worries about possible damage to the nasal lining, problems with smell, and the build-up of nanoparticle ingredients in the central nervous system [28]. Currently, scientists are still working on creating reliable lab models that can effectively mimic the human sense of smell and how it transports substances. This progress is important because it limits the ability to carefully test and design formulations before moving on to studies in living organisms [29].

This review looks at these gaps by offering a detailed and thoughtful overview of how N2B drug delivery systems work, the ways they are made, their uses in treatment, and how they are being applied in clinical settings. The current research has many studies focusing on individual formulations, but there are few comparative studies and systematic evaluations that look at how well these findings can be applied in clinical settings. This review seeks to gather and evaluate the present evidence, point out new methods that show real potential for practical use, and outline important research areas that are necessary for moving the next wave of intranasal CNS treatments from early research stages to actual clinical use [30].

## 3. ANATOMY AND PHYSIOLOGY OF THE NASAL CAVITY

### 3.1 Structural Organization

The nasal cavity is a complicated structure that has two sides, separated by the nasal septum. It is surrounded by the floor, roof, and sidewalls. The side walls have three turbinates superior, middle, and inferior that help expand the surface area of the nasal lining to about 150–180 $cm^2$ in adults. The lining of the nasal epithelium is varied: the front part, called the vestibule, has a type of skin called stratified squamous epithelium. The area responsible for breathing, known as the respiratory region, is covered with a special kind of tissue called pseudostratified ciliated columnar epithelium. Lastly, the olfactory region, which is found at the top of the nasal cavity near a structure called the cribriform plate, contains unique cells known as olfactory sensory neurons that help us smell. The part of the nose that is responsible for smell in humans takes up about 2 to 10 square centimetres of the entire area of the nose [31].

The blood that goes to the nasal cavity comes from branches of the maxillary, facial, and ophthalmic arteries, as well as from the carotid artery [4]. The area of the respiratory epithelium, which has a big surface area and a lot of blood vessels, is a key place for absorbing drugs into the body after they are given through the nose. However, drugs taken in from this area go into the bloodstream and are affected by the liver's first pass metabolism, how they bind to proteins in the blood, and how the kidneys clear them. This process decreases the amount that finally gets to the central nervous system (CNS) [4].

### 3.2 Olfactory Epithelium and Neuronal Pathways

The olfactory epithelium has special cells called bipolar olfactory sensory neurons, supporting cells known as sustentacular cells, cells from Bowman's glands, and basal stem cells. The olfactory sensory neurons are special because they are directly exposed to the outside world. Their unmyelinated axons go through small openings in the cribriform plate to connect in the olfactory bulb. From there, signals are sent to various higher brain areas and limbic structures. The direct link between the nasal cavity and the brain something that is special compared to other senses allows for the movement

of drugs to the central nervous system through the olfactory pathway.

The trigeminal nerve, which is the fifth cranial nerve, gives sensory feeling to the nasal lining through its branches called the ophthalmic and maxillary branches. The trigeminal nerve endings are found all over the nasal cavity, including in the area used for breathing. This creates an additional route for N2B drugs to travel, allowing them to reach deeper parts of the brain through the brainstem [32].The smell pathway and the touch pathway work together to create two different but helpful ways for delivering drugs straight from the nose to the brain.

**Table no. 3**

| Region | Epithelium Type | Surface Area | Function | Role in Drug Delivery |
|---|---|---|---|---|
| **Vestibular** | Stratified squamous | Small | Protection | Minimal absorption |
| **Respiratory** | Ciliated columnar | Large | Air filtration | Systemic absorption |
| **Olfactory** | Specialized neurons | Small (2–10%) | Smell | Direct brain delivery |

## 4. MECHANISMS OF NOSE-TO-BRAIN DRUG TRANSPORT

### 4.1 Olfactory Pathway

The movement of drugs through the olfactory pathway can happen in two main ways: through cells (called intracellular, which includes transcellular and neuronal routes) and outside of cells (known as extracellular, which includes paracellular and perineural routes). In the pathway inside cells or neurons, drugs enter olfactory sensory neurons through a process called endocytosis or by simply passing through the cell membrane. After that, they are moved along the axons, both forward (toward the olfactory bulb) and backward, until they arrive at the olfactory bulb. From the olfactory bulb, the drugs can then access larger structures in the central nervous system (CNS). This process happens at a slow pace, with transport speeds noted to be around 2.5 mm per hour for slow axonal transport [26].

In the extracellular pathway, medications move through the nasal lining into the layer of tissue underneath, called the lamina propria. From there, they travel along the spaces around the nerves and blood vessels of the olfactory nerve bundles. They pass through small openings in the cribriform plate, entering the subarachnoid space, and finally reach the olfactory bulb. This pathway outside of cells is usually quicker and might be the main way that nanoparticles and bigger molecules travel [16]. Transport between sustentacular cells can occur through spaces between them, but tight junctions restrict this path for larger water-loving molecules.

### 4.2 Trigeminal Pathway

The trigeminal pathway offers another way for N2B to be delivered, which is especially important for reaching the brainstem, spinal cord, and back parts of the brain. Once the drug molecules are absorbed through the nasal lining, they move along the axons of the trigeminal nerve. They then enter the brain through the trigeminal ganglion and the pons. Research with fluorescently marked nanoparticles has shown that drugs spread not just in the olfactory bulb but also in the brainstem and cervical spinal cord after being given through the nose. This supports the idea that the trigeminal pathway is involved in how the drugs are transported [33].

### 4.3 Systemic Absorption Route

Some of the medicine given through the nose is taken in through the nasal tissues into the

bloodstream and may later pass through the blood-brain barrier, especially if the molecules are small and fat-soluble. Even though this roundabout way of getting drugs from the nose to the brain through the blood can help increase drug levels in the central nervous system (CNS), it still faces the same challenges from the blood-brain barrier (BBB) as regular methods of delivering drugs throughout the body. Overall, this approach is usually seen as less effective for targeting the CNS. Smaller lipophilic drugs are more likely to pass through the blood-brain barrier compared to larger molecules like peptides and proteins [4].

### 4.4 Cerebrospinal Fluid and Lymphatic Routes

Once drugs enter the cerebrospinal fluid (CSF) through these pathways, they can spread widely throughout the subarachnoid space and reach deeper parts of the central nervous system [4]. (CNS) through the movement of the CSF. This way of distributing through CSF might be especially important for large biological molecules and tiny particles.

## 5. FORMULATION STRATEGIES FOR ENHANCED NOSE-TO-BRAIN DELIVERY

### 5.1 Lipid-Based Nanoparticles

Lipid-based nanoparticles, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have gained a lot of interest for delivering N2B. This is because they are safe for the body, break down naturally, can hold both water-loving and fat-loving drugs, and can shield their contents from being broken down by enzymes. SLNs are the first type of solid lipid nanocarriers. They have a solid lipid structure that stays solid at body temperature, can hold a lot of medicine, and are very stable [34]. NLCs, known as second-generation solid lipid nanoparticles, use a mix of solid and liquid lipids in their structure. This combination helps to improve how much drug they can hold and decreases the amount of drug that might leak out while being stored [34].

Studies done in living organisms show that using intranasal solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) greatly improve how much medicine reaches and targets the brain compared to traditional solutions. For instance, when haloperidol-loaded solid lipid nanoparticles (SLNs) were given through the nose to rat models of Parkinson's disease, they reached a drug targeting efficiency (DTE %) of 597.57. In contrast, when the drug was given through an intravenous route, the drug transport percentage (DTP %) was 83.27%. This clearly shows the benefits of using the olfactory and trigeminal nerve pathways for drug transport [34]. Chitosan-coated NLCs have demonstrated better mucoadhesive qualities, which help them stay in the nose longer and improve their contact with the olfactory epithelium.

### 5.2 Polymeric Nanoparticles

Polymeric nanoparticles are a flexible option for delivering N2B. They allow for various designs, can be adjusted to release drugs at different rates, and can be modified on their surface to stick better to mucus and target specific areas for better absorption. Poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA) are the two most commonly used materials for this purpose. Both of these have been approved for use in humans. When they break down, they produce lactic acid and glycolic acid, which the body can easily process without causing any inflammation [16].

Chitosan nanoparticles are especially appealing for delivering drugs through the nose because they have a strong positive charge on their surface. This positive charge helps them stick to the negatively charged nasal lining, making it easier for them to

attach and be absorbed by the cells. Chitosan nanoparticles can easily pass through the blood-brain barrier and help keep the medicine in the nose for a longer time [16]. Changing the surface of polymer nanoparticles with substances like wheat germ agglutinin (WGA) or rabies virus glycoprotein (RVG) peptide can improve how well neurons take them up and help them move back along the axons.

Dendrimers are a type of polymeric nanocarrier. They are macromolecules that are highly branched and uniform in size, with a carefully designed structure. Researchers have studied them for delivering anti-Alzheimer medications through the nose. The many surface functional groups they have allow for the attachment of several targeting ligands and drugs at the same time.

### 5.3 Nanoemulsions and Microemulsions

Nanoemulsions are stable mixtures that consist of tiny droplets, usually measuring between 20 and 200 nanometres in size. They can remain stable due to their thermodynamic properties or their kinetic behaviour. Their tiny particle size helps them get deep into the nose and makes it easier for the body to absorb them through the nasal lining. Nanoemulsions can be made into nasal sprays, which makes them easy to use and good for taking multiple times. Nanoemulsions coated with chitosan have shown improved ability to stick to mucous membranes and better effectiveness in reaching the brain for various central nervous system medication [35]. Microemulsions, which have droplet sizes ranging from 10 to 140 nanometres, provide stable conditions, clear appearance, and a strong ability to dissolve drugs that are both fat-loving and water-loving. They have been researched a lot for targeting the brain through the nose [26].

### 5.4 Liposomes

Liposomes are small bubbles made of phospholipid layers that look a lot like the membranes found in living cells. They are very compatible with the body and can hold both water-loving drugs in their watery center and fat-loving drugs within their layers. The surface can be changed with polyethylene glycol (PEGylation) to make it stay in the body longer and reduce how quickly it gets cleared by mucus and cilia. It can also be modified with special targeting molecules to improve how well the nerve cells responsible for smell take it up. Research on how liposomes placed in the nose spread in the body has shown that their surface charge and the addition of PEG (a type of polymer) greatly influence how they are distributed in the brain after being delivered through the nose. Specifically, liposomes that are positively charged tend to gather more in the olfactory bulb, which is the part of the brain responsible for the sense of smell [33]. Liposomes packed with cholesterol given through the nose have shown potential in models of Huntington's disease.

### 5.5 Exosomes and Extracellular Vesicles

Exosomes are tiny vesicles that come from cells, usually measuring between 30 and 150 nanometres. Almost all types of cells can produce them. These vesicles play a natural role in communication between cells and have a unique ability to pass through biological barriers, including the blood-brain barrier (BBB). Their biological background gives them low ability to provoke an immune response and high compatibility with living tissues, which makes them appealing options for delivering drugs. After being given through the nose, tiny extracellular vesicles from mesenchymal stem cells have been found to spread quickly and broadly across the brain, likely using the path around blood vessels [19]. In a Phase I/II clinical trial, giving exosomes

from donated human fat stem cells through the nose to patients with mild to moderate Alzheimer's disease was shown to be safe and helped improve their thinking abilities [36].

### 5.6 Mucoadhesive and In Situ Gelling Systems

Mucoadhesive formulations use forces like electrical attraction, hydrogen bonds, or water-repelling interactions between the ingredients and the mucosal surface to make the medicine stay in the nose longer and improve how well the drug is absorbed. Polymers like chitosan, hyaluronic acid, carbopol, and hydroxypropyl methylcellulose (HPMC) are commonly used for this reason. In situ gelling systems are liquid products that turn into a gel when they touch the inside of the nose. This change happens because of variations in temperature, pH, or the strength of ions, which helps them stay in contact longer. A specially designed nasal gel that delivers methylene blue has shown improvement in memory and thinking problems in a model of Alzheimer's disease [37].

**Table no. 4**

| Carrier Type | Advantages | Limitations | Example Drugs |
|---|---|---|---|
| **SLNs** | High stability, controlled release | Limited drug loading | Haloperidol |
| **NLCs** | Improved drug loading | Complex composition | Antipsychotics |
| **PLGA nanoparticles** | Biodegradable, controlled release | Costly preparation | Rivastigmine |
| **Liposomes** | Biocompatible, versatile | Stability issues | Cholesterol |
| **Nanoemulsions** | Enhanced absorption | Low stability | CNS drugs |
| **Exosomes** | Natural carriers, high targeting | Expensive, scalability issues | miRNA, proteins |

## 6. THERAPEUTIC APPLICATIONS IN CNS DISORDERS

### 6.1 Alzheimer's Disease

Alzheimer's disease is a condition that gets worse over time and affects the brain. It is marked by the build-up of amyloid-beta plaques outside brain cells, tangles made of tau protein inside the cells, inflammation in the brain, and a gradual decline in thinking and memory skills. It is the leading cause of dementia and impacts over 50 million people around the globe. The medications that are currently approved for treatment like acetylcholinesterase inhibitors such as donepezil and rivastigmine, along with the NMDA receptor antagonist memantine only help with the symptoms and do not stop the disease from getting worse. The blood-brain barrier (BBB) creates a significant challenge for treatments aimed at changing the course of diseases related to amyloid and tau problems.

Using the nose for delivering medicine has been studied a lot for treating Alzheimer's disease. Nano-carriers that use nanotechnology improve how well medicines work in the body. They help drugs get through the nose more easily, cross the blood-brain barrier effectively, and stay in the brain for a longer time [35]. Lipid nanoparticles, polymer-based nanoparticles like PLGA-PEG systems, dendrimers, liposomes, and nanoemulsions have all been studied for delivering anti-Alzheimer's drugs through the nose. This includes medicines like rivastigmine, galantamine, huperzine A, memantine, and some experimental biologics. Huperzine A, which is put into specially designed tiny particles and given through the nose to rats, greatly slowed down the activity of acetylcholinesterase, lowered the excessive phosphorylation of tau, reduced amyloid-beta problems, and helped improve thinking abilities [37].

Clinical studies have also advanced. There are ongoing clinical trials, such as NCT04388982, NCT02795052, and NCT03724136, that are looking into nasal treatments like insulin, anti-amyloid antibodies, and neuropeptides to help manage Alzheimer's disease [36]. Intranasal insulin has been tested in several Phase II and III trials, showing positive effects on memory and daily functioning in patients with early Alzheimer's disease.

### 6.2 Parkinson's Disease

Parkinson's disease is the second most common disease that affects the nervous system. It is marked by the gradual loss of nerve cells that produce dopamine in a part of the brain called the substantia nigra pars compacta. This condition also involves the buildup of a protein called alpha-synuclein in structures known as Lewy bodies, which leads to problems with the brain's motor circuits that help control movement. The main signs of the condition are slow movement, stiffness, and shaking. There are also important non-motor symptoms like trouble with thinking, feeling sad, and issues with the automatic functions of the body [4]. The main treatment focuses on using dopamine replacement therapy with levodopa-carbidopa. However, using it for a long time can lead to movement problems, including dyskinesia.

Using nasal sprays to deliver Parkinson’s disease medications has been explored to boost how much of the drug reaches the brain and to lessen side effects in other parts of the body. Many types of tiny carriers, such as lipid nanoparticles, polymer nanoparticles, nanoemulsions, and nanomicelles, have been studied. For instance, PEG-PLA micelles have been proven to carry baicalein to the brain through the nose to help treat brain damage caused by oxidative stress and inflammation [4]. Giving plasmid DNA nanoparticles that carry the gene for glial cell line-derived neurotrophic factor (GDNF) through the nose greatly raised the level of GDNF in the brain. This method helped protect dopamine neurons and kept the density of dopaminergic fibers intact in rat models. This shows that using intranasal gene therapy could be a promising approach for treating early-stage Parkinson's disease [38]. Clinical trials have been done to test intranasal glutathione, intranasal insulin, rotigotine, and apomorphine for Parkinson's disease (PD). One of the registered trials is NCT03128450 [36].

### 6.3 Epilepsy

Epilepsy is a long-lasting brain condition marked by repeated seizures that happen due to unusual electrical activity in the brain. About 30% of people with epilepsy do not become free from seizures even with the antiseizure medicines that are available. Also, using these drugs for a long time can lead to harmful effects on the body [3]. Nasal benzodiazepines, especially midazolam and diazepam, have been approved for quickly treating groups of seizures and are some of the most developed nasal treatments for the central nervous system. The quick effect of directly transporting to N2B makes intranasal benzodiazepines very useful for handling seizures in emergencies outside of hospitals.

In addition to quick treatments, researchers have looked into using tiny carriers to deliver seizure medications through the nose over a long time. This method aims to better target the brain and lessen side effects on the rest of the body. Nanoparticulate formulations of valproic acid (VPA) given through the nose have shown better absorption in the brain and lower exposure in the rest of the body compared to taking it by mouth. This helps to tackle the issue of VPA attaching to plasma proteins when it is given systemically [36]. A clinical trial (NCT05886205) is currently taking

place to test the use of nasal delivery for treating refractory focal epilepsy.

### 6.4 Brain Tumors

Primary brain tumors, especially glioblastoma multiforme (GBM), have a very poor outlook and are well-known for being hard to treat with standard chemotherapy. This is mainly because of the blood-brain barrier and the tumors' natural resistance to drugs. The intranasal method has been looked into as a way to directly deliver chemotherapy and immunotherapy drugs to the brain. Giving curcumin nanoparticles through the nose has been found to help reduce inflammation in the brain and lessen neurological problems in mice that have experienced bleeding in the brain [5]. Self-assembled nanomicelles that have been changed with peptides targeting brain tumors are used to deliver siRNA to glioma cells through intranasal administration. This method has shown to successfully treat glioma in preclinical models [1].

Nanomicelles wrapped in hyaluronan for delivering siRNA have shown better transport and effectiveness in treating glioma, leading to notable survival improvements in rodent models of glioma [1]. The ability to send immunotherapy drugs, viruses that attack cancer, and gene-editing tools straight to glioma cells through the nose introduces an exciting new area in the study of brain tumors.

### 6.5 Depression and Psychiatric Disorders

Major depressive disorder, anxiety disorders, and schizophrenia create a significant burden on society and are not effectively treated in many patients. This is partly because many medications do not reach the central nervous system well enough. The intranasal method has specific benefits for delivering psychotropic medications because it avoids the blood-brain barrier and allows the medicine to work quickly, which is very important for antidepressants and anxiety medications. Health authorities for treating depression that does not respond to other treatments have approved intranasal esketamine (Spravato), which is a form of ketamine. It is the first nasal spray medication that works directly on the central nervous system to be commonly used in medical practice.

Recent progress in using tiny particles that can be sprayed into the nose for mental health issues includes systems made from haloperidol, risperidone, and new types of antidepressants. Kisku and others looked at new advancements in using intranasal nanomedicine for mental health conditions. They pointed out that there have been important improvements in how well drugs reach the brain and how effective they are across different types of medications [5]. Solid lipid nanoparticles designed for delivering schizophrenia medication directly to the brain have shown that they can release the drug steadily over time and have better drug movement in the body compared to traditional forms of medication [5].

**Table no. 5**

| Disease | Drug | Carrier System | Outcome | Study Type |
|---|---|---|---|---|
| **Alzheimer's** | Huperzine A | Nanoparticles | Improved cognition, reduced amyloid | Preclinical |
| **Alzheimer's** | Insulin | Intranasal solution | Improved memory | Clinical |
| **Parkinson's** | Baicalein | PEG-PLA micelles | Neuroprotection | Preclinical |
| **Parkinson's** | GDNF gene | DNA nanoparticles | Increased neuron survival | Preclinical |
| **Epilepsy** | Midazolam | Intranasal spray | Rapid seizure control | Approved |
| **Epilepsy** | Valproic acid | Nanoparticles | Increased brain uptake | Preclinical |
| **Brain Tumor** | siRNA | Nanomicelles | Tumor suppression | Preclinical |

| | | | | |
|---|---|---|---|---|
| **Depression** | Esketamine | Intranasal spray | Rapid antidepressant effect | Approved |

## 7. CHALLENGES AND LIMITATIONS OF NOSE-TO-BRAIN DELIVERY

### 7.1 Mucociliary Clearance

The biggest physical challenge to getting N2B drugs to work well is mucociliary clearance (MCC). The inside of the nose is lined with a steady layer of mucus that is produced by goblet cells and glands located beneath the surface. This mucus helps catch particles and germs that are breathed in. Mucociliary clearance moves mucus—and any drugs or tiny particles trapped in it—towards the back of the throat at speeds of 5–15 mm per minute. This leads to the quick removal of the drug that has settled in the nose, with an average time for half of it to clear being around 15–20 minutes. This greatly limits the time that drugs can be absorbed through the nose and reduces how well regular nasal medications work.

### 7.2 Enzymatic Degradation

The lining of the nose has many different types of enzymes that help with metabolism. These include cytochrome P450 enzymes, monoamine oxidases, proteases, and peptidases. These enzymes can break down drug molecules, especially peptides and proteins, before they can be absorbed into the body. Nanoencapsulation offers some protection against the breakdown of drugs by keeping them safely within a layer made of polymers or lipids. However, the other ingredients used in the formulation must also be safe and not harmful to the cells in the nasal lining. Using it many times can lead to itching in the nose, nosebleeds, changes or loss in the sense of smell, sinus infections, and damage to the lining of the nose [4].

### 7.3 Limited Nasal Volume and Dose

The highest amount that can be put into one nostril at a time is about 100 to 200 microliters without it spilling out or being sucked back in. This limits the total amount of medicine that can be given through the nose at one time, creating difficulties for medications that need a large dose to work effectively. It is important to come up with ways to increase how much medicine can be packed into a product and to make sure it releases slowly over time.

### 7.4 Variability in Nasal Deposition

The effectiveness of how drugs are delivered to the olfactory area, which is important for direct N2B transport, can change a lot based on the design of the delivery device, the way the spray is shaped, the size of the particles, the anatomy of the patient, and how congested their nose is. Traditional nasal spray devices mainly deliver the medicine to the front part of the nose and the breathing area instead of reaching the back part of the nose where the sense of smell is located. New delivery devices, like bidirectional systems (such as Optinose) and sprays that work when you breathe, have been created to enhance how medicines are delivered to the sense of smell.

**Table no. 6**

| Challenge | Description | Impact on Drug Delivery |
|---|---|---|
| **Mucociliary clearance** | Rapid removal of drug | Reduced residence time |
| **Enzymatic degradation** | Metabolism in nasal mucosa | Drug loss before absorption |
| **Limited dose volume** | Small nasal capacity | Restricts drug amount |
| **Deposition variability** | Device/patient differences | Inconsistent delivery |

## 8. RECENT ADVANCES AND FUTURE DIRECTIONS

### 8.1 Cell-Penetrating Peptides and Surface Functionalization

Cell-penetrating peptides (CPPs) are short chains of amino acids that have both water-loving and water-repelling parts. They can cross cell membranes and help deliver attached substances inside cells. When CPPs are used to modify the surfaces of nanoparticles, they can significantly improve how well olfactory neurons take them in and help with the transport along the axons to the olfactory bulb. In the same way, attaching targeting molecules like wheat germ agglutinin, transferrin, and RVG peptide to the surface has been found to enhance the accuracy of uptake by nerve cells and the backward transport of signals in early studies.

### 8.2 Exosome-Based and Bioinspired Delivery

Exosomes and other types of extracellular vesicles have gained a lot of attention in research as new drug carriers because of their natural biological background. They can easily pass through the blood-brain barrier (BBB) and have the ability to transport nucleic acids, proteins, and small molecules to the central nervous system (CNS). Exosomes from plants, like those from Pueraria lobata, have shown a great ability to pass through cell membranes and endosomes, effectively delivering large biological molecules inside cells. They also provide extra protection for mitochondria in models of Parkinson's disease. Engineered exosomes that are tagged with targeting ligands (like DSPE-PEG-RVG) show better cellular absorption and greater concentration in the brain.

### 8.3 Stimuli-Responsive Systems

Nanoparticle and gel systems that react to certain triggers like pH, temperature, redox potential, or enzyme activity can release drug payloads. This means they can potentially control when and where drugs are released in the nasal cavity or brain tissue. Gels that change from liquid to gel at body temperature can stay in the nose longer. Coatings made from special polymers can be designed to break down at the slightly acidic pH found in the nasal lining, allowing the drug to be released right where it needs to be absorbed.

### 8.4 Clinical Translation Status

The area of N2B drug delivery is moving forward to be used in clinical settings. There are over 130 clinical trials underway that are testing intranasal neurotherapeutic treatments in different stages, including Phase 1, Phase 2, and Phase 3 [26]. Some important achievements are intranasal midazolam (Nayzilam) and diazepam (Valtoco) used for treating groups of seizures, intranasal esketamine (Spravato) for depression that doesn't improve with other treatments, and intranasal naloxone (Narcan) for helping with opioid overdoses. There are hopeful tests happening for Alzheimer's disease (AD) using treatments like nasal insulin, exosomes, and antibody pieces. For Parkinson's disease (PD), they are looking at nasal glutathione and a combination of levodopa and carbidopa. There are also studies for treating brain tumors [36]. Creating standard pharmacokinetic models, testing them in lab nasal models, and having clear rules for N2B products will be very important for speeding up progress in this area.

## 9. CONCLUSION

Nose-to-brain drug delivery is one of the most exciting areas in treating conditions of the central nervous system. It provides a non-invasive, easy approach for patients and is based on solid scientific principles. This method allows drugs to

bypass the blood-brain barrier and deliver them directly to the brain. The direct connections in the body from the olfactory and trigeminal nerves, along with new improvements in nanocarrier technology, have made it possible to create a variety of intranasal products. These include lipid nanoparticles, polymeric nanoparticles, nanoemulsions, liposomes, exosomes, and muco-adhesive gels. These products greatly improve how well drugs can reach the central nervous system compared to traditional formulations.

Many strong studies before clinical trials show that these systems work well for a wide range of central nervous system disorders, such as Alzheimer's disease, Parkinson's disease, epilepsy, brain tumors, and mental health issues. Many products have either received approval from regulators or are in the later stages of clinical trials, highlighting the promising potential of this area. Still, there are important challenges to address, such as how well mucus moves out of the airways, the breakdown by enzymes, the small amount of space in the nose, differences in how medicine settles in the nose, and the safety of using nasal sprays repeatedly over a long time.

Future improvements in delivery systems inspired by biology, especially those using exosomes and specially designed cell-penetrating peptides, along with smart formulations that respond to stimuli and better devices for targeting the sense of smell, are likely to boost the clinical potential of delivering the N2B drug. To better understand how the nose works, how drugs interact with the nasal lining, and how nerve cells related to smell transport substances, we need strong models that connect lab results to real-life outcomes and simpler ways to navigate regulations. This knowledge is crucial for quickly turning promising N2B treatments into safe and effective therapies for the significant medical needs in brain and nervous system disorders.

## 10. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this review article.

## 11. ACKNOWLEDGMENT

The authors are grateful to their respective institution/department for providing the necessary facilities and support to complete this review work.

## REFERENCES

1. Tang L, Zhang R, Wang Y, Zhang X, Yang Y, Zhao B, Yang L. A simple self-assembly nanomicelle based on brain tumor-targeting peptide-mediated siRNA delivery for glioma immunotherapy via intranasal administration. Acta Biomaterialia. 2023 Jan 1;155:521-37.doi:10.1016/j.actbio.2022.11.013
2. Awad R, Avital A, Sosnik A. Polymeric nanocarriers for nose-to-brain drug delivery in neurodegenerative diseases and neurodevelopmental disorders. Acta Pharmaceutica Sinica B. 2023 May 1;13(5):1866-86.doi:10.1016/j.apsb.2022.07.003
3. Drath I, Richter F, Feja M. Nose-to-brain drug delivery: from bench to bedside. Translational neurodegeneration. 2025 May 19;14(1):23. doi: 10.1186/s40035-025-00481-w
4. Zhang X, Wang M, Liu Z, Wang Y, Chen L, Guo J, Zhang W, Zhang Y, Yu C, Bie T, Yu Y. Transnasal-brain delivery of nanomedicines for neurodegenerative diseases. Frontiers in Drug Delivery. 2023 Aug 11;3:1247162.doi: 10.3389/fddev.2023.1247162

5. Kisku A, Nishad A, Agrawal S, Paliwal R, Datusalia AK, Gupta G, Singh SK, Dua K, Sulakhiya K. Recent developments in intranasal drug delivery of nanomedicines for the treatment of neuropsychiatric disorders. Frontiers in Medicine. 2024 Sep 19;11:1463976. doi:10.3389/fmed.2024.1463976
6. Thorne RG, Pronk GJ, Padmanabhan V, Frey WH 2nd. 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. doi:10.1016/j.neuroscience.2004.05.029
7. Illum L. Transport of drugs from the nasal cavity to the central nervous system. European journal of pharmaceutical sciences. 2000 Jul 1;11(1):1-8. doi:10.1016/s0928-0987(00)00087-7
8. Prego C, Garcia M, Torres D, Alonso MJ. Transmucosal macromolecular drug delivery. Journal of Controlled Release. 2005 Jan 3;101(1-3):151-62. doi:10.1016/j.jconrel.2004.07.030
9. Talegaonkar S, Mishra PR. Intranasal delivery: an approach to bypass the blood brain barrier. Indian J Pharmacol. 2004;36(3):140-147.
10. Daneman R, Prat A. The blood–brain barrier. Cold Spring Harbor perspectives in biology. 2015 Jan 1;7(1):a020412. doi:10.1101/cshperspect.a020412
11. Pardridge WM. Drug transport across the blood–brain barrier. Journal of cerebral blood flow & metabolism. 2012 Nov;32(11):1959-72.doi:10.1038/jcbfm.2012.126
12. Abbott NJ, Khan EU, Rollinson CM, Reichel A, Janigro D, Dombrowski SM, Dobbie MS, Begley DJ. Drug resistance in epilepsy: the role of the blood–brain barrier. InMechanisms of Drug Resistance in Epilepsy: Novartis Foundation Symposium 243 2002 Mar 25 (Vol. 243, pp. 38-53). Chichester, UK: John Wiley & Sons, Ltd. doi: 10.1002/0470846356.ch4
13. Ding S, Khan AI, Cai X, Song Y, Lyu Z, Du D, Dutta P, Lin Y. Overcoming blood–brain barrier transport: Advances in nanoparticle-based drug delivery strategies. Materials today. 2020 Jul 1;37:112-25. doi: 10.1016/j.mattod.2020.02.001
14. Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview. Therapeutic delivery. 2014 Jun 1;5(6):709-33. doi:10.4155/tde.14.41
15. Nazar H, Fatouros DG, Van Der Merwe SM, Bouropoulos N, Avgouropoulos G, Tsibouklis J, Roldo M. Thermosensitive hydrogels for nasal drug delivery: the formulation and characterisation of systems based on N-trimethyl chitosan chloride. European Journal of Pharmaceutics and Biopharmaceutics. 2011 Feb 1;77(2):225-32. doi: 10.1016/j.ejpb.2010.11.022
16. Formica ML, Real DA, Picchio ML, Catlin E, Donnelly RF, Paredes AJ. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. Applied Materials Today. 2022 Dec 1;29:101631. doi:10.1016/j.apmt.2022.101631
17. Kabanov AV, Gendelman HE. Nanomedicine in the diagnosis and therapy of neurodegenerative disorders. Progress in polymer science. 2007 Aug 1;32(8-9):1054-82 .doi:10.1016/j.progpolymsci.2007.05.014
18. Wen Z, Yan Z, Hu K, Pang Z, Cheng X, Guo L, Zhang Q, Jiang X, Fang L, Lai R. Odorranalectin-conjugated nanoparticles: preparation, brain delivery and pharmacodynamic study on Parkinson's disease following intranasal administration.

Journal of controlled release. 2011 Apr 30;151(2):131-8. doi:10.1016/j.jconrel.2011.02.022

19. Shen W, You T, Xu W, Xie Y, Wang Y, Cui M. Rapid and widespread distribution of intranasal small extracellular vesicles derived from mesenchymal stem cells throughout the brain potentially via the perivascular pathway. Pharmaceutics. 2023 Nov 3;15(11):2578.doi:10.3390/pharmaceutics15112578
20. Zhuang X, Xiang X, Grizzle W, Sun D, Zhang S, Axtell RC, Ju S, Mu J, Zhang L, Steinman L, Miller D. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. Molecular Therapy. 2011 Oct 1;19(10):1769-79. doi:10.1038/mt.2011.164
21. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Advanced drug delivery reviews. 2012 May 15;64(7):614-28. doi:10.1016/j.addr.2011.11.002
22. Agosti E, Zeppieri M, Antonietti S, Battaglia L, Ius T, Gagliano C, Fontanella MM, Panciani PP. Navigating the nose-to-brain route: a systematic review on lipid-based nanocarriers for central nervous system disorders. Pharmaceutics. 2024 Feb 27;16(3):329. doi: 10.3390/pharmaceutics16030329
23. Bhattacharyya M, Kalra V, Gulati S. Intranasal Midazolam vs Rectal Diazepam in Acute Childhood Seizures. Pediatric Neurology. 2006 May;34(5):355–9.doi:10.1016/j.pediatrneurol.2005.09.006
24. Daly EJ, Singh JB, Fedgus M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2018;75(2):139-148. doi:10.1001/jamapsychiatry.2017.3739
25. Krieter P, Chiang N, Gyaw S, Skolnick P, Crystal R, Keegan F, Aker J, Beck M, Harris J. Pharmacokinetic properties and human use characteristics of an FDA-approved intranasal naloxone product for the treatment of opioid overdose. The Journal of Clinical Pharmacology. 2016 Oct;56(10):1243-53.doi:10.1002/jcph.759
26. Huang Q, Chen Y, Zhang W, Xia X, Li H, Qin M, Gao H. Nanotechnology for enhanced nose-to-brain drug delivery in treating neurological diseases. Journal of controlled release. 2024 Feb 1;366:519-34. doi:10.1016/j.jconrel.2023.12.054
27. Kozlovskaya L, Abou-Kaoud M, Stepensky D. Quantitative analysis of drug delivery to the brain via nasal route. Journal of controlled release. 2014 Sep 10;189:133-40.doi:10.1016/j.jconrel.2014.06.053
28. Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: how, why and what for?. Journal of Pharmacy & Pharmaceutical Sciences. 2009 Oct 12;12(3):288-311.doi:10.18433/j3nc79
29. Williams G, Suman JD. In vitro anatomical models for nasal drug delivery. Pharmaceutics. 2022 Jun 26;14(7):1353.. doi:10.3390/pharmaceutics14071353
30. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate SR, Green PS. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Archives of neurology. 2012 Jan 9;69(1):29-38.doi:10.1001/archneurol.2011.233
31. Du L, Chen L, Liu F, Wang W, Huang H. Nose-to-brain drug delivery for the treatment of CNS disease: New development and strategies. International review of neurobiology. 2023 Jan 1;171:255-97.doi:10.1016/bs.irn.2023.05.014

32. Rajput A, Pingale P, Dhapte-Pawar V. Nasal delivery of neurotherapeutics via nanocarriers: Facets, aspects, and prospects. Frontiers in pharmacology. 2022 Sep 13;13:979682.doi:10.3389/fphar.2022.979682
33. Kurano T, Kanazawa T, Ooba A, Masuyama Y, Maruhana N, Yamada M, Iioka S, Ibaraki H, Kosuge Y, Kondo H, Suzuki T. Nose-to-brain/spinal cord delivery kinetics of liposomes with different surface properties. Journal of Controlled Release. 2022 Apr 1;344:225-34.doi:10.1016/j.jconrel.2022.03.017
34. Zheng Y, Cui L, Lu H, Liu Z, Zhai Z, Wang H, Shao L, Lu Z, Song X, Zhang Y. Nose to brain: exploring the progress of intranasal delivery of solid lipid nanoparticles and nanostructured lipid carriers. International journal of nanomedicine. 2024 Dec 31:12343-68. doi:10.2147/IJN.S497480
35. Dighe S, Jog S, Momin M, Sawarkar S, Omri A. Intranasal drug delivery by nanotechnology: advances in and challenges for Alzheimer's disease management. Pharmaceutics. 2023 Dec 29;16(1):58.doi:10.3390/pharmaceutics16010058
36. Chen Y, Zhang C, Huang Y, Ma Y, Song Q, Chen H, Jiang G, Gao X. Intranasal drug delivery: The interaction between nanoparticles and the nose-to-brain pathway. Advanced drug delivery reviews. 2024 Apr 1;207:115196. doi:10.1016/j.addr.2024.115196
37. Liu Y, Tan Y, Cheng G, Ni Y, Xie A, Zhu X, Yin C, Zhang Y, Chen T. Customized intranasal hydrogel delivering methylene blue ameliorates cognitive dysfunction against Alzheimer's disease. Advanced Materials. 2024 May;36(19):2307081.doi:10.1002/adma.202307081
38. Saha P, Kathuria H, Pandey MM. Intranasal nanotherapeutics for brain targeting and clinical studies in Parkinson's disease. Journal of Controlled Release. 2023 Jun 1;358:293-318. doi:10.1016/j.jconrel.2023.04.021

HOW TO CITE: Paramveer Dutt, Charanpreet Singh, Jasmeen Kaur, Kiranjeet Kaur, Shivani Kumari, Nose-to-Brain Drug Delivery Systems for Central Nervous System Disorders: Mechanisms, Formulation Strategies, and Therapeutic Applications, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 1500-1517. https://doi.org/10.5281/zenodo.20567077