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Nose-to-Brain Drug Delivery via Intranasal Route: Nanocarrier-Based Strategies for Neurodegenerative and Central Nervous System Disorders

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Abstract

Background: The treatment of central nervous system disorders is fundamentally constrained by the blood-brain barrier, a highly selective physiological interface that excludes more than 98% of small molecule drugs and virtually all macromolecular therapeutics from the brain parenchyma. The nose-to-brain delivery pathway, exploiting the unique anatomical continuity between the nasal mucosa and the central nervous system via the olfactory and trigeminal nerve networks, offers a non-invasive alternative route that allows drugs to bypass the blood-brain barrier and reach brain tissue directly. Neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and epilepsy — for which current systemic pharmacotherapy is severely hampered by poor CNS penetration — represent particularly compelling targets for intranasal nose-to-brain drug delivery strategies.

Objective: This review critically examines the anatomical basis, transport mechanisms, nanocarrier platforms, formulation design considerations, characterization strategies, and therapeutic applications of nose-to-brain drug delivery for CNS disorders, with emphasis on advances reported in the published literature up to 2022.

Results and Discussion: Multiple nanocarrier platforms including mucoadhesive nanoparticles, lipid nanoparticles, solid lipid nanoparticles, nanoemulsions, cubosomes, and in situ gelling systems have been investigated for intranasal CNS delivery, collectively demonstrating substantially higher brain drug concentrations and improved pharmacodynamic outcomes in animal models compared to equivalent intravenous or oral doses. The olfactory epithelium and trigeminal nerve pathways are the principal routes of nose-to-brain transport, with transport efficiency critically dependent on particle size, surface charge, mucoadhesion, and formulation viscosity.

Conclusion: Nose-to-brain drug delivery via nanocarrier-loaded intranasal formulations represents a scientifically sound and pharmacologically promising approach to CNS drug delivery that addresses the fundamental limitation imposed by the blood-brain barrier. Translation to clinical practice requires resolution of key questions regarding human olfactory transport efficiency, dosing volume constraints, and nasal mucociliary clearance management.

Keywords: *Nose-to-brain delivery; intranasal drug delivery; blood-brain barrier; nanoparticles; olfactory pathway; trigeminal pathway; Alzheimer's disease; Parkinson's disease; mucoadhesive formulations; CNS drug delivery*

1. Introduction

Central nervous system disorders represent one of the greatest unmet therapeutic challenges in modern medicine. Alzheimer's disease affects an estimated 55 million people worldwide, Parkinson's disease affects over 10 million,

epilepsy approximately 50 million, and glioblastoma multiforme carries a median survival of only 15 months despite aggressive multimodal therapy. The pharmacological management of these conditions is profoundly constrained not primarily by a lack of active therapeutic molecules, but by the inability of most drugs to reach the brain parenchyma at therapeutically relevant concentrations following systemic administration [1,2].

The blood-brain barrier is a highly specialized anatomical and functional interface between the systemic circulation and the brain interstitium, formed by cerebral capillary endothelial cells connected by extremely tight junctions, supported by pericytes, and enveloped by astrocytic end-feet processes. This structure restricts paracellular transport to molecules below approximately 400 Daltons with high lipophilicity, and actively expels many lipophilic molecules through ATP-binding cassette efflux transporters including P-glycoprotein and BCRP. It has been estimated that over 98% of small molecule drugs and essentially all peptides, proteins, nucleic acids, and nanoparticles administered systemically do not achieve therapeutic brain concentrations due to blood-brain barrier exclusion [3,4]. Strategies to overcome this barrier — including osmotic blood-brain barrier disruption, focused ultrasound-mediated transient opening, and intracerebroventricular injection — achieve improved brain penetration but carry significant risks of neurological injury, infection, or haemorrhage that limit clinical applicability.

The nose-to-brain pathway represents a fundamentally different approach: instead of attempting to breach or circumvent the blood-brain barrier after drug has entered the systemic circulation, it exploits the unique anatomical connection between the nasal cavity and the central nervous system that exists in the olfactory and trigeminal nerve networks. The olfactory nerve is the only cranial nerve whose sensory neurons have their cell bodies in the nasal epithelium and whose axons project directly into the brain without passing through the blood-brain barrier. This creates an anatomical conduit through which drugs applied to the nasal mucosa can be transported along olfactory and trigeminal neuronal pathways directly into the olfactory bulb, brain stem, and broader CNS compartments [5,6].

The clinical use of intranasal drug delivery for CNS effects is not without precedent. Intranasal sumatriptan for migraine, intranasal desmopressin for diabetes insipidus, and intranasal midazolam for acute seizure management are established clinical products that demonstrate the feasibility of achieving pharmacodynamic CNS effects through nasal administration. However, these products are not designed to exploit the nose-to-brain transport mechanism specifically; rather, they rely primarily on systemic absorption through nasal mucosal blood vessels. The deliberate design of formulations to maximize olfactory and trigeminal nerve transport — through mucoadhesive nanocarriers that increase nasal residence time, particles sized and charged to facilitate transcellular uptake by olfactory neurons, and viscosity-modifying agents that slow mucociliary clearance — is the defining feature of contemporary nose-to-brain formulation research [7,8].

This review provides a comprehensive examination of the anatomical and physiological basis of nose-to-brain transport, the nanocarrier platforms developed for intranasal CNS delivery, formulation design principles and characterization methods, and therapeutic applications in Alzheimer's disease, Parkinson's disease, epilepsy, depression, glioblastoma, and other CNS conditions. A critical analysis of the translational literature identifies important methodological limitations in current preclinical research and key scientific questions that must be addressed before clinical adoption of nose-to-brain nanocarrier delivery can be realized.

2. Scientific Background

2.1 Anatomy of the Nasal Cavity and Olfactory Region

The nasal cavity is divided by the nasal septum into two passages, each lined by a mucous membrane that transitions from squamous epithelium in the nasal vestibule to pseudostratified ciliated columnar epithelium in the respiratory region and to the specialized olfactory epithelium in the superior third of the nasal cavity. The olfactory epithelium, covering approximately 2 to 10 square centimeters of the superior nasal turbinate and adjacent nasal septum in humans, contains olfactory sensory neurons, sustentacular supporting cells, Bowman's gland secretory cells, and basal progenitor cells. Olfactory sensory neurons are bipolar neurons whose apical dendrites project microvilli and cilia into the nasal lumen to detect odorant molecules, and whose unmyelinated axons fasciculate into olfactory fila that pass through the cribriform plate of the ethmoid bone to synapse in the olfactory bulb [9,10].

The nasal cavity is also innervated by branches of the trigeminal nerve (cranial nerve V), specifically the ophthalmic and maxillary divisions, which provide sensory innervation to the nasal mucosa and turbinates. Trigeminal nerve terminals are distributed throughout the respiratory and olfactory epithelia, and perivascular trigeminal nerve sheaths create an additional pathway for drug transport along blood vessels and nerve trunks from the nasal mucosa into the brain stem and cerebellum through the pons and medulla [11].

2.2 The Blood-Brain Barrier as a Drug Delivery Challenge

The blood-brain barrier is formed by specialized cerebral capillary endothelial cells characterized by the expression of continuous tight junctions comprising claudin-5, occludin, and zonula occludens proteins that seal the paracellular space between adjacent endothelial cells to a transendothelial electrical resistance of 1500 to 2000 Ω·cm² — approximately 50- to 100-fold higher than peripheral vascular endothelium. This structural impermeability, combined with the low rate of transcytosis in brain endothelial cells and the active efflux of substrates by P-glycoprotein, BCRP, and multidrug resistance proteins, creates an extraordinarily effective pharmacokinetic barrier [12,13].

The consequences for CNS drug discovery and development are severe: a study by Pardridge estimated that approximately 100% of large molecule drugs and over 98% of small molecule drugs do not cross the blood-brain barrier at therapeutically relevant concentrations. Of the approximately 7000 drugs in clinical use, only around 5% are effective for CNS diseases, and this low proportion has not improved substantially despite decades of drug discovery investment targeting CNS conditions. The need for drug delivery strategies that bypass rather than overcome the blood-brain barrier is therefore a fundamental and enduring challenge in neuropharmacology [14].

2.3 Nose-to-Brain Transport Pathways

Three principal pathways mediate nose-to-brain drug transport. The olfactory pathway involves transcellular transport of drug or nanocarrier across the olfactory epithelium into the perineural space surrounding olfactory axon fascicles, followed by transport along the axon bundles through the cribriform plate into the olfactory bulb. From the olfactory bulb, drug distributes to olfactory cortex, hippocampus, amygdala, and other limbic structures via olfactory tract projections, and to deeper brain regions through olfactory system connectivity. The trigeminal pathway involves transport along perivascular and perineural spaces of trigeminal nerve branches from the nasal mucosa into the brain stem, providing access to the pons, medulla, and cerebellum. The systemic absorption pathway involves drug absorption through nasal mucosal blood vessels into systemic circulation, after which brain penetration is subject to blood-brain barrier restriction — this pathway is undesirable for drugs with poor blood-brain barrier permeability and represents the dominant route only when olfactory and trigeminal transport is not specifically optimized [15,16].

3. Classification of Intranasal Drug Delivery Systems for Nose-to-Brain Delivery

3.1 Mucoadhesive Solutions and Suspensions

The simplest nose-to-brain formulations are aqueous solutions or suspensions of drug with added mucoadhesive polymers such as chitosan, sodium carboxymethylcellulose, carbopol, or hydroxypropyl methylcellulose that increase the viscosity of the formulation and prolong its retention on the nasal mucosa by resisting mucociliary clearance. Increased nasal residence time allows more drug to be transported across the olfactory epithelium before being cleared to the nasopharynx. While these formulations offer simplicity and ease of preparation, they provide limited drug protection against enzymatic degradation in nasal secretions and do not facilitate the transcellular uptake mechanisms that are uniquely accessible to nanocarrier systems [17].

3.2 Nanoparticle-Based Systems

Polymeric nanoparticles fabricated from PLGA, chitosan, albumin, or zein and sized between 100 and 400 nanometers represent the most extensively investigated nanocarrier class for nose-to-brain delivery. Their small size facilitates uptake by pinocytosis and clathrin-mediated endocytosis in olfactory sensory neurons and sustentacular cells of the olfactory epithelium, initiating intracellular transport along olfactory axons toward the brain. Surface modification with mucoadhesive polymers including chitosan, thiolated chitosan, or cell-penetrating peptides enhances epithelial adhesion and transcellular permeation [18,19].

3.3 Lipid Nanoparticles and Nanoemulsions

Solid lipid nanoparticles and nanostructured lipid carriers for intranasal delivery exploit the lipophilicity of their lipid matrix to enhance partitioning into the lipid-rich olfactory epithelial cell membranes and facilitate transcellular transport. Nanoemulsions — thermodynamically stable or kinetically stable submicron oil-in-water dispersions stabilized by surfactants — provide a liquid vehicle for intranasal delivery that combines drug solubilization, mucosal permeation enhancement by surfactant components, and prolonged nasal residence time through their viscosity and bioadhesive properties [20,21].

3.4 In Situ Gelling Systems

Thermosensitive or pH-triggered in situ gelling formulations are liquid at room temperature during nasal administration but form a viscous gel upon contact with the nasal mucosa at body temperature or at physiological pH. Poloxamer 407, gellan gum, and combinations of chitosan with beta-glycerophosphate are the most commonly employed gelling systems. The transition from liquid to gel at the nasal mucosa dramatically increases residence time by converting a low-viscosity spray into a gel depot that resists mucociliary clearance while providing sustained drug release over hours. These systems are particularly valuable for drugs requiring prolonged nasal contact to achieve sufficient olfactory transport [22,23].

3.5 Cubosomes and Hexosomes

Cubosomes are bicontinuous cubic phase liquid crystalline nanoparticles formed by certain monoglycerides, most commonly glyceryl monoolein, in aqueous medium in the presence of a stabilizer such as poloxamer 407. Their three-dimensional periodic lipid bilayer structure provides large internal surface area for drug loading, controlled drug release, and excellent mucoadhesive properties. Hexosomes adopt an inverse hexagonal liquid crystalline phase and share similar structural advantages. Both systems have been investigated for intranasal delivery of CNS drugs including risperidone, carbamazepine, and sumatriptan, demonstrating superior olfactory transport and brain drug concentrations compared to conventional nasal solutions [24].

Table 1: Classification of nose-to-brain intranasal drug delivery systems with characteristics, nanocarrier platforms, and CNS drug examples

System Type	Key Materials	Transport Advantage	Release Profile	CNS Drug Examples
Mucoadhesive solutions	Chitosan, CMC, carbopol	Increased nasal residence	Immediate	Sumatriptan, midazolam
Polymeric nanoparticles	PLGA, chitosan, albumin	Neuronal endocytosis, axonal transport	Controlled release	Rivastigmine, dopamine, siRNA
Solid lipid nanoparticles	Glyceryl behenate, beeswax	Lipid membrane partitioning	Sustained	Quetiapine, olanzapine, haloperidol
Nanostructured lipid carriers	Tripalmitin + liquid lipid	Enhanced drug loading, penetration	Sustained	Nimodipine, ropinirole
Nanoemulsions	Oil, surfactant, co-surfactant	Permeation enhancement, solubilization	Rapid to moderate	Carbamazepine, lorazepam
In situ gelling systems	Poloxamer 407, gellan gum	Gel depot, prolonged residence	Sustained	Donepezil, ropinirole, diazepam
Cubosomes / hexosomes	Glyceryl monoolein, poloxamer	High surface area, mucoadhesion	Controlled	Risperidone, carbamazepine

CMC: carboxymethylcellulose; PLGA: poly(lactic-co-glycolic acid); siRNA: small interfering RNA.

4. Formulation Design and Development

4.1 Particle Size and Surface Charge Optimization

Particle size is the most critical physicochemical variable governing the efficiency of nanocarrier uptake by olfactory epithelial cells and subsequent axonal transport toward the brain. Studies comparing particles of different

sizes in olfactory transport models have consistently demonstrated superior olfactory neuron uptake for particles in the 100 to 200 nanometer range, with substantially reduced uptake for particles above 300 nanometers. The size constraint reflects the dimensions of the pinocytotic and clathrin-coated pit endocytic pathways that mediate nanoparticle internalization in olfactory neurons and sustentacular cells. Particles below 50 nanometers may be too small for optimal mucoadhesive interaction but can diffuse rapidly through the mucus layer [25,26].

Surface charge profoundly influences both mucus penetration and cellular uptake. The nasal mucus is a negatively charged polyanionic gel network due to the presence of mucin glycoproteins with sulfate and carboxylate groups; positively charged nanoparticles interact electrostatically with mucin and become trapped in the mucus gel, which paradoxically increases residence time and olfactory epithelium contact. Chitosan-coated nanoparticles, which carry a positive charge at physiological pH due to protonated amine groups, combine mucoadhesion through electrostatic interaction with mucin and transient tight junction opening that facilitates paracellular transport across the olfactory epithelium, making chitosan the most extensively investigated surface coating for nose-to-brain nanocarriers [27].

4.2 Mucoadhesive Polymers and Nasal Residence Time

Mucociliary clearance, which removes nasal mucus and associated particles from the olfactory and respiratory epithelia within 20 to 30 minutes in healthy subjects, is the principal competing process limiting nose-to-brain transport efficiency. Mucoadhesive polymers incorporated into nanocarrier surface coatings or formulation matrices bind to mucin glycoproteins through non-covalent interactions including hydrogen bonding, hydrophobic interaction, and electrostatic attraction, physically anchoring the formulation to the nasal mucosa and resisting clearance by ciliary beating. Thiolated chitosan, also termed thiomers, forms covalent disulfide bonds with cysteine-rich mucin domains, providing substantially stronger and more durable mucoadhesion than unmodified chitosan and have been demonstrated to increase nasal drug residence time by up to fourfold compared to non-mucoadhesive controls [28,29].

4.3 Permeation Enhancers for Olfactory Epithelial Transport

Chemical permeation enhancers are incorporated into nasal formulations to increase the permeability of the olfactory epithelium to drug molecules and nanocarriers by transiently disrupting the tight junctions between olfactory epithelial cells or by extracting membrane lipids to increase transcellular fluidity. Surfactants including sodium lauryl sulfate and bile salts, fatty acids including caprylic acid and oleic acid, and chelating agents including EDTA have been used as nasal permeation enhancers. The application of permeation enhancers to the olfactory region presents a delicate balance: sufficient enhancement of transport must be achieved without causing irreversible damage to the olfactory neuroepithelium, which is not directly regenerated in adult humans and whose impairment would cause permanent anosmia [30].

4.4 pH and Isotonicity Considerations

The pH of nasal formulations must be maintained within the range compatible with nasal mucosal tolerance, typically pH 4.5 to 6.5, as more acidic or alkaline formulations cause mucosal irritation, ciliary dysfunction, and patient discomfort that reduces acceptability and compliance. Isotonicity matching to nasal fluid osmolarity of approximately 300 mOsm/kg is similarly important to prevent osmotic stress to the olfactory epithelial cells. The pH and ionic strength of the formulation also influence the charge state of ionizable drugs and the surface charge of pH-sensitive nanocarriers, which in turn affect mucoadhesion and olfactory epithelial cell interaction [31].

5. Preparation Methods

5.1 Emulsification-Solvent Evaporation for Polymeric Nanoparticles

PLGA and other polyester nanoparticles for intranasal delivery are most commonly prepared by the emulsification-solvent evaporation method, in which the polymer and lipophilic drug are dissolved in a water-immiscible organic solvent and emulsified in an aqueous phase containing a stabilizer such as polyvinyl alcohol. Evaporation of the organic solvent causes nanoparticle solidification and precipitation. Hydrophilic drugs are encapsulated by the double emulsification method (water-in-oil-in-water), in which an aqueous drug solution is first emulsified in the polymer-containing organic phase to form a primary emulsion, which is then re-emulsified in a larger aqueous phase [32].

5.2 Nanoprecipitation

Nanoprecipitation, or the solvent displacement method, involves the rapid addition of a polymer-drug solution in a water-miscible organic solvent (typically acetone or ethanol) into an aqueous phase containing

a stabilizer under continuous stirring. The rapid solvent-water exchange causes nucleation and growth of polymer nanoparticles around the drug. This method produces particles of narrow size distribution with PDI values below 0.15, requires no high-energy input, and is suitable for both hydrophobic and amphiphilic polymers. Nanoprecipitation is favored for preparation of intranasal nanoparticles from PVP, polycaprolactone, and Eudragit polymers [33].

5.3 High-Shear Homogenization and Ultrasonication for Nanoemulsions

Nanoemulsions for intranasal delivery are prepared by high-shear homogenization or probe ultrasonication of a coarse emulsion of the drug-containing oil phase in an aqueous continuous phase stabilized by a surfactant-cosurfactant blend. High-pressure homogenization at pressures of 500 to 1000 bar produces droplets of 100 to 300 nanometers with narrow size distribution suitable for nasal administration. The oil phase is typically medium-chain triglycerides, castor oil, or eucalyptus oil, the latter providing additional nasal permeation enhancement attributed to its monoterpene content. Surfactant combinations including Tween 80 and Span 20 or lecithin and poloxamer provide thermodynamic or kinetic stabilization [34].

5.4 Hot and Cold Homogenization for Lipid Nanoparticles

Solid lipid nanoparticles for intranasal brain delivery are prepared by hot homogenization — melting the solid lipid matrix above its melting point, dispersing the drug in the melt, emulsifying with an aqueous surfactant solution at the same temperature using a high-pressure homogenizer, then cooling the nanoemulsion to solidify the lipid matrix — or by cold homogenization, in which the drug-lipid melt is solidified by liquid nitrogen and the resulting solid mass ground into powder before homogenization with cold surfactant solution. Cold homogenization is preferred for thermolabile drugs including proteins and peptides that cannot tolerate the elevated temperatures of hot processing [35].

5.5 Preparation of In Situ Gelling Nasal Formulations

In situ nasal gels are prepared as cold liquid solutions of the gelling polymer, drug, and formulation excipients that undergo sol-gel transition upon nasal application. Poloxamer 407-based gels are prepared by the cold method, in which poloxamer is dispersed in cold water (2 to 8°C) under gentle stirring to fully hydrate the polymer, followed by addition of drug and other excipients. The resulting solution is liquid at refrigerated storage temperature but gels rapidly at nasal cavity temperature (34°C) through micellar packing. Gellan gum-based in situ gels are triggered by the ionic composition of nasal fluid (calcium and sodium ions), forming a gel depot upon contact with the mucosa [36].

6. Characterization and Evaluation

6.1 Physicochemical Characterization

Dynamic light scattering is used to measure hydrodynamic diameter and polydispersity index of nanocarriers for intranasal delivery. Optimal nose-to-brain nanocarriers fall in the 100 to 300 nanometer size range with PDI values below 0.25. Zeta potential is a critical parameter for predicting both mucoadhesion (positive zeta potential indicates electrostatic interaction with anionic mucin) and colloidal stability (absolute values exceeding 30 mV indicate electrostatically stabilized dispersions). Morphological characterization by TEM or AFM confirms nanoparticle shape and reveals surface features including polymer coatings [37].

6.2 Mucoadhesion Testing

In vitro mucoadhesion of nasal nanoformulations is assessed by measuring changes in the rheological properties of nasal mucus or purified mucin solution following mixing with the nanoparticle formulation. An increase in viscosity, storage modulus (G'), or loss modulus (G'') of the mucin gel upon addition of nanoparticles indicates mucoadhesive interaction. The mucin particle method measures adsorption of mucin onto nanoparticle surfaces by zeta potential shift or changes in particle size before and after incubation with mucin solution. Rotating cylinder or flow-through methods using excised sheep nasal mucosa provide more physiologically relevant mucoadhesion data [38].

6.3 In Vitro Drug Release and Nasal Permeation

Drug release from nasal nanocarriers is assessed using dialysis bag methods or Franz diffusion cells with a suitable membrane. For nose-to-brain formulation development, ex vivo permeation across excised sheep olfactory mucosa mounted in a modified Ussing chamber provides pharmacokinetically relevant data on the rate and extent of drug permeation across the olfactory epithelial barrier, enabling calculation of apparent

permeability coefficients. Sheep nasal mucosa is the preferred model owing to its similar thickness, ciliation pattern, and enzymatic activity profile to human nasal mucosa [39].

6.4 Drug Targeting Efficiency and Direct Transport Percentage

The key pharmacokinetic parameters for evaluating nose-to-brain delivery efficiency are the drug targeting efficiency (DTE%) and direct transport percentage (DTP%), calculated from brain and plasma drug concentration-time profiles in animal studies. DTE% compares the ratio of brain-to-plasma AUC following intranasal administration to the same ratio following intravenous administration, with values greater than 100% indicating net drug targeting to the brain above what would be predicted from systemic absorption alone. DTP% estimates the fraction of brain drug concentration attributable to direct nose-to-brain transport rather than systemic absorption and blood-brain barrier penetration [40].

6.5 In Vivo Brain Distribution Studies

Fluorescent or radiolabeled nanoparticles administered intranasally are tracked in rodent brain tissue by fluorescence microscopy, autoradiography, or gamma scintigraphy to confirm olfactory and trigeminal pathway transport. Quantitative pharmacokinetic studies measure drug concentrations in olfactory bulb, cerebral cortex, hippocampus, cerebellum, and brain stem at multiple time points following intranasal administration, allowing construction of regional brain pharmacokinetic profiles and comparison with intravenous or oral dosing. The presence of significantly higher olfactory bulb concentrations compared to other brain regions at early time points following intranasal administration is considered strong evidence of olfactory pathway-mediated direct transport rather than systemic absorption [41].

7. Mechanism of Nose-to-Brain Drug Delivery

7.1 Olfactory Pathway Transport

Transport along the olfactory pathway begins with contact between the intranasally administered formulation and the olfactory epithelium in the superior nasal cavity. Drug molecules or nanocarriers must first penetrate the mucus layer overlying the olfactory epithelium, either by diffusion through the aqueous mucus channels between mucin fibers (for small hydrophilic molecules or mucus-penetrating nanoparticles) or by mucoadhesive immobilization at the mucus surface followed by gradual dissolution and diffusion. Transcellular transport across olfactory epithelial cells occurs by transcytosis in sustentacular cells, or by direct uptake into olfactory sensory neuron dendrites by endocytosis or pinocytosis. Once internalized in olfactory neuron cytoplasm, nanocarriers are transported along the olfactory axon toward the olfactory bulb by active axonal transport mechanisms including dynein-mediated retrograde transport [42,43].

7.2 Trigeminal Pathway Transport

The trigeminal pathway provides an additional and arguably clinically underappreciated route for nose-to-brain drug transport, particularly relevant for drugs targeting the brain stem, cerebellum, and spinal cord, which are less accessible via olfactory pathway projections. Drug molecules absorbed through the nasal respiratory epithelium enter perivascular and perineural spaces surrounding trigeminal nerve branches and are transported centrally along perineurial sheaths into the brain stem where the trigeminal nerve nuclei are located. The trigeminal pathway has been implicated in the observed nose-to-brain transport of molecules that do not appear to concentrate specifically in the olfactory bulb, including some nanoparticle formulations that show broad brain stem distribution following intranasal administration [44].

7.3 Lymphatic Transport and Systemic Absorption

A portion of intranasally administered drug is inevitably absorbed into the systemic circulation through the richly vascularized nasal respiratory mucosa, providing systemic drug exposure that may contribute to brain concentrations through blood-brain barrier-dependent mechanisms for drugs with sufficient CNS permeability. The nasal-associated lymphoid tissue (NALT) and cervical lymphatics also provide a drainage pathway from the nasal mucosa to systemic lymphatic circulation. For immunological applications including nasal vaccines, NALT-mediated antigen uptake and immune activation is the desired pathway rather than a secondary route [45].

8. Therapeutic Applications

8.1 Alzheimer's Disease

Alzheimer's disease, characterized by progressive accumulation of amyloid-beta plaques and neurofibrillary tau tangles in the hippocampus and cortex with associated neuroinflammation and cholinergic deficit,

represents perhaps the most compelling clinical target for nose-to-brain drug delivery owing to the severity of blood-brain barrier restriction for most investigational disease-modifying agents. Rivastigmine-loaded chitosan nanoparticles and solid lipid nanoparticles administered intranasally in rat models of Alzheimer's disease achieved brain drug concentrations three- to fivefold higher than equivalent oral doses while demonstrating superior performance in Morris water maze and passive avoidance cognitive behavioral tests compared to oral and intravenous controls [46,47].

Intranasal delivery of insulin has attracted particular clinical interest for Alzheimer's disease following the observation that insulin receptors are highly expressed in hippocampal and cortical neurons and that central insulin signaling improves synaptic plasticity and reduces amyloid-beta production. Clinical studies including the SNIFF (Study of Nasal Insulin to Fight Forgetfulness) trials demonstrated that intranasal insulin administration improved memory performance and preserved cerebrospinal fluid biomarker profiles in mild cognitive impairment and early Alzheimer's disease, providing clinical proof-of-concept for nose-to-brain delivery of a macromolecular therapeutic [48].

8.2 Parkinson's Disease

Parkinson's disease, characterized by progressive degeneration of dopaminergic neurons in the substantia nigra with consequent striatal dopamine deficiency, is a particularly logical target for intranasal nose-to-brain delivery because the substantia nigra and striatum are connected to olfactory and limbic brain regions that are accessible via the olfactory pathway. Dopamine itself cannot be administered systemically due to its inability to cross the blood-brain barrier, while its prodrug levodopa requires co-administration of dopa decarboxylase inhibitors and causes dose-limiting motor fluctuations with long-term use. Intranasal ropinirole-loaded nanoparticles and dopamine-loaded liposomes targeted to the olfactory epithelium demonstrated significantly higher striatal dopamine levels and improved rotarod performance in 6-OHDA-lesioned Parkinson's disease rat models compared to oral or intravenous drug administration [49,50].

8.3 Epilepsy and Acute Seizure Management

Intranasal administration of benzodiazepines for acute seizure termination is the most clinically advanced nose-to-brain application, with nasal midazolam and diazepam solutions approved for acute seizure rescue therapy in adults and children. These approvals demonstrate that the nasal route achieves sufficiently rapid CNS drug delivery for seizure termination — an indication requiring drug action within minutes — validating nose-to-brain pharmacokinetics clinically. Building on this established precedent, nanoparticle and in situ gel formulations of clonazepam, lorazepam, and carbamazepine for both acute rescue and chronic seizure prophylaxis have been investigated, with intranasal nanoformulations demonstrating superior seizure threshold elevation and anticonvulsant duration compared to conventional nasal solutions in animal models [51].

8.4 Brain Tumors

Glioblastoma multiforme, the most common and aggressive primary brain tumor, is characterized by its diffuse infiltrative growth within brain parenchyma behind an intact blood-brain barrier, creating an environment that is essentially inaccessible to systemically administered chemotherapy at the required tumoricidal concentrations without neurotoxic plasma levels. Intranasal delivery of temozolomide, paclitaxel, and curcumin-loaded nanoparticles have been investigated as local nose-to-brain chemotherapy approaches. Temozolomide-loaded chitosan nanoparticles administered intranasally produced brain concentrations three- to fourfold higher than equivalent oral doses in rat glioma models and demonstrated tumor growth inhibition in orthotopic glioblastoma implantation models [52].

8.5 Depression and Psychiatric Disorders

Intranasal delivery of antidepressants and antipsychotics offers potential advantages of reduced systemic side effects, avoidance of first-pass hepatic metabolism, and more rapid CNS onset compared to oral dosing. Quetiapine-loaded solid lipid nanoparticles for intranasal delivery in schizophrenia demonstrated DTE values exceeding 400% compared to intravenous administration in rat studies, indicating predominant nose-to-brain transport rather than systemic absorption. Olanzapine intranasal nanoparticles and in situ gels similarly achieved brain-targeting efficiency significantly greater than 100% with reduced peripheral exposure compared to oral dosing, supporting further preclinical development [53].

9. Recent Advances

9.1 Exosome-Mediated Nose-to-Brain Delivery

Exosomes derived from mesenchymal stem cells, macrophages, and other cell types have emerged as biologically inspired nose-to-brain delivery vehicles owing to their natural capacity to cross biological barriers including the blood-brain barrier and olfactory epithelium. Intranasal administration of curcumin-loaded macrophage-derived exosomes in mouse models of brain inflammation demonstrated significantly higher brain curcumin concentrations and reduced neuroinflammatory markers compared to free curcumin solution, with the exosomal surface proteins hypothesized to facilitate uptake by olfactory epithelial cells through receptor-mediated mechanisms [54].

9.2 Cell-Penetrating Peptide-Functionalized Nanoparticles

Surface functionalization of intranasal nanoparticles with cell-penetrating peptides including rabies virus glycoprotein peptide (RVG29), wheat germ agglutinin, and penetratin has been investigated as a strategy to enhance transcellular uptake by olfactory sensory neurons and improve axonal transport efficiency. RVG29, a 29-amino acid peptide derived from the rabies virus glycoprotein that binds the acetylcholine receptor expressed on neuronal cell membranes, was reported to increase brain uptake of coated nanoparticles following intranasal administration in mice by a factor of approximately three compared to unconjugated nanoparticles of identical size and composition [55].

9.3 mRNA and siRNA Delivery via Intranasal Route

Intranasal delivery of nucleic acid therapeutics for CNS gene therapy and gene silencing represents a frontier application of nose-to-brain technology. Lipid nanoparticles loaded with siRNA targeting alpha-synuclein, a protein whose aggregation drives Parkinson's disease pathology, were reported to achieve measurable alpha-synuclein mRNA knockdown in the olfactory bulb and substantia nigra following intranasal administration in mice, demonstrating that the olfactory pathway is accessible to LNP-mediated nucleic acid delivery. The development of intranasal LNP formulations optimized for olfactory epithelial cell uptake and neuronal transport represents an intersection of mRNA-LNP technology and nose-to-brain delivery principles [56].

9.4 Thermosensitive Nanocomposite Gels

Nanocomposite in situ gelling systems, in which drug-loaded nanoparticles are dispersed within a thermosensitive or mucoadhesive gel matrix, combine the olfactory transport advantages of nanoparticles with the extended nasal residence time provided by the gel phase. Rivastigmine-loaded PLGA nanoparticles dispersed in a poloxamer 407-chitosan thermosensitive gel demonstrated twofold higher olfactory bulb drug concentrations and significantly prolonged brain pharmacokinetic profiles compared to nanoparticles administered without gel vehicle in rat studies, supporting the concept that nanoparticle-in-gel composites provide additive transport enhancement beyond either component alone [57].

10. Comparative Analysis

The nose-to-brain route is best evaluated in comparison with alternative strategies for CNS drug delivery, each of which carries its own risk-benefit profile. Systemic intravenous or oral administration remains the standard clinical approach but is fundamentally limited by blood-brain barrier exclusion for the majority of therapeutic molecules. Intrathecal and intracerebroventricular administration achieve high CNS drug concentrations but require neurosurgical implantation of delivery devices, carry risks of infection, catheter malfunction, and CSF leakage, and are reserved for conditions requiring direct intrathecal therapy such as spinal muscular atrophy and intractable pain. Focused ultrasound-mediated transient blood-brain barrier opening is a non-invasive approach that enables systemic drugs to enter the brain during a therapeutic window, but requires dedicated equipment, expertise, and carries risks of microhemorrhage and cerebral edema [58,59].

The intranasal route avoids all surgical risks, requires no specialized equipment beyond a nasal spray device, enables self-administration, and exploits a natural neuroanatomical connection to the brain. Its principal limitations relative to direct CNS injection are lower delivery efficiency (typically 0.1 to 1% of administered dose reaching brain tissue via olfactory transport in animal models), restriction of olfactory transport to the olfactory bulb and olfactory-connected brain regions in the first instance, and variability in olfactory epithelium area and function between individuals and in conditions such as rhinitis, nasal polyps, and COVID-19-associated anosmia.

Table 2: Comparative evaluation of nose-to-brain intranasal delivery versus alternative CNS drug delivery strategies

Parameter	Oral / IV	Intrathecal	Focused Ultrasound BBB Opening	Convection-Enhanced Delivery	Nose-to-Brain (Nasal)
BBB bypass	No	Yes	Transient	Yes	Yes (olfactory route)
Invasiveness	None	High (surgical)	Low-moderate	High (neurosurgical)	None
Self-administration	Yes	No	No	No	Yes
Brain targeting efficiency	Poor (BBB limited)	Very high	High (during opening)	Very high (local)	Moderate
Biologic delivery	Not feasible	Yes	Limited	Yes	Yes (nanocarriers)
Safety profile	Systemic toxicity	Infection, CSF leak	Microhemorrhage risk	Infection, edema	Nasal irritation

BBB: blood-brain barrier; CSF: cerebrospinal fluid; IV: intravenous.

11. Advantages and Limitations

11.1 Advantages

- Direct anatomical connection between olfactory epithelium and olfactory bulb provides a physiological bypass of the blood-brain barrier without pharmacological or physical disruption of this critical protective structure
- Non-invasive, self-administered route requiring only a nasal spray device — eliminates surgical risks associated with direct CNS administration methods
- Rapid onset of CNS drug action demonstrated clinically for nasal midazolam and sumatriptan, relevant for acute seizure termination and migraine treatment
- Avoidance of first-pass hepatic metabolism improves systemic bioavailability for drugs with high hepatic extraction ratios and reduces metabolite-related toxicity
- Access to Langerhans cell-equivalent nasal-associated lymphoid tissue enables nasal vaccine delivery with mucosal immune system activation and secretory IgA production
- Nanocarrier formulations provide drug protection against enzymatic degradation in nasal secretions and enable controlled drug release for sustained CNS exposure from a single administration
- Versatility to deliver small molecules, peptides, proteins, and nucleic acid cargoes when appropriately formulated in nanocarrier systems

11.2 Limitations

- The olfactory epithelium covers only 2 to 10 square centimeters of nasal mucosa in humans — a substantially smaller proportion of total nasal surface area than in rodents, creating a significant species-dependent limitation in olfactory transport efficiency
- Mucociliary clearance removes nasally administered formulations from the olfactory region within 20 to 30 minutes, severely limiting the contact time available for olfactory epithelial transport unless mucoadhesive formulations are employed
- Maximum nasal dosing volume of approximately 100 to 200 microliters per nostril constrains the total drug dose deliverable intranasally, limiting applicability to potent drugs with therapeutic doses in the milligram range or below

- Nasal conditions including rhinitis, sinusitis, nasal polyps, mucosal edema, and COVID-19-associated olfactory dysfunction alter both the available olfactory epithelial surface area and mucociliary clearance rates, introducing significant intra- and inter-individual variability in drug delivery
- The fraction of intranasally administered dose reaching brain tissue via direct olfactory transport is typically estimated at 0.1 to 1% in animal studies — dramatically lower than for direct CNS administration — and may be even lower in humans with proportionally smaller olfactory epithelium
- Long-term olfactory epithelial safety of repeated intranasal nanoparticle administration has not been established, with limited data on cumulative nasal mucosal toxicity and olfactory function preservation with chronic dosing

12. Clinical Translation and Marketed Products

The clinical translation of nose-to-brain drug delivery exists on a spectrum from well-established clinical products that achieve nasal CNS delivery primarily through systemic absorption to early-stage investigational nanocarrier systems designed specifically for olfactory pathway transport. At the established end of the spectrum, intranasal sumatriptan (Imitrex Nasal), zolmitriptan (Zomig Nasal), desmopressin, and nasal midazolam (Nayzilam) and diazepam (Valtoco) for seizure rescue represent approved products with documented CNS activity via the nasal route, providing important precedents for regulatory acceptance of nasal CNS delivery.

The most compelling clinical evidence for olfactory pathway-mediated nose-to-brain drug delivery comes from the SNIFF clinical trials of intranasal insulin for Alzheimer's disease, which demonstrated cognitive benefits consistent with CNS insulin effects in the absence of systemic hypoglycemia — a pharmacodynamic signature indicating direct CNS delivery without meaningful systemic absorption. This provided proof-of-concept clinical evidence that olfactory pathway transport of a peptide can achieve therapeutically relevant brain concentrations in humans. Additional phase 2 clinical trials of intranasal oxytocin for autism spectrum disorder, intranasal glutathione for Parkinson's disease, and intranasal NAD+ for neurocognitive function were in progress or had reported preliminary results as of 2022 [60].

Table 3: Clinically approved intranasal CNS products and selected nose-to-brain clinical programmes (as of 2022)

Product / Programme	Drug	CNS Indication	Delivery Mechanism	Clinical Status
Imitrex Nasal (GSK)	Sumatriptan	Migraine	Systemic absorption + CNS	Approved — standard clinical use
Nayzilam (UCB)	Midazolam	Acute seizure rescue	Systemic absorption + CNS	FDA approved (2019)
Valtoco (Neurelis)	Diazepam	Acute seizure rescue	Systemic absorption + CNS	FDA approved (2020)
SNIFF Trials (NIH/Craft)	Insulin	Alzheimer's disease	Olfactory direct transport	Phase 2 — cognitive benefit demonstrated
Intranasal oxytocin (multiple)	Oxytocin	Autism, social cognition	Olfactory + trigeminal	Phase 2 — mixed results (2022)
IN glutathione (Perlmutter)	Glutathione	Parkinson's disease	Olfactory direct transport	Phase 2 — ongoing (2022)

IN: intranasal; NIH: National Institutes of Health; GSK: GlaxoSmithKline; UCB: Union Chimique Belge.

13. Critical Analysis

The nose-to-brain drug delivery literature is subject to several methodological concerns that limit the strength of conclusions that can be drawn from the preclinical evidence base. The most serious and pervasive issue is the systematic overestimation of nose-to-brain transport efficiency in rodent models relative to what is achievable in humans. The olfactory epithelium covers approximately 50% of the total nasal mucosal surface in rats but only 3 to 8% in humans. When a standard nasal volume is administered to rats, a substantially higher proportion of the dose reaches the olfactory region than occurs in humans receiving an equivalent nasal volume. Published DTE% and DTP% values derived from rat studies therefore systematically overestimate the direct nose-to-brain transport component that can be expected in clinical application, yet this limitation is rarely acknowledged with appropriate quantitative context in the primary literature [61].

The pharmacokinetic methodology used to calculate DTE% and DTP% has been criticized for making assumptions that inflate the apparent contribution of direct nose-to-brain transport. The standard DTP% calculation assumes that the fraction of brain drug derived from systemic circulation can be estimated from the brain-to-plasma ratio following intravenous administration, then subtracted from the total brain drug observed after intranasal dosing to yield the direct transport component. However, this calculation does not account for differences in brain regional blood flow, protein binding changes at different plasma concentrations, or the possibility that intranasal administration alters cerebrovascular tone through locally absorbed vasoactive compounds in nasal formulations. Several independent analyses have suggested that calculated DTP% values may overestimate direct nasal transport by factors of two to ten in typical study designs [62].

A further limitation is the near-universal reliance on anesthetized animal models for intranasal administration studies. Anesthesia substantially alters nasal mucociliary function, vascular tone, and breathing pattern in ways that affect drug deposition in the olfactory versus respiratory regions and mucociliary clearance rate. Studies comparing intranasal pharmacokinetics in conscious versus anesthetized animals have reported significant differences in both drug deposition pattern and subsequent brain pharmacokinetics, calling into question the translational validity of pharmacokinetic parameters derived from anesthetized rodent studies [63].

The clinical data from intranasal insulin trials in Alzheimer's disease, while encouraging as proof-of-concept, highlight a reproducibility challenge within the field. The initial SNIFF-2 trial reported cognitive benefits of intranasal insulin in mild cognitive impairment and early Alzheimer's disease, but a subsequent larger trial (SNIFF-3) using a different insulin formulation device failed to replicate these findings, attributed to differences in intranasal drug deposition patterns between the two delivery devices rather than failure of the nose-to-brain concept itself. This negative trial underscores how critically device design and drug deposition characteristics — factors rarely systematically optimized in preclinical nose-to-brain research — can determine clinical outcome [64].

14. Conclusion

Nose-to-brain drug delivery via the intranasal route represents a scientifically compelling and anatomically grounded approach to bypassing the blood-brain barrier for the treatment of CNS disorders. The olfactory and trigeminal nerve pathways provide natural neuroanatomical conduits from the nasal cavity to the brain that can be exploited by rationally designed nanocarrier formulations to achieve selective CNS drug targeting without surgical intervention or pharmacological blood-brain barrier disruption. The clinical approvals of intranasal midazolam and diazepam for acute seizure rescue demonstrate that nasally administered drugs can achieve pharmacodynamically meaningful CNS concentrations within clinically relevant time frames, while the SNIFF trials of intranasal insulin provide early evidence that olfactory pathway transport of peptide macromolecules is achievable in humans.

The nanocarrier platforms developed for nose-to-brain delivery — including chitosan nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, cubosomes, and in situ gelling composites — collectively demonstrate the formulation versatility required to accommodate diverse drug physicochemical properties and therapeutic requirements. The extension of nose-to-brain delivery to nucleic acid payloads including siRNA and mRNA using lipid nanoparticle platforms represents an emerging frontier with significant potential for CNS gene therapy.

Critical appraisal of the preclinical literature reveals important methodological limitations including the systematic overestimation of nose-to-brain transport efficiency from rodent models with disproportionately large olfactory epithelium, the pharmacokinetic calculation assumptions embedded in DTE% and DTP% methodology, and the confounding effects of anesthesia on nasal drug deposition and clearance. The translational gap between rodent pharmacokinetics and human clinical efficacy — illustrated starkly by the contrasting outcomes of SNIFF-2 and SNIFF-3 intranasal insulin trials — underscores the need for more rigorous clinical pharmacokinetic characterization and human olfactory deposition studies before nose-to-brain nanocarrier products can advance confidently through clinical development.

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