NOSE-TO-BRAIN DRUG DELIVERY: A REVIEW

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Abstract

The blood-brain barrier (BBB) represents a major challenge in the treatment of neurological disorders by restricting the entry of many therapeutic agents into the central nervous system (CNS). Nose-to-brain drug delivery has emerged as a promising, non-invasive approach to enhance CNS drug delivery by utilizing the olfactory and trigeminal pathways. This route is particularly advantageous for delivering drugs with poor brain penetration, including peptides, proteins, nucleic acids, and other therapeutic molecules. However, its effectiveness is limited by several factors, including mucociliary clearance, enzymatic degradation, short nasal residence time, restricted dose volume, and variable drug deposition. To overcome these limitations, various formulation strategies, including mucoadhesive polymers, permeation enhancers, in situ gels, liposomes, nanoemulsions, polymeric nanoparticles, solid lipid nanoparticles, and dendrimers, have been investigated. These systems may improve drug stability, enhance nasal retention, facilitate absorption, and provide controlled drug release. Nose-to-brain delivery is being explored for the management of several neurological conditions, including Alzheimer's disease, Parkinson's disease, epilepsy, migraine, brain tumors, stroke, and CNS infections. Recent advances in nanotechnology, thermoresponsive formulations, precision nasal delivery devices, and computational approaches have further expanded its potential. Nevertheless, challenges related to formulation safety, reproducible drug deposition, biodistribution, and clinical translation remain. Further pharmacokinetic investigations, long-term safety assessments, and well-designed clinical trials are essential to establish its therapeutic effectiveness. Overall, nose-to-brain drug delivery represents a promising strategy for improving CNS drug targeting and advancing the treatment of neurological disorders.

Keywords: *Nose-to-brain drug delivery, intranasal drug delivery, blood-brain barrier, central nervous system, nanocarriers, nanoparticles, neurological disorders.*

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1. INTRODUCTION

1.1. Central Nervous System Drug Delivery and the Blood-Brain Barrier

The treatment of neurological disorders remains a major challenge because of the restricted entry of therapeutic agents into the central nervous system (CNS). The blood-brain barrier (BBB) is a highly selective neurovascular interface composed of brain microvascular endothelial cells, tight junctions, transport systems, pericytes, astrocytic interactions, and basement membranes. Although the BBB protects the brain from potentially harmful substances and maintains a stable neuronal environment, it also limits the delivery of many therapeutic agents. Hydrophilic drugs, peptides, proteins, and nucleic acids generally exhibit poor BBB permeability and may require specialized transport mechanisms or advanced drug delivery systems. In contrast, certain small, lipophilic molecules can cross the BBB more readily, depending on their physicochemical properties and interactions with transporters (Dhuria et al., 2010; Lochhead and Thorne, 2012; Illum, 2003; Ong et al., 2014; Erd et al., 2018; Kashyap and Shukla, 2019).

1.2. Limitations of Conventional Drug Administration

Conventional routes of drug administration, including oral and parenteral delivery, often result in considerable systemic exposure before therapeutic concentrations are achieved in the brain. Factors such as first-pass metabolism, plasma protein binding, renal clearance, peripheral toxicity, and active efflux transport across the BBB can further reduce the amount of drug reaching the CNS. Consequently, increasing the administered dose does not necessarily improve brain drug concentrations and may increase the risk of adverse effects. These limitations have encouraged the development of alternative delivery approaches that improve CNS drug availability while minimizing unnecessary systemic exposure. Nose-to-brain drug delivery is one such approach, designed to exploit the anatomical connections between the nasal cavity and the brain (Patel and Thakkar, 2022; Mustafa et al., 2016; Falcone et al., 2014; Hanson and Frey, 2008; Thorne et al., 1995; Banks, 2016).

1.3. Concept and Scientific Rationale of Nose-to-Brain Drug Delivery

Nose-to-brain drug delivery refers to the administration of therapeutic agents through the nasal cavity to facilitate their transport to the CNS. This approach primarily involves the olfactory and trigeminal pathways, which provide potential routes for drug transport that may partially bypass the BBB. The olfactory epithelium, located in the upper region of the nasal cavity, is anatomically connected to the olfactory bulb through nerve fibres passing across the cribriform plate. Similarly, branches of the trigeminal nerve innervate the nasal mucosa and provide anatomical connections with different regions of the CNS. Depending on the drug's

physicochemical characteristics, formulation composition, and site of deposition, therapeutic agents may reach the brain through neuronal or perineural pathways. However, some of the administered drug may also enter systemic circulation through the highly vascularized nasal mucosa. Therefore, increased brain exposure following intranasal administration does not necessarily confirm direct nose-to-brain transport (Crowe et al., 2018; Mistry et al., 2009; Born et al., 2002; Djupesland, 2013; Agrawal et al., 2018; Fan et al., 2018).

1.4. Advantages and Potential of Nose-to-Brain Drug Delivery

Nose-to-brain drug delivery offers several potential advantages over conventional administration routes, including non-invasive administration, rapid drug absorption, avoidance of gastrointestinal degradation, and partial avoidance of hepatic first-pass metabolism. It may also improve the delivery of selected therapeutic agents with limited BBB permeability, including peptides, proteins, and other macromolecules. Depending on the formulation and delivery device, intranasal administration may reduce systemic exposure while improving drug availability at the intended site of action. Furthermore, its potential for convenient administration and improved patient compliance makes it an attractive approach for selected neurological conditions. Nevertheless, these benefits depend on formulation characteristics, nasal deposition, drug properties, and device performance. Direct brain targeting, improved therapeutic efficacy, and reduced systemic toxicity must therefore be established through appropriate pharmacokinetic, biodistribution, and safety studies rather than assumed solely from the intranasal route of administration (Kanazawa, 2015; Muntimadugu et al., 2016; Katare et al., 2017; Costa et al., 2019).

2. ANATOMY AND PHYSIOLOGY OF THE NASAL CAVITY

The anatomy and physiology of the nasal cavity play a crucial role in nose-to-brain drug delivery. The nasal cavity provides potential pathways for transporting therapeutic agents to the central nervous system (CNS), primarily through the olfactory and trigeminal nerve systems. However, the efficiency of drug transport depends on nasal anatomy, mucosal characteristics, formulation properties, and the site of drug deposition. Understanding these factors is essential for developing effective intranasal drug delivery systems (Dhuria et al., 2009; Ugwoke et al., 2005; Costantino et al., 2007).

2.1. Nasal Regions

The nasal cavity is broadly divided into the respiratory and olfactory regions, which differ in their anatomical structure and physiological functions. The respiratory region occupies most of the nasal cavity and contains a highly vascularized mucosal surface that supports air

conditioning and systemic drug absorption. Consequently, drugs deposited in this region may enter the bloodstream and subsequently reach the brain through systemic circulation.

In contrast, the olfactory region occupies a relatively small area in the upper nasal cavity but is particularly important for nose-to-brain drug delivery. It contains olfactory sensory neurons that establish anatomical connections with the olfactory bulb, providing a potential pathway for drug transport toward the CNS. The accessibility of this region and the distribution of deposited formulations are important determinants of delivery efficiency. Furthermore, differences in nasal anatomy between experimental animals and humans must be considered when interpreting preclinical findings and predicting clinical performance (Dhuria et al., 2009; Stella and Borchardt, 2007; Ugwoke et al., 2005; Costantino et al., 2007; Mathias and Hussain, 2010).

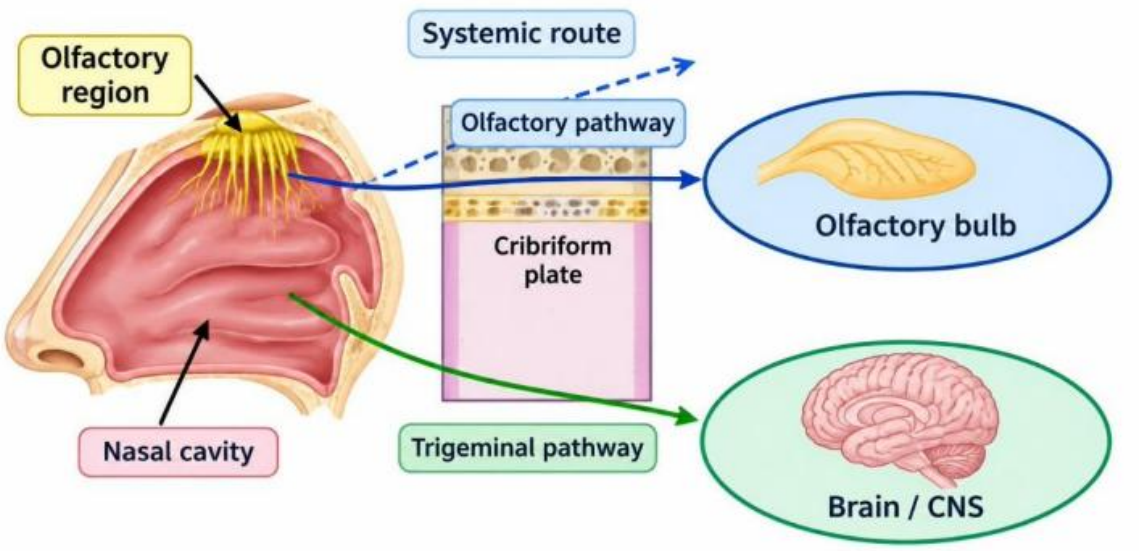


Figure 1: Conceptual anatomical routes discussed in the literature. Direct transport is formulationand deposition-dependent.

2.2. Nasal Mucosa

The nasal mucosa consists of epithelial cells, mucus-secreting glands, ciliated cells, blood vessels, and immune components that protect the respiratory tract from environmental particles and microorganisms. The mucus layer acts as a protective barrier but can also restrict drug diffusion and interaction with the nasal epithelium. Ciliary movement continuously transports mucus toward the nasopharynx, resulting in mucociliary clearance that reduces the residence time of conventional nasal formulations and may limit drug absorption.

Several formulation characteristics influence drug deposition, retention, and absorption across the nasal mucosa, including viscosity, pH, osmolarity, droplet size, and mucoadhesive

properties. Mucoadhesive polymers and in situ gelling systems may prolong nasal residence time and improve contact between the formulation and the mucosal surface. Nevertheless, these systems must be carefully optimized to avoid irritation or interference with normal mucociliary function (Ugwoke et al., 2005; Costantino et al., 2007; Jiang et al., 2010; Inoue et al., 2018; Lombardo et al., 2021).

2.3. Olfactory Epithelium

The olfactory epithelium contains olfactory sensory neurons, supporting cells, basal cells, and glandular structures. The axons of olfactory sensory neurons pass through the cribriform plate and connect with the olfactory bulb. This anatomical arrangement provides a potential route for transporting drugs from the nasal cavity toward the CNS without requiring initial passage across the BBB.

Drug transport through the olfactory region may occur through extracellular movement along perineural pathways or through neuronal uptake and transport. The relative contribution of these mechanisms depends on the physicochemical properties of the drug, carrier characteristics, formulation composition, and deposition within the olfactory region. Therefore, effective targeting requires not only a suitable formulation but also sufficient and reproducible delivery to the relevant nasal site (Haque et al., 2012; Patel et al., 2019; Butola and Nainwal, 2024; Ghosh et al., 2024; Xu et al., 2024).

2.4. Trigeminal Innervation

The trigeminal nerve provides another potential pathway for nose-to-brain drug transport. Its ophthalmic and maxillary branches innervate portions of the nasal cavity and establish connections with different regions of the CNS, including the brainstem. Following intranasal administration, certain drugs and nanocarriers may interact with trigeminal nerve-associated pathways, potentially contributing to their distribution within the CNS.

The involvement of the trigeminal and olfactory pathways varies according to the drug's molecular properties, formulation characteristics, site of deposition, and experimental model. Both pathways may contribute to brain exposure, although their relative importance is not always clearly established. Consequently, appropriate pharmacokinetic and biodistribution studies are required to distinguish direct neural transport from drug absorption into systemic circulation followed by subsequent distribution to the brain (Mustafa et al., 2016; Falcone et al., 2014; Crowe et al., 2018; Mistry et al., 2009).

3. BLOOD-BRAIN BARRIER AND CNS DELIVERY

3.1. Structure of the Blood-Brain Barrier

The blood-brain barrier (BBB) is a specialized neurovascular interface that regulates the movement of substances between the bloodstream and the central nervous system (CNS). It consists primarily of brain endothelial cells connected by tight junctions, supported by a basement membrane, extracellular matrix, pericytes, and astrocytic end-feet. These structural components maintain brain homeostasis and protect neural tissue from potentially harmful substances while allowing the controlled entry of essential nutrients and selected molecules.

Drug transport across the BBB occurs through several mechanisms, including passive diffusion, carrier-mediated transport, receptor-mediated transcytosis, and regulated transcellular pathways. However, the restrictive nature of the barrier limits the penetration of many therapeutic agents, particularly hydrophilic compounds, peptides, proteins, and other macromolecules. Understanding these transport mechanisms is essential for developing effective CNS drug delivery systems and evaluating alternative approaches, such as nose-to-brain delivery (Drath et al., 2025; Correale et al., 2026; Nguyen and Duong, 2025; Zheng et al., 2024).

3.2. Efflux Transporters and Metabolic Barriers

Efflux transporters, particularly P-glycoprotein, contribute significantly to the restricted accumulation of many drugs within the brain. These transporters can actively move susceptible compounds from brain endothelial cells back into the bloodstream, reducing their penetration into CNS tissues. In addition, peripheral distribution, plasma protein binding, enzymatic degradation, and systemic drug metabolism can reduce the amount of an administered dose available to reach the brain.

Consequently, a drug that demonstrates promising pharmacological activity under in vitro conditions may not achieve sufficient concentrations in the brain following conventional administration. These limitations highlight the importance of evaluating drug permeability, brain distribution, and pharmacokinetic behaviour when developing CNS therapeutics. Nose-to-brain delivery is being investigated as an alternative approach to improve CNS exposure while potentially reducing the limitations associated with systemic administration (Lee and Minko, 2021; Sonvico et al., 2018; Falcone et al., 2014).

3.3. BBB Bypass Versus BBB Disruption

Nose-to-brain drug delivery aims to exploit anatomical connections between the nasal cavity and the CNS to facilitate drug transport without necessarily requiring passage across the BBB. This approach differs from strategies that deliberately increase BBB permeability or disrupt its structural integrity. Although BBB disruption may improve the entry of selected

therapeutic agents, it can also expose neural tissue to potentially harmful circulating substances and compromise normal barrier function.

The objective of an effective nose-to-brain delivery system is therefore to improve drug availability within the CNS while preserving BBB integrity and minimizing unnecessary systemic exposure. However, the extent of direct transport depends on the formulation, nasal deposition, drug characteristics, and contribution of systemic absorption. Appropriate pharmacokinetic and biodistribution studies are consequently required to demonstrate whether increased brain exposure results from direct transport or conventional systemic distribution (Prabakaran et al., 2022; Craft et al., 2020; Chapman et al., 2018).

4. MECHANISMS OF NOSE-TO-BRAIN TRANSPORT

Nose-to-brain drug delivery involves several potential transport mechanisms that facilitate the movement of therapeutic agents from the nasal cavity toward the CNS. The major pathways include olfactory-associated transport, trigeminal nerve-associated transport, and systemic absorption followed by distribution to the brain. In addition, paracellular, transcellular, and vesicular processes may contribute to drug movement across nasal epithelial barriers. The relative contribution of each mechanism depends on drug properties, carrier characteristics, formulation composition, and the site of nasal deposition (Crowe et al., 2018; Agrawal et al., 2018; Haque et al., 2012; Chapman et al., 2018).

4.1. Olfactory Neuronal Pathway

The olfactory pathway is considered an important potential route for direct drug transport from the nasal cavity to the CNS. Following deposition in the olfactory region, therapeutic agents may move along pathways associated with olfactory sensory neurons toward the olfactory bulb. Transport may occur through extracellular movement along perineural spaces or through cellular uptake and intracellular neuronal transport.

The efficiency of this pathway is influenced by molecular size, surface characteristics, formulation composition, and the extent of deposition within the olfactory region. Nanocarriers may facilitate drug transport by protecting therapeutic agents from degradation and modifying their interactions with nasal tissues. However, the extent to which individual formulations use neuronal or extracellular pathways must be established experimentally (Crowe et al., 2018; Agrawal et al., 2018; Haque et al., 2012; Chapman et al., 2018).

4.2. Trigeminal Pathway

The trigeminal pathway provides another potential route for transporting therapeutic agents from the nasal cavity to the CNS. Branches of the trigeminal nerve innervate the nasal mucosa and connect with central nervous system structures, including the brainstem.

Following intranasal administration, certain drugs and nanocarriers may move along nerve-associated pathways, contributing to drug distribution within CNS regions.

The extent of trigeminal transport depends on the formulation, drug characteristics, nasal deposition site, and experimental conditions. Evidence from intranasal transport studies suggests that olfactory and trigeminal pathways may operate simultaneously. However, their relative contributions can vary, and the detection of a drug in brain tissue alone does not establish which pathway was responsible (Mistry et al., 2009; Marcello and Chiono, 2023; Xu et al., 2024).

4.3. Systemic Nose-to-Blood-to-Brain Pathway

The nasal mucosa is highly vascularized, allowing intranasally administered drugs to enter systemic circulation. Once absorbed into the bloodstream, these drugs may subsequently reach the brain according to their distribution characteristics and ability to cross the BBB. Therefore, brain exposure following intranasal administration may result from a combination of direct transport and systemic absorption.

Distinguishing between these mechanisms is essential when evaluating the effectiveness of nose-to-brain formulations. An increased brain drug concentration after intranasal administration does not, by itself, demonstrate direct transport from the nasal cavity. Comparative pharmacokinetic studies involving intranasal and intravenous administration, together with plasma and regional brain concentration measurements, can help establish the relative contribution of direct and systemic pathways (Fan et al., 2018; Tashima, 2020; Di Scala et al., 2022).

4.4. Paracellular, Transcellular, and Vesicular Transport

In addition to nerve-associated pathways, drugs must interact with the nasal epithelial barrier to reach underlying tissues. Paracellular transport involves movement between adjacent epithelial cells, whereas transcellular transport occurs through the cells themselves. Vesicular transport may facilitate the cellular uptake and intracellular movement of selected therapeutic agents.

Small molecules with suitable physicochemical properties may cross epithelial membranes through passive diffusion, while macromolecules and hydrophilic compounds may require specialized transport mechanisms or formulation-assisted delivery. Nanocarriers can modify drug solubility, surface charge, hydrophobicity, mucus interactions, and cellular uptake. Surface modification and targeted carrier design may further improve interactions with nasal tissues, although their effectiveness and safety depend on the materials and formulation

employed (Sonvico et al., 2018; Lee and Minko, 2021; Marcello and Chiono, 2023; Nguyen and Duong, 2025).

5. BARRIERS AND CHALLENGES IN NOSE-TO-BRAIN DRUG DELIVERY

Despite its potential advantages, nose-to-brain drug delivery faces several physiological, formulation-related, and technological challenges. These limitations can affect drug absorption, nasal retention, deposition accuracy, therapeutic performance, and long-term safety.

5.1. Mucociliary Clearance

Mucociliary clearance is one of the major physiological barriers to intranasal drug delivery. The nasal mucosa continuously produces mucus, which traps foreign particles and is transported toward the nasopharynx by coordinated ciliary movement. Although this mechanism protects the respiratory tract, it also reduces the residence time of administered formulations and may limit drug absorption.

Mucoadhesive polymers and in situ gelling systems can potentially prolong nasal residence time and improve contact between the formulation and mucosal surface. However, excessive mucoadhesion or increased viscosity may interfere with normal mucus transport and ciliary function. Therefore, formulation design must balance prolonged retention with preservation of normal nasal physiology (Jiang et al., 2010; Inoue et al., 2018; Lombardo et al., 2021; Lee and Minko, 2021).

5.2. Enzymatic Degradation

The nasal mucosa contains enzymes, including peptidases, that may degrade susceptible therapeutic molecules before they reach their intended site of action. This is particularly important for peptides, proteins, and other biologically active molecules that may be sensitive to enzymatic degradation.

Protective encapsulation, suitable carrier systems, and carefully selected enzyme inhibitors may help improve drug stability during nasal administration. Nevertheless, excipients and permeation enhancers must be evaluated for local tolerability, epithelial compatibility, and potential toxicity. Formulation strategies should therefore improve drug protection without compromising nasal tissue integrity (Sonvico et al., 2018; Falcone et al., 2014; Kozlovskaya et al., 2014).

5.3. Limited Dose Volume

The nasal cavity can accommodate only a limited volume of formulation without leakage, drainage, or swallowing. This restriction presents a challenge for drugs requiring high doses or formulations with low drug-loading capacity. Consequently, effective nose-to-brain

systems should aim to optimize drug concentration, loading efficiency, solubility, and deposition while maintaining acceptable formulation properties.

Concentrated formulations and nanocarrier-based systems may help address some of these limitations, particularly for drugs with poor aqueous solubility. However, increasing drug concentration or excipient content must not compromise formulation stability, nasal tolerability, or patient comfort (Liu, 2011; Kumar et al., 2017).

5.4. Variability in Nasal Deposition

The location and distribution of a nasal formulation are influenced by device design, droplet size, spray pattern, administration technique, head position, nasal anatomy, and breathing conditions. Formulations deposited primarily in the respiratory region may exhibit different absorption and transport characteristics from those reaching the upper nasal cavity.

Reproducible deposition within the intended nasal region is therefore essential for consistent drug delivery. Specialized nasal devices and optimized spray characteristics may improve deposition, but their performance must be evaluated under clinically relevant conditions. Differences between animal and human nasal anatomy further complicate the translation of preclinical findings into clinical applications (Wen, 2011; Krishnan et al., 2017; Djupesland, 2013).

5.5. Safety and Long-Term Use

The safety of intranasal formulations is an important consideration, particularly when repeated administration or long-term treatment is required. Potential concerns include mucosal irritation, epithelial damage, inflammation, altered mucociliary function, and toxicity associated with certain excipients or nanocarriers. The nature and severity of these effects depend on formulation composition, concentration, exposure duration, and the characteristics of the delivery system.

Comprehensive safety evaluation should include nasal histopathology, assessment of ciliary function, inflammatory markers, systemic exposure, and the potential accumulation or degradation of nanocarrier materials. Formulations intended for repeated use require particular attention to local tolerability and long-term effects. Establishing an appropriate balance between enhanced drug delivery and acceptable safety is essential for successful clinical development (Lee and Minko, 2021; Sonvico et al., 2018; Drath et al., 2025).

6. STRATEGIES TO IMPROVE NOSE-TO-BRAIN DRUG DELIVERY

Several formulation and device-based strategies have been investigated to improve nasal residence time, enhance drug permeation, increase delivery efficiency, and promote transport

toward the central nervous system (CNS). These approaches aim to overcome physiological barriers while maintaining nasal mucosal integrity and ensuring patient acceptability.

6.1. Mucoadhesive Polymers

Mucoadhesive polymers, including carbomers, cellulose derivatives, and chitosan, can improve contact between the formulation and nasal mucosa, thereby prolonging residence time and potentially enhancing drug absorption. Chitosan is particularly attractive because of its mucoadhesive properties and potential to enhance epithelial permeability. However, the concentration and properties of the polymer must be optimized to avoid excessive viscosity, impaired mucociliary clearance, or local irritation (Jiang et al., 2010; Upadhaya et al., 2020; Vitorino et al., 2019).

6.2. Permeation Enhancers

Permeation enhancers, such as surfactants, bile salts, and fatty acids, may temporarily increase epithelial permeability and facilitate drug absorption across the nasal mucosa. Their effectiveness depends on the type and concentration of the enhancer, the physicochemical properties of the drug, and the characteristics of the formulation.

An ideal permeation enhancer should improve drug transport while preserving epithelial integrity and normal mucosal function. Therefore, its effects on tissue viability, reversibility of barrier changes, local irritation, and systemic exposure should be systematically evaluated before clinical application (Sonvico et al., 2018; Alwali et al., 2026; Patel and Thakkar, 2022).

6.3. In Situ Gelling Systems

In situ gelling formulations are administered as relatively low-viscosity liquids that undergo gel formation under conditions encountered within the nasal cavity. Thermosensitive and ion-sensitive systems are examples of approaches used to improve nasal retention and reduce rapid drainage. Prolonged contact with the mucosa may provide additional time for drug absorption and potentially improve delivery efficiency.

However, formulation development must consider gelation temperature, gel strength, viscosity, isotonicity, sprayability, and patient comfort. The formulation should remain easy to administer while providing sufficient retention without interfering with normal mucociliary function (Alwali et al., 2026; Liu, 2011; Papakyriakopoulou and Valsami, 2025).

6.4. Targeting Ligands and Cell-Penetrating Peptides

Targeting ligands can be incorporated into drug delivery systems to promote interactions with selected receptors or cellular uptake mechanisms. Cell-penetrating peptides, including Tat-

derived sequences, have also been investigated for facilitating the intracellular delivery of therapeutic agents and nucleic acids.

These approaches may improve cellular uptake or influence the distribution of nanocarriers within nasal and CNS tissues. Nevertheless, their performance depends on ligand specificity, surface density, cargo characteristics, and interactions with biological barriers. Potential immunogenicity, cytotoxicity, off-target interactions, and manufacturing complexity must also be considered when developing these systems (Nguyen and Duong, 2025; Lee and Minko, 2021; Sonvico et al., 2018).

6.5. Device-Assisted Targeting

Nasal delivery devices play an important role in determining formulation deposition and distribution within the nasal cavity. Specialized devices and optimized administration techniques can potentially improve delivery toward the upper nasal region, including areas associated with olfactory transport. Consequently, effective nose-to-brain delivery requires coordinated optimization of the formulation and its delivery device. Even a well-designed formulation may show limited performance if it fails to reach the intended anatomical region. Reproducibility of deposition, ease of administration, and suitability for clinical use are therefore important considerations in device development (Djupesland, 2013; D'Souza et al., 2026; Bang et al., 2026; Krishnan et al., 2017).

7. NANOTECHNOLOGY-BASED NOSE-TO-BRAIN DRUG DELIVERY

Nanotechnology-based delivery systems have attracted considerable interest because they can improve drug solubilization, protect unstable therapeutic molecules, modify release characteristics, and influence interactions with nasal biological barriers. Different nanocarriers offer distinct advantages depending on the drug's physicochemical properties, therapeutic requirements, and intended transport mechanism.

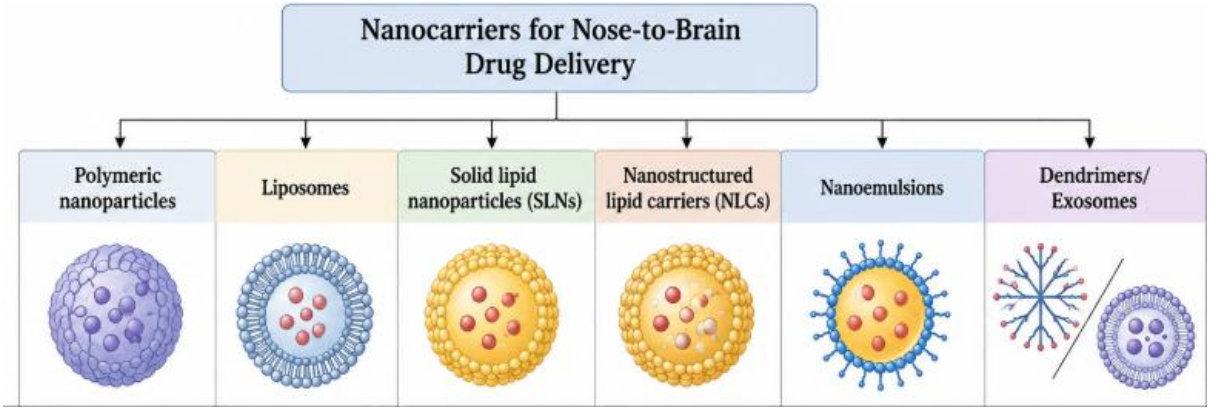


Figure 2: Classification of nanocarriers for nose-to-brain drug delivery

7.1. Polymeric Nanoparticles

Polymeric nanoparticles can encapsulate hydrophilic or hydrophobic therapeutic agents and provide controlled or sustained drug release. Biodegradable polymers, including poly(lactic-co-glycolic acid) (PLGA), and mucoadhesive materials such as chitosan have been investigated for intranasal drug delivery. Their composition and surface properties can be modified to influence drug loading, release behaviour, mucus interactions, and cellular uptake.

These systems may protect drugs from degradation and improve their residence within the nasal cavity. However, particle size, polymer composition, surface charge, drug-loading efficiency, degradation behaviour, and potential toxicity must be carefully optimized. The ability of a polymeric nanoparticle to improve brain delivery should also be established through appropriate pharmacokinetic and biodistribution studies (Lombardo et al., 2021; Gandhi et al., 2024; Nguyen and Duong, 2025; Lee and Minko, 2021).

7.2. Liposomes

Liposomes are vesicular carriers composed primarily of phospholipid bilayers. Their structure enables the incorporation of hydrophilic compounds within the aqueous core and lipophilic compounds within the lipid bilayer. Intranasal liposomes may improve drug solubilization, protect sensitive therapeutic agents, and modify their release and interaction with biological membranes.

Their performance depends on vesicle size, lipid composition, surface charge, encapsulation efficiency, physical stability, and susceptibility to degradation or leakage. Although liposomes offer formulation flexibility, their ability to achieve effective nose-to-brain delivery requires evaluation of nasal retention, drug release, tissue distribution, and long-term stability (Mulet et al., 2026; Costa et al., 2019).

7.3. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLNs) consist of drug-containing solid lipid matrices stabilized by surfactants, whereas nanostructured lipid carriers (NLCs) generally combine solid and liquid lipids to modify matrix structure and drug incorporation. Both systems have been investigated for improving the delivery of poorly water-soluble drugs and protecting encapsulated molecules from environmental degradation.

These carriers may offer controlled drug release, improved formulation stability, and opportunities for surface modification. NLCs may also provide greater flexibility in drug loading because of their less-ordered lipid matrices. However, drug expulsion during storage, lipid polymorphic transitions, particle aggregation, and surfactant-related toxicity remain

important formulation challenges. Recent research has explored SLNs and NLCs for intranasal delivery of therapeutics intended for neurological disorders (Zheng et al., 2024; Kaushal et al., 2026; Nguyen and Duong, 2025).

7.4. Nanoemulsions and Micelles

Nanoemulsions and micelles are useful approaches for improving the apparent solubility and delivery of poorly water-soluble drugs. Nanoemulsions consist of nanoscale oil droplets dispersed in an aqueous phase and stabilized by surfactants, whereas micelles form through the self-assembly of amphiphilic molecules under suitable conditions. These systems can enhance drug solubilization and influence interactions between the formulation and nasal mucosa.

Their performance depends on composition, droplet or aggregate size, surfactant concentration, physical stability, drug-release characteristics, and compatibility with nasal tissues. In particular, surfactant levels must be optimized to achieve adequate solubilization without causing unacceptable irritation or epithelial damage. Formulation stability and reproducibility are also essential for ensuring consistent delivery (Fan et al., 2018; Lombardo et al., 2021).

7.5. Dendrimers and Nanogels

Dendrimers are highly branched, nanoscale macromolecules with multiple functional groups that can be used for drug attachment, encapsulation, or surface modification. Their structural features allow considerable flexibility in the design of drug-loading and targeting strategies. However, surface chemistry, generation, dose, and charge can influence their biological interactions and toxicity.

Nanogels are nanoscale, cross-linked polymer networks containing substantial amounts of water. They may be particularly useful for hydrophilic therapeutic agents and can be designed to respond to environmental stimuli, potentially enabling controlled drug release. Their performance depends on polymer composition, cross-linking density, swelling behaviour, drug-loading capacity, and degradation characteristics. Both systems require careful evaluation of nasal compatibility, drug-release behaviour, and potential toxicity before their suitability for nose-to-brain delivery can be established (Gandhi et al., 2024; Nguyen and Duong, 2025).

7.6. Exosomes and Extracellular Vesicles

Exosomes and other extracellular vesicles are membrane-bound structures that participate in intercellular communication and can carry biologically active molecules. Their endogenous

membrane characteristics and potential biocompatibility have generated interest in their use as carriers for therapeutic molecules intended for CNS delivery.

Nevertheless, several challenges limit their translation into reproducible pharmaceutical products. These include variability in the biological source, isolation and purification methods, particle characterization, cargo consistency, storage stability, and potential biological contaminants. Scalable manufacturing and appropriate quality-control procedures are also essential. Further investigation is required to establish their transport mechanisms, therapeutic effectiveness, and safety following intranasal administration (Qiu et al., 2025; Nguyen and Duong, 2025; Morim et al., 2026).

8. PHARMACEUTICAL FORMULATIONS AND DEVICES

The effectiveness of nose-to-brain drug delivery depends on the physicochemical properties of the formulation, its interaction with the nasal mucosa, and the ability of the delivery device to achieve reproducible deposition. Different pharmaceutical formulations offer distinct advantages in terms of drug stability, residence time, ease of administration, and patient acceptability. Therefore, formulation and device selection should be guided by the therapeutic agent, intended site of deposition, and required delivery performance (Djupesland, 2013; Drath et al., 2025; Papakyriakopoulou and Valsami, 2025).

8.1. Nasal Solutions and Sprays

Nasal solutions and sprays are widely used because they are relatively simple to administer and can provide rapid drug absorption. Metered-dose nasal sprays offer the additional advantage of delivering a predefined volume per actuation, which may improve dose consistency. However, liquid formulations may have a short residence time because of mucociliary clearance, drainage, and swallowing.

The performance of a nasal spray depends on formulation viscosity, surface tension, droplet size, spray pattern, and device characteristics. Appropriate matching of the formulation and delivery device is therefore essential to improve deposition, dosing reproducibility, and patient convenience (Liu, 2011; Wen, 2011; Djupesland, 2013).

8.2. Nasal Powders

Dry powder formulations may offer advantages over liquid formulations, including improved storage stability and reduced dependence on aqueous vehicles. Depending on their composition and packaging, powders may also reduce certain formulation-related microbial stability concerns. Their performance, however, depends on particle size, flow properties, moisture sensitivity, dissolution rate, and deposition behaviour.

Particle engineering is particularly important because the powder must be delivered to the intended nasal region and dissolve or release its drug effectively. Formulation development should also consider nasal tolerability, dose uniformity, and the potential for particle loss during administration (Djupesland, 2013; Kumar et al., 2017; Papakyriakopoulou and Valsami, 2025).

8.3. Nasal Gels and Thermoresponsive Systems

Nasal gels can increase formulation retention and reduce rapid drainage from the nasal cavity. Thermoresponsive systems are designed to undergo a sol-gel transition in response to temperature changes, allowing administration as a relatively fluid preparation followed by gel formation under nasal conditions. Such systems may prolong contact with the mucosal surface and support sustained drug release.

Nevertheless, the gelation temperature, viscosity, gel strength, isotonicity, and ease of administration must be carefully optimized. Excessive gel strength or viscosity may interfere with spreading and mucociliary clearance, while unsuitable gelation characteristics may reduce patient comfort and formulation performance (Alwali et al., 2026; Liu, 2011; Papakyriakopoulou and Valsami, 2025).

8.4. Advanced Drug Delivery Devices

Advanced nasal delivery devices aim to improve deposition in specific regions of the nasal cavity, including the upper nasal region associated with olfactory transport. Device geometry, airflow, spray characteristics, administration technique, and nasal anatomy can all influence deposition patterns. Specialized delivery approaches may improve access to targeted regions, but increased deposition does not automatically establish enhanced direct brain delivery.

Accordingly, the performance of advanced devices should be evaluated using deposition studies alongside pharmacokinetic, biodistribution, and clinical outcome assessments where appropriate. Integration of device design with formulation characteristics is essential for achieving reproducible administration and meaningful therapeutic benefits (Djupesland, 2013; D'Souza et al., 2026; Bang et al., 2026; Krishnan et al., 2017).

9. THERAPEUTIC APPLICATIONS OF NOSE-TO-BRAIN DRUG DELIVERY

Nose-to-brain delivery is being investigated for several neurological and psychiatric conditions in which conventional drug delivery may be limited by the blood-brain barrier (BBB), systemic adverse effects, or the physicochemical properties of therapeutic agents. The strength of evidence varies considerably across applications, and the benefits of intranasal administration should be distinguished from evidence demonstrating direct transport from the nasal cavity to the brain.

9.1. Alzheimer's Disease

Alzheimer's disease is a major area of research because of the need for effective delivery of therapeutics targeting neurodegeneration, amyloid-related processes, and impaired neuronal signalling. Intranasal insulin has been investigated for its potential effects on brain insulin signalling and cognitive function. Other experimental approaches include nanocarrier-based delivery of antioxidants, anti-amyloid agents, and neuroprotective molecules.

Nanocarriers may help protect sensitive therapeutic agents and improve their formulation properties. However, clinical findings for intranasal insulin have not been consistently positive, and evidence of clinical benefit remains insufficient to establish it as an approved intranasal treatment for Alzheimer's disease. Further controlled clinical studies are needed to clarify the effects of dose, formulation, treatment duration, and patient characteristics (Agrawal et al., 2018; Muntimadugu et al., 2016; de la Monte, 2013; Craft et al., 2020; Chapman et al., 2018).

9.2. Parkinson's Disease

Parkinson's disease is another important target for nose-to-brain research. Investigated approaches include the delivery of levodopa-related compounds, dopamine-associated therapeutics, antioxidants, neurotrophic factors, and other neuroprotective agents. Nanocarriers are being explored to improve drug stability, modify release, and potentially increase drug exposure in relevant CNS regions.

Although preclinical studies have reported promising findings for selected formulations, translation into clinical practice remains challenging. Future investigations must establish reproducible brain exposure, therapeutic efficacy, appropriate dosing, and long-term safety in humans (Pathak and Akhtar, 2016; Kiran et al., 2022; Mulet et al., 2026).

9.3. Epilepsy

Intranasal drug delivery has an established clinical role in the rapid treatment of seizure clusters and other selected seizure emergencies. Midazolam and diazepam nasal products provide practical alternatives when oral administration is unsuitable or immediate treatment is required. Their clinical utility demonstrates the value of the nasal route for delivering CNS-active medicines.

However, the therapeutic effectiveness of these products should not be interpreted as proof of direct olfactory transport into the brain. Their benefits are associated with the pharmacological action of the drugs following intranasal administration, including systemic absorption and subsequent CNS activity. Nanocarrier-based approaches for epilepsy remain

an area of investigation (Costa et al., 2019; U.S. Food and Drug Administration [FDA], 2021, 2025).

9.4. Migraine

Intranasal administration is useful in migraine management, particularly when nausea or vomiting makes oral administration difficult. Nasal formulations of migraine medications, including zolmitriptan, provide an alternative route that can support drug absorption without requiring gastrointestinal administration.

For established intranasal migraine treatments, the principal clinical advantage is the availability of a convenient alternative administration route. Direct nose-to-brain transport may be relevant to experimental formulations, but it should not be assumed to explain the therapeutic effect of currently marketed nasal products (FDA, 2013; Qiu et al., 2025).

9.5. Brain Tumors

Glioblastoma and other brain tumors present substantial drug-delivery challenges because of the BBB, heterogeneous tumor vasculature, and the complex tumor microenvironment. Nose-to-brain delivery has been investigated as a potential strategy for increasing exposure to selected tumor regions while limiting systemic drug distribution.

Research includes intranasal delivery of chemotherapy agents, gene-based therapeutics, and other experimental molecules using nanoparticle and biomaterial-based systems. Nevertheless, effective penetration into tumor tissue, distribution throughout the tumor, therapeutic activity, and safety must be established experimentally. Evidence of improved delivery in preclinical models does not by itself demonstrate clinical efficacy (Upadhaya et al., 2020; Marcello and Chiono, 2023; Qiu et al., 2025).

9.6. Depression and Other Psychiatric Disorders

Intranasal delivery has been investigated for antidepressants, antipsychotics, neuropeptides, and other agents intended to affect CNS function. Potential advantages include avoidance of gastrointestinal administration and the possibility of rapid absorption for suitable drug molecules. Nanocarrier-based formulations may further influence solubility, stability, and drug distribution.

However, rapid absorption after intranasal administration does not necessarily establish direct brain targeting. Controlled clinical studies are needed to determine whether specific formulations provide meaningful improvements in therapeutic response, tolerability, or patient outcomes compared with conventional routes (Katare et al., 2017; Vitorino et al., 2019; Qiu et al., 2025).

9.7. Stroke and Neuroinflammation

Experimental nose-to-brain strategies for stroke and neuroinflammatory conditions include the delivery of neuroprotective proteins, anti-inflammatory agents, nucleic acids, and biologically active factors. The objective is to achieve adequate drug exposure in affected CNS regions while minimizing unwanted systemic effects.

The major challenges include the time-sensitive nature of treatment, the need for sufficient regional drug distribution, and the difficulty of demonstrating therapeutic benefit in clinically relevant models. Studies should establish whether the formulation reaches the intended tissue, engages the relevant biological target, and improves meaningful outcomes without causing unacceptable adverse effects (Lochhead and Thorne, 2012; Qiu et al., 2025; Drath et al., 2025).

9.8. CNS Infections and Other Neurological Disorders

Intranasal administration has also been explored for selected antimicrobial agents, analgesics, and other compounds intended to act within or affect the CNS. The potential usefulness of the route depends on the drug's physicochemical properties, the disease process, the required site of action, and the ability of the formulation to achieve adequate exposure.

These applications require disease-specific evidence because effective nasal absorption does not guarantee sufficient concentrations at the site of infection or within the relevant CNS compartment. Further studies should evaluate tissue distribution, therapeutic efficacy, and local and systemic safety (Ong et al., 2014; Qiu et al., 2025).

10. EVALUATION OF NOSE-TO-BRAIN DRUG DELIVERY SYSTEMS

A comprehensive evaluation strategy is essential for determining the quality, performance, and safety of nose-to-brain formulations. Assessment should extend beyond particle characteristics or total brain drug concentration to include drug release, nasal compatibility, regional biodistribution, pharmacokinetic performance, and evidence of therapeutic activity.

10.1. Physicochemical Characterization

For nanocarrier-based formulations, important characterization parameters include particle size, polydispersity index (PDI), zeta potential, morphology, drug loading, encapsulation efficiency, pH, osmolality, viscosity, and physical stability. Surface properties and the composition of the carrier may influence interactions with mucus, cellular uptake, drug release, and formulation deposition.

These parameters should be selected according to the type of delivery system and intended route of administration. For example, lipid-based carriers require assessment of lipid composition and physical stability, whereas polymeric systems may require additional evaluation of polymer characteristics, degradation, and release behaviour. Appropriate

analytical methods and predefined acceptance criteria are necessary to ensure reproducibility between batches (Lombardo et al., 2021; Gandhi et al., 2024; Nguyen and Duong, 2025; Zheng et al., 2024; Kaushal et al., 2026).

10.2. In Vitro and Ex Vivo Studies

In vitro and ex vivo studies are used to investigate drug release, mucoadhesion, interactions with mucin, epithelial permeability, and tissue compatibility. Suitable cell-based models may help evaluate drug uptake and the effects of formulations on epithelial integrity. Ex vivo nasal tissues can provide additional information about tissue penetration and local tolerability.

However, no single experimental model fully reproduces the complexity of the nasal cavity or the anatomical connections between the nose and CNS. Static cell cultures may not adequately represent mucus movement, ciliary activity, tissue architecture, or neuronal pathways. Consequently, results should be interpreted in relation to the limitations of the selected model and supported by complementary studies where appropriate (Erd et al., 2018; Drath et al., 2025).

10.3. In Vivo Pharmacokinetics and Biodistribution

In vivo studies are important for determining drug exposure in plasma and different brain regions following intranasal administration. Where scientifically appropriate, intranasal administration should be compared with intravenous administration or other relevant control routes to distinguish direct nose-to-brain transport from systemic absorption followed by distribution to the brain.

Pharmacokinetic parameters may include maximum concentration ($C_{\max}$), time to maximum concentration ($T_{\max}$), area under the concentration-time curve (AUC), and elimination half-life. Brain-targeting efficiency and drug-targeting efficiency may also be calculated using clearly defined equations and appropriate plasma and brain exposure data.

These metrics require careful interpretation because their values depend on the study design, sampling schedule, analytical method, and comparator route. Measurements of total brain concentration alone cannot conclusively establish direct transport or demonstrate that the drug has reached the intended pharmacological target (Tashima, 2020; Di Scala et al., 2022; Kozlovskaya et al., 2014).

10.4. Histopathology and Safety Assessment

Safety evaluation should examine the potential effects of repeated administration on nasal tissue and other organs. Relevant assessments include epithelial integrity, inflammation, tissue necrosis, ciliary structure and function, and other indicators of local irritation. Systemic

exposure and the distribution or accumulation of carrier materials should also be considered, particularly for persistent or slowly degradable nanoparticles.

The choice of safety tests should reflect the composition of the formulation, intended treatment duration, administration frequency, and potential exposure to degradation products. Long-term studies are particularly important when formulations are intended for chronic neurological conditions (Sonvico et al., 2018; Lee and Minko, 2021; Drath et al., 2025).

11. PRECLINICAL AND CLINICAL TRANSLATION

Translating promising nose-to-brain formulations from laboratory research into clinical practice requires evidence that the delivery system performs reliably in humans and provides meaningful therapeutic benefits. Differences in nasal anatomy, administration methods, formulation deposition, and drug disposition can limit the predictive value of preclinical findings.

11.1. Animal Models

Rodents, particularly rats, are frequently used in nose-to-brain research because they allow controlled administration, tissue sampling, and investigation of drug distribution. These models are valuable for studying transport mechanisms and evaluating preliminary safety and efficacy.

However, rodents differ from humans in nasal anatomy, the relative proportions of olfactory and respiratory regions, and aspects of nasal airflow and administration. These differences may affect deposition and the apparent contribution of direct transport pathways. Animal findings should therefore be interpreted cautiously and supported by studies designed to address species-specific limitations (Erd et al., 2018; Krishnan et al., 2017; Bang et al., 2026).

11.2. Human Evidence

Human studies have investigated the pharmacokinetics, tolerability, and clinical effects of several intranasally administered drugs. Nevertheless, demonstrating direct anatomical transport from the nasal cavity to the human brain is more difficult than detecting labelled compounds or measuring brain concentrations in experimental animals.

Human investigations should use appropriate pharmacokinetic controls, validated analytical techniques, and imaging or other assessment methods when suitable. Researchers must distinguish evidence that an intranasal drug produces a CNS-related effect from evidence that the drug reaches the brain through a direct nose-to-brain pathway (Banks, 2016; Drath et al., 2025; Liu, 2011).

11.3. Clinical Development

Clinical development of nose-to-brain systems requires the integration of formulation quality, delivery-device performance, pharmacokinetics, efficacy, and safety. Intranasal insulin and intranasal CNS-active rescue medications illustrate different aspects of clinical development: insulin has been investigated as an experimental approach for neurological conditions, whereas selected nasal rescue medications have established clinical uses for specific indications.

These examples should not be treated as equivalent evidence for direct brain targeting. Clinical studies must distinguish the effectiveness of intranasal administration from proof of direct CNS transport. Dose selection, device usability, patient adherence, formulation consistency, and long-term tolerability are also important factors affecting successful translation (Craft et al., 2020; Chapman et al., 2018; FDA, 2021, 2025).

12. ARTIFICIAL INTELLIGENCE AND COMPUTATIONAL APPROACHES

Artificial intelligence (AI) and computational methods offer potential tools for optimizing formulation composition, predicting drug-carrier interactions, and improving the design of nasal delivery systems. Their value depends on the quality of the input data, the relevance of the models, and experimental validation of the predictions. Emerging sensing and organ-on-a-chip technologies may also contribute to the development and evaluation of advanced delivery platforms (Advanced Sensing and Delivery Technologies for Nose-to-Brain Administration, 2026).

12.1. Formulation Optimization

Machine learning models may be used to investigate relationships between formulation variables-such as polymer concentration, lipid composition, surfactant level, particle size, and drug-release rate-and measured performance outcomes. When combined with design-of-experiments approaches, these methods may help identify influential variables, explore nonlinear relationships, and prioritize formulations for experimental testing.

However, predictions are only as reliable as the data and modelling assumptions on which they are based. Experimental confirmation, independent validation, and transparent reporting of model performance are necessary before computationally selected formulations can be considered suitable for further development.

12.2. Molecular and Pharmacokinetic Prediction

Computational approaches, including molecular docking, molecular dynamics, and pharmacokinetic modelling, may help investigate drug-carrier interactions, potential ligand-receptor binding, and predicted drug disposition. These methods can support the selection of

candidate materials and targeting ligands and help generate hypotheses about possible delivery mechanisms.

Nevertheless, computational predictions do not independently establish nasal permeability, direct brain transport, therapeutic target engagement, or clinical efficacy. Such predictions should be validated using appropriate physicochemical, biological, pharmacokinetic, and safety studies.

12.3. Personalized Nasal Delivery

In the future, imaging-derived information about individual nasal anatomy may support the development of more personalized administration strategies. Computational models could help investigate how nasal geometry and device characteristics influence deposition and identify factors that contribute to variability between patients.

Integration of patient-specific anatomy with device design and formulation properties remains an emerging area. Its clinical value will depend on whether personalized approaches can improve reproducibility, drug exposure, usability, or therapeutic outcomes compared with standard delivery methods.

13. REGULATORY AND SAFETY CONSIDERATIONS

The development of nose-to-brain formulations requires systematic quality control, safety assessment, and evidence of consistent performance. These requirements are particularly important for nanocarrier-based systems because their composition, surface properties, manufacturing conditions, and interactions with biological tissues may influence both therapeutic performance and safety.

13.1. Quality by Design

Quality by Design (QbD) provides a systematic framework for identifying critical quality attributes, critical material attributes, and critical process parameters that influence product performance. For nose-to-brain nanocarriers, relevant attributes may include particle size distribution, surface characteristics, drug loading, encapsulation efficiency, release behaviour, residual solvents, and physical stability.

Manufacturing controls should also address microbial quality, aggregation, batch-to-batch variability, and compatibility between the formulation and its delivery device. A well-defined quality framework can help improve reproducibility and support the development of robust formulations suitable for further preclinical and clinical evaluation (Nguyen and Duong, 2025; Drath et al., 2025).

13.2. Nanocarrier-Specific Safety

Safety assessment should consider the biological fate of carrier materials, their degradation products, possible accumulation in tissues, immunogenicity, and toxicity following repeated administration. The nature and extent of these risks depend on the carrier composition, particle characteristics, dose, exposure duration, and route of administration.

Biological carriers, including extracellular vesicles, present additional challenges related to source variability, purification, characterization, cargo consistency, and potency. Appropriate studies should establish local nasal tolerability, systemic safety, and the potential for unintended effects before clinical use is considered (Sonvico et al., 2018; Lee and Minko, 2021; Morim et al., 2026).

13.3. Manufacturing and Scale-Up

Successful scale-up requires the preservation of critical formulation characteristics when moving from laboratory preparation to larger-scale manufacturing. Changes in mixing, homogenization, sterilization, filling, storage, or device compatibility may affect particle size, stability, drug loading, and release behaviour.

Consequently, formulation development should be integrated with manufacturing-process design and delivery-device selection from an early stage. Appropriate process validation, analytical controls, stability testing, and batch consistency are essential for producing a reliable pharmaceutical product. These considerations are particularly important for complex nanocarriers and biologically derived delivery systems (Nguyen and Duong, 2025; Drath et al., 2025).

14. CURRENT RESEARCH GAPS AND FUTURE PERSPECTIVES

Despite substantial progress in nasal formulations, nanocarrier engineering, and delivery-device design, several challenges continue to limit the clinical translation of nose-to-brain drug delivery. Addressing these limitations requires a coordinated approach that integrates mechanistic research, formulation development, quantitative evaluation, and clinical validation.

14.1. Major Research Gaps

Important research gaps include incomplete understanding of transport mechanisms, inconsistent definitions of direct nose-to-brain delivery, species differences between preclinical models and humans, and limited human data on regional brain biodistribution. Other challenges include restricted nasal dose volumes, variable deposition in the upper nasal cavity, uncertainty regarding the long-term safety of some nanocarriers, and the complexity of regulatory assessment.

A further limitation is that increased brain drug concentration does not necessarily establish direct transport, target engagement, or therapeutic benefit. Future studies should use suitable control routes, validated analytical methods, regional brain measurements, and pharmacokinetic comparisons to distinguish direct delivery from systemic absorption. Standardized experimental designs and transparent reporting would improve the comparability and reproducibility of findings (Banks, 2016; Fan et al., 2018; Dhuria et al., 2009; Wen, 2011).

14.2. Future Directions

Future research may benefit from combining complementary formulation strategies, including mucoadhesive materials, mucus-interacting surface modifications, controlled-release systems, receptor-targeting ligands, and lipid-polymer hybrid carriers. Extracellular vesicles and other emerging biological delivery systems may also offer opportunities, provided that their manufacturing consistency and safety can be established.

Advances in precision nasal devices may improve deposition reproducibility, while computational modelling and AI-based optimization may help prioritize promising formulation candidates. Organ-on-a-chip platforms and organoid models could provide additional tools for investigating biological barriers and evaluating selected formulation characteristics under more representative conditions. Nevertheless, these approaches require validation before their predictions can be applied confidently to clinical development (Bang et al., 2026; Nguyen and Duong, 2025; Advanced Sensing and Delivery Technologies for Nose-to-Brain Administration, 2026).

15. CONCLUSION

Nose-to-brain drug delivery is a promising approach for delivering drugs to the central nervous system. It may help overcome some limitations of conventional drug delivery and improve drug absorption into the brain. Different nanocarriers, such as polymeric nanoparticles, liposomes, and solid lipid nanoparticles, can improve drug stability, solubility, and release. However, challenges such as mucociliary clearance, limited dose volume, variable nasal deposition, and safety concerns remain. Further research is needed to improve formulation performance and establish its effectiveness in humans. Overall, nose-to-brain drug delivery has significant potential for treating neurological disorders, but more clinical studies are required to confirm its safety and therapeutic benefits.

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17. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

7. References

- Advanced sensing and delivery technologies for nose-to-brain administration: From nanocarriers to sensor-integrated organ-on-chips. (2026). PubMed record: https://pubmed.ncbi.nlm.nih.gov/42076632/
- Agrawal, M., Saraf, S., Saraf, S., et al. (2018). Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs. Journal of Controlled Release, 281, 139-177. https://doi.org/10.1016/j.jconrel.2018.05.011
- Alwali, B., Parumasivam, T., & Al-Tabakha, M. M. (2026). Intranasal drug delivery: Unlocking the nose-to-brain route for central nervous system therapies. International Journal of Pharmaceutics: X, 11, 100521. https://doi.org/10.1016/j.ijpx.2026.100521
- Arora, D., Bhatt, S., Kumar, M., et al. (2020). Intranasal lipid particulate drug delivery systems: An update on clinical challenges and biodistribution studies of cerebroactive drugs in Alzheimer's disease. Current Pharmaceutical Design, 26, 3281-3299. https://doi.org/10.2174/1381612826666200331085854
- Bang, K. Y., Walenga, R., Chopski, S., et al. (2026). Intranasal drug delivery to the brain for neurodegenerative diseases: Current efforts and challenges in delivery platforms and modeling. Advanced Drug Delivery Reviews, 238, 115938. https://doi.org/10.1016/j.addr.2026.115938
- Banks, W. A. (2016). From blood-brain barrier to blood-brain interface: New opportunities for CNS drug delivery. Nature Reviews Drug Discovery, 15, 201-209. https://doi.org/10.1038/nrd.2015.21
- Born, J., Lange, T., Kern, W., McGregor, G. P., Bickel, U., & Fehm, H. L. (2002). Sniffing neuropeptides: A transnasal approach to the human brain. Nature Neuroscience, 5, 514-516. https://doi.org/10.1038/nn849
- Butola, M., & Nainwal, N. (2024). Non-invasive techniques of nose-to-brain delivery using nanoparticulate carriers: Hopes and hurdles. AAPS PharmSciTech, 25, 256. https://doi.org/10.1208/s12249-024-02946-z
- Chapman, C. D., Schiöth, H. B., Grillo, C. A., & Benedict, C. (2018). Intranasal insulin in Alzheimer's disease: Food for thought. Neuropharmacology, 136(Part B), 196-201. https://doi.org/10.1016/j.neuropharm.2017.11.037

- Correale, J., Mattera, V., & Pasquini, J. M. (2026). Intranasal delivery route for neurodegenerative diseases: Recent insights and future directions. Drug Delivery and Translational Research, 16(1), 76-94. https://doi.org/10.1007/s13346-025-01919-4
- Costa, C., Moreira, J. N., Amaral, M. H., Sousa Lobo, J. M., & Silva, A. C. (2019). Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. Journal of Controlled Release, 295, 187-200. https://doi.org/10.1016/j.jconrel.2018.12.049
- Costantino, H. R., Illum, L., Brandt, G., Johnson, P. H., & Quay, S. C. (2007). Intranasal delivery: Physicochemical and therapeutic aspects. International Journal of Pharmaceutics, 337, 1-24. https://doi.org/10.1016/j.ijpharm.2007.03.025
- Craft, S., Raman, R., Chow, T. W., et al. (2020). Safety, efficacy, and feasibility of intranasal insulin for the treatment of mild cognitive impairment and Alzheimer disease dementia: A randomized clinical trial. JAMA Neurology, 77(9), 1099-1109. https://doi.org/10.1001/jamaneurol.2020.1840
- Crowe, T. P., West Greenlee, M. H., Kanthasamy, A. G., & Hsu, W. H. (2018). Mechanism of intranasal drug delivery directly to the brain. Life Sciences, 195, 44-52. https://doi.org/10.1016/j.lfs.2017.12.025
- de la Monte, S. M. (2013). Intranasal insulin therapy for cognitive impairment and neurodegeneration: Current state of the art. Expert Opinion on Drug Delivery, 10(12), 1699-1709. https://doi.org/10.1517/17425247.2013.856877
- Dhuria, S. V., Hanson, L. R., & Frey, W. H. II. (2009). Novel vasoconstrictor formulation to enhance intranasal targeting of neuropeptide therapeutics to the central nervous system. Journal of Pharmacology and Experimental Therapeutics, 328, 312-320. https://doi.org/10.1124/jpet.108.145565
- Dhuria, S. V., Hanson, L. R., & Frey, W. H. II. (2010). Intranasal delivery to the central nervous system: Mechanisms and experimental considerations. Journal of Pharmaceutical Sciences, 99, 1654-1673. https://doi.org/10.1002/jps.21924
- Di Scala, C., Armstrong, N., Chahinian, H., Chabrière, E., Fantini, J., & Yahi, N. (2022). AmyP53, a therapeutic peptide candidate for the treatment of Alzheimer's and Parkinson's disease: Safety, stability, pharmacokinetics parameters and nose-to-brain delivery. International Journal of Molecular Sciences, 23(21), 13383. https://doi.org/10.3390/ijms232113383

- Djupesland, P. G. (2013). Nasal drug delivery devices: Characteristics and performance in a clinical perspective-A review. Drug Delivery and Translational Research, 3, 42-62. https://doi.org/10.1007/s13346-012-0108-9
- Drath, I., Richter, F., & Feja, M. (2025). Nose-to-brain drug delivery: From bench to bedside. Translational Neurodegeneration, 14, 23. https://doi.org/10.1186/s40035-025-00481-w
- D'Souza, A. A., DiFrancesco, V., Yang, A., Bleier, B. S., & Amiji, M. M. (2026). Differential targeting of olfactory epithelium and respiratory epithelium in nose-to-brain drug delivery. Expert Opinion on Drug Delivery, 23(1), 17-36. https://doi.org/10.1080/17425247.2025.2568093
- Erd, F., Bors, L. A., Farkas, D., Bajza, Á., & Gizurarson, S. (2018). Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Research Bulletin, 143, 155-170. https://doi.org/10.1016/j.brainresbull.2018.10.009
- Falcone, J. A., Salameh, T. S., Yi, X., et al. (2014). Intranasal administration as a route for drug delivery to the brain: Evidence for a unique pathway for albumin. Journal of Pharmacology and Experimental Therapeutics, 351, 54-60. https://doi.org/10.1124/jpet.114.216705
- Falcone, J. A., Salameh, T. S., Yi, X., et al. (2014). Intranasal administration as a route for drug delivery to the brain: Evidence for a unique pathway for albumin. Journal of Pharmacology and Experimental Therapeutics, 351, 54-60. https://doi.org/10.1124/jpet.114.216705
- Fan, Y., Chen, M., Zhang, J., Maincent, P., Xia, X., & Wu, W. (2018). Updated progress of nanocarrier-based intranasal drug delivery systems for treatment of brain diseases. Critical Reviews in Therapeutic Drug Carrier Systems, 35(5), 433-467. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2018024697
- Gandhi, S., Shastri, D. H., Shah, J., Nair, A. B., & Jacob, S. (2024). Nasal delivery to the brain: Harnessing nanoparticles for effective drug transport. Pharmaceutics, 16(4), 481. https://doi.org/10.3390/pharmaceutics16040481
- Ghosh, A., Majie, A., Karmakar, V., et al. (2024). In-depth mechanism, challenges, and opportunities of delivering therapeutics in brain using intranasal route. AAPS PharmSciTech, 25, 96. https://doi.org/10.1208/s12249-024-02810-0
- Hanson, L. R., & Frey, W. H. II. (2008). Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and the brain. BMC Neuroscience, 9(Suppl. 3), S5. https://doi.org/10.1186/1471-2202-9-S3-S5

- Haque, S., Md, S., Fazil, M., et al. (2012). Venlafaxine-loaded chitosan nanoparticles for brain targeting: Pharmacokinetic and pharmacodynamic evaluation. Carbohydrate Polymers, 89, 72-79. https://doi.org/10.1016/j.carbpol.2012.02.051
- Hasan, N., Imran, M., Kesharwani, P., et al. (2021). Intranasal delivery of naloxone-loaded solid lipid nanoparticles as a promising simple and non-invasive approach for the management of opioid overdose. International Journal of Pharmaceutics, 599, 120428. https://doi.org/10.1016/j.ijpharm.2021.120428
  https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/021450Orig1s007ltr.pdf
- Illum, L. (2003). Nasal drug delivery-Possibilities, problems and solutions. Journal of Controlled Release, 87, 187-198. https://doi.org/10.1016/S0168-3659(02)00363-2
- Inoue, D., Tanaka, A., Kimura, S., et al. (2018). The relationship between in vivo nasal drug clearance and in vitro nasal mucociliary clearance: Application to prediction of nasal drug absorption. European Journal of Pharmaceutical Sciences, 117, 21-26. https://doi.org/10.1016/j.ejps.2018.01.032
- Jiang, L., Gao, L., Wang, X., Tang, L., & Ma, J. (2010). The application of mucoadhesive polymers in nasal drug delivery. Drug Development and Industrial Pharmacy, 36, 323-336. https://doi.org/10.1080/03639040903170750
- Kanazawa, T. (2015). Brain delivery of small interfering ribonucleic acid and drugs through intranasal administration with nano-sized polymer micelles. Medical Devices: Evidence and Research, 8, 57-64. https://doi.org/10.2147/MDER.S70856
- Kashyap, K., & Shukla, R. (2019). Drug delivery and targeting to the brain through nasal route: Mechanisms, applications and challenges. Current Drug Delivery, 16, 887-901. https://doi.org/10.2174/1567201816666191029122740
- Katare, Y. K., Piazza, J. E., Bhandari, J., et al. (2017). Intranasal delivery of antipsychotic drugs. Schizophrenia Research, 184, 2-13. https://doi.org/10.1016/j.schres.2016.11.027
- Kaushal, V., Hafeez, A., Usmani, S. A., & Alam, S. (2026). Solid lipid nanoparticle-mediated intranasal drug delivery for brain targeting: A comprehensive review. CNS & Neurological Disorders-Drug Targets. https://doi.org/10.2174/0118715273422409260129045318
- Kiran, P., Debnath, S. K., Neekhra, S., et al. (2022). Designing nanoformulation for the nose-to-brain delivery in Parkinson's disease: Advancements and barrier. Wiley

Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 14, e1768. https://doi.org/10.1002/wnan.1768

- Kozlovskaya, L., Abou-Kaoud, M., & Stepensky, D. (2014). Quantitative analysis of drug delivery to the brain via nasal route. Journal of Controlled Release, 189, 133-140. https://doi.org/10.1016/j.jconrel.2014.06.053
- Krishnan, J. K. S., Arun, P., Chembukave, B., et al. (2017). Effect of administration method, animal weight and age on the intranasal delivery of drugs to the brain. Journal of Neuroscience Methods, 286, 16-21. https://doi.org/10.1016/j.jneumeth.2017.05.012
- Kumar, H., Mishra, G., Sharma, A. K., et al. (2017). Intranasal drug delivery: A non-invasive approach for the better delivery of neurotherapeutics. Pharmaceutical Nanotechnology, 5(3), 203-214. https://doi.org/10.2174/2211738505666170515113936
- Lee, D., & Minko, T. (2021). Nanotherapeutics for nose-to-brain drug delivery: An approach to bypass the blood-brain barrier. Pharmaceutics, 13(12), 2049. https://doi.org/10.3390/pharmaceutics13122049
- Liu, X. (2011). Clinical trials of intranasal delivery for treating neurological disorders-A critical review. Expert Opinion on Drug Delivery, 8(12), 1681-1690. https://doi.org/10.1517/17425247.2011.633508
- Lochhead, J. J., & Thorne, R. G. (2012). Intranasal delivery of biologics to the central nervous system. Advanced Drug Delivery Reviews, 64, 614-628. https://doi.org/10.1016/j.addr.2011.11.002
- Lombardo, R., Musumeci, T., Carbone, C., & Pignatello, R. (2021). Nanotechnologies for intranasal drug delivery: An update of literature. Pharmaceutical Development and Technology, 26, 824-845. https://doi.org/10.1080/10837450.2021.1950186
- Marcello, E., & Chiono, V. (2023). Biomaterials-enhanced intranasal delivery of drugs as a direct route for brain targeting. International Journal of Molecular Sciences, 24(4), 3390. https://doi.org/10.3390/ijms24043390
- Mathias, N. R., & Hussain, M. A. (2010). Non-invasive systemic drug delivery: Developability considerations for alternate routes of administration. Journal of Pharmaceutical Sciences, 99, 1-20. https://doi.org/10.1002/jps.21793
- Mistry, A., Stolnik, S., & Illum, L. (2009). Nanoparticles for direct nose-to-brain delivery of drugs. International Journal of Pharmaceutics, 379, 146-157. https://doi.org/10.1016/j.ijpharm.2009.06.019

- Morim, E., Sarmento, B., & Pacheco, C. (2026). Nanocarrier-based intranasal drug delivery for enhanced neurological disorders treatment. Drug Delivery and Translational Research, 16(3), 761-779. https://doi.org/10.1007/s13346-025-02019-z
- Mulet I Piera, X., Del Campo-Montoya, R., Cuadrado-Tejedor, M., et al. (2026). Intranasal delivery of lipid-based nanoparticles for the treatment of neurodegenerative diseases: Advances, challenges and future perspectives. Expert Opinion on Drug Delivery, 23(2), 333-351. https://doi.org/10.1080/17425247.2025.2587903
- Muntimadugu, E., Dhommati, R., Jain, A., et al. (2016). Intranasal delivery of nanoparticle-encapsulated tarenflurbil: A potential brain-targeting strategy for Alzheimer's disease. European Journal of Pharmaceutical Sciences, 92, 224-234. https://doi.org/10.1016/j.ejps.2016.05.012
- Mustafa, G., Alrohaimi, A. H., Bhatnagar, A., et al. (2016). Brain targeting by intranasal drug delivery (INDD): A combined effect of trans-neural and para-neuronal pathway. Drug Delivery, 23, 933-939. https://doi.org/10.3109/10717544.2014.923064
- Nguyen, T. T. L., & Duong, V. A. (2025). Advancements in nanocarrier systems for nose-to-brain drug delivery. Pharmaceuticals, 18(5), 615. https://doi.org/10.3390/ph18050615
- Ong, W. Y., Shalini, S. M., & Costantino, L. (2014). Nose-to-brain drug delivery by nanoparticles in the treatment of neurological disorders. Current Medicinal Chemistry, 21, 4247-4256. https://doi.org/10.2174/092986732166614071610313O
- Ong, W. Y., Shalini, S. M., & Costantino, L. (2014). Nose-to-brain drug delivery by nanoparticles in the treatment of neurological disorders. Current Medicinal Chemistry, 21, 4247-4256. https://doi.org/10.2174/092986732166614071610313O
- Papakyriakopoulou, P., & Valsami, G. (2025). The nasal route for nose-to-brain drug delivery: Advanced nasal formulations for CNS disorders. Expert Opinion on Drug Delivery, 22(6), 823-839. https://doi.org/10.1080/17425247.2025.2489553
- Patel, A., Surti, N., & Mahajan, A. (2019). Intranasal drug delivery: Novel delivery route for effective management of neurological disorders. Journal of Drug Delivery Science and Technology, 52, 130-137. https://doi.org/10.1016/j.jddst.2019.04.017
- Patel, D., & Thakkar, H. (2022). Formulation considerations for improving intranasal delivery of CNS-acting therapeutics. Therapeutic Delivery, 13, 371-381. https://doi.org/10.4155/tde-2022-0018
- Pathak, K., & Akhtar, N. (2016). Nose-to-brain delivery of nanoformulations for neurotherapeutics in Parkinson's disease: Defining the preclinical, clinical and toxicity

issues. Current Drug Delivery, 13(8), 1205-1221. https://doi.org/10.2174/156720181366616060712340 9

- Prabakaran, A., Agrawal, M., Dethe, M. R., et al. (2022). Nose-to-brain drug delivery for the treatment of Alzheimer's disease: Current advancements and challenges. Expert Opinion on Drug Delivery, 19(1), 87-102. https://doi.org/10.1080/17425247.2022.2029845
- Qiu, Y., Huang, S., Peng, L., Yang, L., Zhang, G., Liu, T., Yan, F., & Peng, X. (2025). The nasal-brain drug delivery route: Mechanisms and applications to central nervous system diseases. MedComm, 6(6), e70213. https://doi.org/10.1002/mco2.70213
- Riani, L. R., Seno, G. F. B., Silva, D. M., Toledo, C. R., Paiva, M. R. B., Santos, J. S., Fabri, R. L., Pittella, F., & Tavares, G. D. T. (2026). Chitosan-based nanoparticles for nose-to-brain drug delivery: A real path toward effective CNS therapy? ACS Biomaterials Science & Engineering, 12(5), 2567-2589. https://doi.org/10.1021/acsbiomaterials.6c00137
- Silva, A. M. P., Gonçalves, O. R., Tudella, G. C. N., et al. (2026). Intranasal insulin for mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. Neurological Research, 182(1-2), 36-48. https://doi.org/10.1016/j.neurol.2025.11.005
- Sonvico, F., Clementino, A., Buttini, F., et al. (2018). Surface-modified nanocarriers for nose-to-brain delivery: From bioadhesion to targeting. Pharmaceutics, 10(1), 34. https://doi.org/10.3390/pharmaceutics10010034
- Stella, V. J., & Borchardt, R. T. (2007). Prodrugs and drug delivery to the brain. Advanced Drug Delivery Reviews, 59, 1-2. https://doi.org/10.1016/j.addr.2006.10.001
- Tashima, T. (2020). Shortcut approaches to substance delivery into the brain based on intranasal administration using nanodelivery strategies for insulin. Molecules, 25(21), 5188. https://doi.org/10.3390/molecules25215188
- Thorne, R. G., Emory, C. R., Ala, T. A., & Frey, W. H. II. (1995). Quantitative analysis of the olfactory pathway for drug delivery to the brain. Brain Research, 692, 278-282. https://doi.org/10.1016/0006-8993(95)00637-6
- Trevino, J. T., Quispe, R. C., Khan, F., & Novak, V. (2020). Non-invasive strategies for nose-to-brain drug delivery. Journal of Clinical Trials, 10(7), 439.

- U.S. Food and Drug Administration. (2013). ZOMIG (zolmitriptan) nasal spray: Approval and label information.
- U.S. Food and Drug Administration. (2021). NAYZILAM (midazolam) nasal spray: Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211321s005lbl.pdf
- U.S. Food and Drug Administration. (2025). VALTOCO (diazepam) nasal spray: Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/211635Orig1s012corrected_lbl.pdf
- Ugwoke, M. I., Agu, R., Verbeke, N., & Kinget, R. (2005). Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives. Advanced Drug Delivery Reviews, 57, 1640-1665. https://doi.org/10.1016/j.addr.2005.07.009
- Upadhaya, P. G., Pulakkat, S., & Patravale, V. B. (2020). Nose-to-brain delivery: Exploring newer domains for glioblastoma multiforme management. Drug Delivery and Translational Research, 10(4), 1044-1056. https://doi.org/10.1007/s13346-020-00747-y
- Vitorino, C., Silva, S., Bicker, J., Falcão, A., & Fortuna, A. (2019). Antidepressants and nose-to-brain delivery: Drivers, restraints, opportunities and challenges. Drug Discovery Today, 24(9), 1911-1923. https://doi.org/10.1016/j.drudis.2019.06.001
- Wen, M. M. (2011). Olfactory targeting through intranasal delivery of biopharmaceutical drugs to the brain: Current development. Discovery Medicine, 11(61), 497-503.
- Xu, K., Duan, S., Wang, W., Ouyang, Q., Qin, F., Guo, P., Hou, J., He, Z., Wei, W., & Qin, M. (2024). Nose-to-brain delivery of nanotherapeutics: Transport mechanisms and applications. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 16(2), e1956. https://doi.org/10.1002/wnan.1956
- Zheng, Y., Cui, L., Lu, H., et al. (2024). Nose to brain: Exploring the progress of intranasal delivery of solid lipid nanoparticles and nanostructured lipid carriers. International Journal of Nanomedicine, 19, 12343-12368. https://doi.org/10.2147/IJN.S497480.