

Optimizing neurological treatments with nasal drug delivery systems

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Abstract

The treatment of neurodegenerative diseases and central nervous system disorders is challenging due to the blood-brain barrier (BBB), which restricts the penetration of therapeutic molecules to the brain. Nasal Drug delivery system leverages the unique anatomy of the nasal cavity, allowing for direct access to the brain, bypassing the blood-brain barrier. This, combined with hepatic metabolism and drug elimination, reduces treatment efficacy, requires high doses, and often induces side effects. Nose-to-brain drug delivery bypasses the BBB, increasing drug concentration in the brain. The present review highlights the Mechanisms of Nasal Drug Delivery to the Brain, Advantages and disadvantages of Nasal Drug Delivery to the Brain, Nasal Drug Delivery Devices and recent studies on nose-to-brain drug delivery

Keywords: Nasal delivery; Brain-targeting; Neurogenerative disorders; CNS disorders

1. Introduction

The increasing incidence of brain diseases like Alzheimer's, Parkinson's, stroke, and brain tumours has led to increased research for better therapeutic strategies. However, the blood-brain barrier (BBB) is a significant obstacle in developing new drugs for these diseases. The BBB is a complex multicellular structure with low permeability, limiting the movement of molecules between the blood and the neural tissues of the central nervous system (CNS). The tight junctions of the BBB and the presence of efflux transporters and metabolic enzymes limit the entry of approximately 98% of chemical drugs and nearly 100% of macromolecular drugs into the brain when administered orally or via injection. This bottleneck negatively impacts drug delivery in the CNS. Nasal administration, a systemic route of administration, has led to increased research interest in intranasal drug delivery methods. Studies have shown that some drugs can be administered intranasally, bypassing the BBB to facilitate drug entry into the brain, providing a promising approach to brain-targeted drug delivery. This approach aims to overcome the limitations imposed by the BBB and improve the effectiveness of brain-targeted drug delivery [1].

2. Mechanisms of Nasal Drug Delivery to the Brain

For the purposes of drug delivery, the nasal cavity is divided into the respiratory area and the olfactory area, with the latter situated high up in the nares and the former closer to the nostrils. The nasal epithelium is well vascularized, and, within the olfactory area, olfactory neurons are exposed, enabling the transport of drug compounds directly into the brain via the olfactory neurons. It is known that absorption of molecules takes place at the olfactory and respiratory epithelia. The routes of compound transfer through the olfactory area, of the nares, to the olfactory bulb are transcellular through either the sustentacular cells or the exposed olfactory sensory neurons. The route of transfer of compounds through the nasal respiratory epithelium to the brain is via the trigeminal nerves. Transport to other brain areas after entry to the brain (e.g., to the mid brain from the olfactory bulb or to the brain stem from the trigeminal nerve) is thought to be mainly either by extracellular convective bulk flow or via perivascular routes. The paracellular route is not thought

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to be significant. Intranasally dosed nanoparticles have been observed in the olfactory bulb just 5 minutes after dosing, indicating this to be the route of entry for nanoparticle delivery systems. Drug compounds, having crossed the olfactory epithelium, may also be taken up into the general circulation via the nasal vasculature; however, the nasal vasculature is devoid of fenestrations and expresses the tight junction proteins; thus, significant transport to the general circulation via this route will be limited to low molecular weight apolar compounds. A key advantage of the nose-to-brain route is the possibility of reducing plasma exposure, as has been demonstrated, thus eliminating peripheral side effects. The average volume of the human nasal cavity has been measured using magnetic resonance imaging as $16,449.81 \pm 4288.42$ mm³, with the area of the nostril opening being 357.83 ± 108.09 mm². Nostril opening correlates positively with nasal cavity volume. [2,3]

3. Advantages of the nasal-brain drug delivery system

The advantages of nasal-brain drug delivery compared to other existing drug administration routes were largely considered in pharmacological and clinical applications. [4]

- The nasal-brain drug delivery route is a short and simple method that bypasses the blood-brain barrier (BBB) and enables direct drug delivery to the brain through the olfactory nerve. This route improves bioavailability in the brain by avoiding extensive metabolism and drug loss through the gastrointestinal tract or systemic circulation. This approach maintains therapeutic drug concentrations in the brain while minimizing clinically required doses, allowing targeted delivery with reduced side effects in the periphery. Rapid drug delivery to the brain and the expression of drug effects are also possible. Intranasal drug administration is a viable, non-invasive strategy for delivering drugs to the brain, and nasal drug administration is often considered the most feasible alternative to parenteral injections due to its high permeability and fast drug absorption rate, similar to IV injections. This route has been suggested as a viable, non-invasive strategy for delivering drugs to the brain.
- The nasal-brain drug delivery route is gaining attention due to its higher permeability compared to the blood-brain barrier (BBB). This route is particularly effective for delivering peptides and protein drugs, which are difficult to deliver through systemic circulation. The nasal cavity has also been proposed as a route for delivering biological substances, such as oligonucleotides, viral vectors, and stem cells, to the cranial nervous system. For example, calcitonin, a polypeptide hormone, is being used as a nasal spray for postmenopausal osteoporosis treatment. Insulin, reaching 5800 Da, was widely distributed to the brain within 1 hour of intranasal administration to mice. Galanin-like peptide, a neuropeptide of 6500 Da, was distributed to the cranial nervous system, with levels 20 times higher than intravenously. These results suggest that the nasal-brain pathway can deliver substances with high permeability to the brain.
- Drugs with hydrophilicity, hydrophobicity, and ionicity properties can be effectively delivered from the nasal cavity to the brain through proper formulation. Examples include cationic peptides, basic fibroblast growth factor, cationic lipid nanoemulsions, and nanoparticles. Hydrophilic drugs can be administered intranasally through solubilization, while hydrophobic drugs can be easily delivered through nanoformulations and prodrug formulations.
- Nasal-brain drug delivery is beneficial for reducing toxicity due to excessive exposure to drug metabolites. Intranasal drug administration increases parent drug transport to the brain and decreases exposure to metabolites in both plasma and brain compared to oral administration. This decrease is likely due to the avoidance of first-pass metabolism compared to oral and IV routes.
- Nasal-brain drug delivery could be a promising treatment for complex diseases, such as brain tumors, which directly affect the olfactory nerve, often leading to a loss of smell. This route delivers drugs to olfactory cells, allowing for the treatment of brain tumors and olfactory damage. Combining anti-inflammatory drugs or neurostimulating drugs to improve smell with anticancer drugs could lead to a therapeutic effect. Previous studies have reported that intranasal drug delivery leads to drug delivery to the olfactory bulb, a crucial part of the olfactory nervous system.
- Improved formulations can enable controlled drug release from the nasal cavity to the brain. Polymers like pluronic F-127 have a mechanism for drug dissolution and diffusion, depending on their concentration. Increasing concentrations decrease drug release rate. Controlled release applications in the nasal mucosa offer advantages like faster on/off and higher delivery rates for drugs that maintain a certain concentration in the cranial nervous system for extended periods.
- The nasal-brain route is a non-invasive method of drug delivery that is simple and painless, making it easy to apply in clinical practice. It allows for sustained drug release from the nasal mucosa to the brain, reducing the number of doses and reducing the amount of drug administered per dose. This method also offers an alternative to oral drug delivery, making it useful for patients with gastrointestinal problems or those with difficulty

swallowing tablets. Rapid drug delivery through the nasal-brain route is also useful in emergencies like seizures and acute pain, requiring rapid drug action. Formulation improvements could lead to sustained drug release, improved patient adherence, and cost savings.

4. Disadvantages of the nasal-brain drug delivery system

While nasal drug delivery systems offer many advantages, there are also several disadvantages and challenges associated with this method:[5]

- Intranasal drug administration is generally limited in dosage compared to other routes, with small volumes compared to the skin, gastrointestinal tract, and blood vessels. This is supported by the low administrable volumes in the nasal cavity of 25-200 μL . Excessive drug administration can cause the nasal cavity to be easily saturated, increasing drug transport into the systemic circulation and potentially causing side effects.
- Intranasal drug administration can cause swallowing or drainage, leading to variability in drug delivery to the brain. Factors such as administration angle and respiration level can affect nasal deposition efficiency. In nasal spray administration, device plume angle and administration angle are major factors affecting efficiency. Intranasal injections or spray administrations offer effectiveness in delivering drugs to the brain, avoiding the first-pass effect, and providing a quick effect. However, accurate usage and dosage settings remain challenges, as nasally administered solutions and sprays may flow downward and the drug may not stay in the desired nasal cavity area.
- Formulation limitations in drug delivery from the nasal cavity to the brain can be addressed by ensuring stability and minimizing external stresses. Hydrophilic drugs have limited absorption into the cranial nervous system through paracellular or transcellular mechanisms. Therefore, methods like permeation enhancers and nanocarrier formulations are essential for high hydrophilicity drugs, as they can help improve drug concentration and stability.
- Intranasal drug delivery to the brain can be challenging due to nasal cavity diseases and rapid airflow. Direct administration to the site is difficult, and the drug may disappear rapidly due to physical clearance and mucosal ciliary effects. Therefore, nasal mucoadhesives should be considered essential in drug formulation to address these limitations.
- Four major routes for drug delivery from the nasal cavity to the brain are olfactory, respiratory, systemic via BBB, and NALT. These routes can deliver drugs directly or indirectly to the brain. However, the intranasal sites for these routes differ, making drug delivery dependent on the site of administration. A mucoadhesive formulation method may be an effective alternative to overcome this site-dependent drug delivery problem.
- The cranial nervous system is a complex system with no clear pathogenesis or key causes of most cranial nervous-related diseases. Studying these factors and mechanisms is crucial for developing targeted technology for specific areas within the brain nervous system. This will increase drug delivery from the nasal cavity to the brain and minimize side effects by allowing the drug to act only on a specific target within the brain nervous system.
- Frequent and continuous intranasal drug administration can cause irritation and damage to the nasal cavity and brain, potentially causing toxicity to the olfactory nervous system. The continuous use of a permeation enhancer, which promotes formulation permeation, may increase the influx of external pathogens and cause cell transformation. Additionally, components of mucoadhesive applied to the nasal mucosa can cause toxicity to the mucociliary system by long-term retention. While no life-threatening side effects were reported in preclinical and clinical studies of nasal-brain drug delivery, most were the results of single or short-term exposure to the formulations. For example, a hydrogel composed of pluronic F-127 and poloxamer 188 administered as a nasal mucosal adhesive maintained without mucociliary toxicity for 14 days after application. However, since most drugs for long-term use require long-term application, sub-chronic or chronic toxicity and long-term safety evaluation of the formulations are essential.
- Direct drug delivery from the nasal cavity to the brain can cause fatal systemic side effects, potentially disrupting the immune system and causing drug toxicity. To minimize side effects and maximize therapeutic effects, formulation and pharmacometrics studies are necessary. However, nasal-brain drug delivery studies are challenging due to lack of mechanistic clarity and uncertainties about the degree of delivery. Factors like formulation characteristics, administration methods, and physiological variability between individuals can greatly vary the degree of drug delivery. To apply nasal-brain drug delivery clinically for specific drugs, numerous issues need to be resolved, including sufficient verification and confirmation of the safety and effectiveness of nasal-brain drug delivery agents.

5. Nasal Drug Delivery Devices

Efficient nasal drug delivery devices are crucial for improving diagnosis and treatment effectiveness. These devices, including droppers, syringes, pressurized meter dose inhalers, Breathe Powered Bi-directional nasal devices, and pressurized olfactory delivery devices, are used in clinical treatment. The right delivery system depends on the drug formulation type. Powder formulations with high stability often stick to the nasal mucosa before clearing, while liquid formulations are the oldest, cheapest, and simplest method. Popular nasal sprays spread easily and deposit in the olfactory region, but their limitations depend on self-administration techniques.

5.1. Powder Devices

Powder particles are stable and resistant to dissolved substances, allowing them to remain in the nasal mucosa for extended periods. They also have free preservatives, allowing for large dose administration and preventing microbial contamination.

- An insufflator composed of straw or tube with drugs could directly deliver drugs to the olfactory region, although usually local anaesthetics or decongestants are needed before insufflations delivery. Direct Haler, a Danish device designed to deliver fine particles into the nasal cavity, is a popular method for drug delivery from the nose to the brain. It is free from contamination, preservatives, priming, and cleaning. The device targets the nasal valve, using smaller powder particles below 5 μ for olfactory absorption. Bi-Directional technology uses the body's normal breath processes to deliver drugs in liquid or powder form on the nasal epithelium. Optinose, a biopharmaceutical company, proposed closed-palate Bi-Directional™ Breath Powered® DDSs, which use an exhale device to target the drug beyond the nasal valve. Optinose's device has been used to treat patients on the autism spectrum, but a higher dose can lead to adverse effects. A randomized four-way crossover trial using a breath-powered optinose device showed that lower doses are more efficacious than higher doses in producing a cognitive response.
- Dry powder inhalers (DPI) deliver small doses of drug particles to the nasal cavity, such as Teijin Puvlizer Rhinocort®, Rhinocort Turbohaler®, Rhinocort Puvlizer®, and Erizas®. These simple, cheap, and easy-to-operate inhalers are used for treating rhinitis, with doses ranging from μ g to mg. They can be operated without medical supervision.
- Bepak developed Unidose-DP™, a sealed container for delivering a single shot of a drug, with 95% reaching the nasal cavity and 60-70% reaching the nasal vestibular region. SoluVent™ is a powder delivery device that forces the powder to the nasal cavity, used for delivering vaccines. Shin Nippon Biomedical Laboratories designed the μ co™ System for drug absorption and decreased dose requirement, based on a mucoadhesive powder drug carrier. This technology increased drug absorption, decreased doses, and provided high activity and long contact time, enhancing safety in clinical treatment.

5.2. Liquid-Based Devices

Liquid based devices used for intranasal delivery includes following

- Catheter-delivered drugs are a simple method of drug delivery to the nasal cavity, typically accompanied by anesthesia or a sedative. However, mucosa sensitivity makes this method challenging. The solution is filled in the catheter and enters the nostril through blowing with the mouth, causing a major issue.
- Drops and spray pumps are common methods for nasal drug delivery due to their cost-effectiveness and ease of manufacture. However, they pose risks of microbial contamination and chemical instability. Glass droppers are used for single dose drug delivery, while spray pumps provide multidose administration. Despite their cost, spray pumps are often replaced by disposable pipettes in clinical treatment, particularly for nasal decongestion and irrigation purposes.

6. Recent studies on nose-to-brain drug delivery

- **Alzheimer's Disease:** Neurodegenerative diseases, such as Alzheimer's, are irreversible due to the loss of neuronal structure and function. Intranasal delivery has shown efficacy in treating Alzheimer's, with insulin showing greater memory improvement in patients than in healthy individuals. Animal studies have shown that pro-resolving lipid mediators can slow the pathogenesis of the disease. A novel peptide can reduce amyloid beta plaques and enhance cognitive functions. Intranasal delivery of anti-Alzheimer's drug has shown higher bioavailability compared to oral tablets. A study on PEG-PLA nanoparticles loaded with miR132 showed increased expression and improved memory function in mice. To enhance the effectiveness of intranasal

delivery, studies are being conducted to develop permeation enhancers to improve drug transport across the blood-brain barrier.[7]

- **Glioblastoma:** Glioblastoma is a rapidly growing and deadly brain tumor caused by astrocyte mutation. The main cause is unknown, but it originates in the frontal and temporal lobes. Current therapeutics aim to initiate tumor cell apoptosis without causing toxic effects on healthy brain tissue. Nanoparticles loaded with chemotherapeutics, delivered through intranasal routes, have shown promising results in treating glioblastoma. PLGA-based nanoparticles loaded with paclitaxel or doxorubicin targeted the glioblastoma microenvironment, reducing tumor volume through cell death. MicroRNA-21 inhibits pro-apoptotic genes, increasing glioblastoma progression. Self-assembling nanoparticles with anti-tumor peptides reduced miR-21 levels, increasing tumor cell apoptosis.[8]
- **Epilepsy:** Seizures, epilepsy, and neurotransmitter imbalances can cause sudden bursts of neuronal activity, leading to abnormal behaviors and mood changes. Intranasal delivery of carbamazepine nanoparticles can increase antiepileptic drug bioavailability. A self-assembling hydrogel with neuroactive drugs is biocompatible, low in toxicity, and has good recovery capacity. Nasal delivery of this gel increased drug concentration in the brain. Oxytocin, a hormone used to alleviate anxiety symptoms in autism, can be efficiently transferred from the nasal cavity to the brain through intranasal administration.[9]
- **Parkinson's Disease:** Parkinson's disease, a neurodegenerative disorder causing balance and coordination issues, muscle stiffness, and tremors, can be improved by intranasal delivery of conjugated mitochondrial systems. Neuroactive drugs in hydrogels increase residence times in the nasal cavity and concentration in the brain. Combining therapeutics with nanocarriers directly transfers drugs to target cells, enhancing accumulation and improving neuronal signalling and locomotion. Intranasal delivery of biodegradable nanoparticles surface-modified with lactoferrin also increases brain accumulation and cellular uptake. [10]
- **Depression:** Characterized by loss of neuroplasticity, depression is a common mood disorder causing persistent negative emotions and changes in lifestyle. Intranasal delivery of relaxin-3 mimetics demonstrated significant anti-depressant activity in behavior paradigms of rat models. Delivering a thermoresponsive hydrogel loaded with berberine intranasally exhibited high bioavailability in hippocampus and anti-depressant activity. [11]
- **Anxiety:** Anxiety disorders are characterized by enduring and excessive fear, and avoidance of perceived threats such as social situations or body sensations. Anxiety can impair hippocampus function which increases risk of depression and dementia. Anxiolytic effects were observed in animal models post-intranasal delivery of a Quercetin loaded polymeric nanocapsules. [12]
- **Anorexia nervosa:** Nutritional rehabilitation in anorexia nervosa is impeded by fear of food, eating and change leading to treatment resistance. Oxytocin exerts prosocial effects and modulates trust, fear, anxiety and neuroplasticity. Intranasal administration of oxytocin enhances nutritional rehabilitation in patients with anorexia nervosa significantly reducing eating concern and cognitive rigidity.[13]
- **Substance use disorder:** Substance use disorder is the uncontrolled and continuous use of substances, such as drugs or alcohol, which can disrupt neuronal signaling and impair thinking, behavior, and biological functions. Insulin delivery improves brain metabolic activities and reduces impulsivity. Opioid addiction is prevalent and leads to substance abuse deaths. A study found high biodistribution in the brain and reduced opioid overdose in rats administered with naloxone-loaded nanoparticles. [14]
- **Post-traumatic stress disorder:** Post-traumatic stress disorder (PTSD) is a mental health condition triggered by experiencing devastating situations. Intranasal administration of temperature-sensitive hydrogels loaded with PTSD medications has shown enhanced brain targeting and tissue distribution, and anti-PTSD effects. [15]
- **Schizophrenia:** Schizophrenia is a chronic mental health condition influenced by brain chemistry and structure, with genetics and environment playing key roles. Impaired gene expression or chemical imbalances may contribute to the disorder. Anxiety increases the risk of schizophrenia, causing hallucinations, speech disorganization, and abnormal behaviour. Davunetide, a segment of activity-dependent neuroprotective protein (ADNP), is downregulated with schizophrenia, and treatment with Davunetide decreases hyperactivity. Daily intranasal NAP treatment significantly decreased hyperactivity and protected visual memory, supporting further clinical development. [16]
- **Migraine:** Migraine, triggered by stress and hormonal changes, can cause intense headache episodes causing nausea and pain. A nasal spray containing sumatriptan has shown significant pain reduction, and further clinical studies on intranasal administration can evaluate its efficacy and safety. [17]

7. Conclusion

Nasal drug delivery systems have the potential to improve neurological treatment by providing a direct, non-invasive route to the brain, enhancing treatment efficacy, reducing side effects, and improving patient outcomes. Further research and innovation are crucial for unlocking this full potential.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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