www.ijarp.com ISSN 2456-9992 Page: 01-18

International Journal Advanced Research Publications

Research Article

Volume: 02
Issue: 11

NANOCARRIER-MEDIATED NOSE-TO-BRAIN DRUG DELIVERY: OVERCOMING THE BLOOD-BRAIN BARRIER FOR NEUROLOGICAL THERAPEUTICS

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Article Received: 19 October 2026, Article Revised: 08 November 2026, Published on: 27 November 2026

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Doi: https://doi-doi.org/101555/ijarp.9900

ABSTRACT

Effective treatment of neurological disorders is frequently limited by the restricted entry of therapeutic molecules into the central nervous system (CNS). The blood-brain barrier (BBB), formed by specialized brain endothelial cells and supporting neurovascular-unit components, protects neural tissue but also limits the delivery of many potentially useful medicines. Intranasal administration has therefore attracted interest as a non-invasive route that may facilitate direct transport from the nasal cavity to the brain through olfactory and trigeminal pathways. Nanocarriers can further influence this process by protecting drugs from degradation, modifying release, improving mucosal contact, and supporting cellular uptake. This narrative review discusses the anatomy and physiology of the nasal cavity, BBB structure, proposed nose-to-brain transport mechanisms, and major pharmaceutical nanocarriers, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, and dendrimers. Formulation development, physicochemical characterization, mucoadhesive and targeting strategies, and safety considerations are also examined. Representative preclinical studies involving Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, and ischemic stroke are compared, with particular attention to the distinction between in-vitro, animal, and human evidence. Current

findings indicate that selected intranasal nanocarriers can improve brain exposure in experimental models; however, deposition variability, mucociliary clearance, local toxicity, dose reproducibility, and translation from animal anatomy to humans remain important challenges. Progress will depend on standardized pharmacokinetic methods, clinically relevant delivery devices, repeated-dose safety studies, and carefully designed clinical investigations.

KEYWORDS: Nose-to-brain delivery; Intranasal administration; Nanocarriers; Blood-brain barrier; Brain targeting; Neurological disorders.

INTRODUCTION

Neurological disorders represent a diverse group of conditions involving the brain, spinal cord, and peripheral nervous system. Alzheimer's disease, Parkinson's disease, epilepsy, ischemic stroke, and primary brain tumours differ in their causes and pathological processes, but their treatment often shares one major pharmaceutical problem: achieving an effective concentration of a therapeutic agent at the intended site within the central nervous system (CNS). Conventional oral and parenteral administration may produce adequate plasma concentrations while providing insufficient drug exposure in brain tissue. The difficulty becomes more pronounced for hydrophilic molecules, peptides, proteins, nucleic acids, and several cytotoxic agents, many of which have limited ability to cross the blood-brain barrier (BBB). Consequently, the development of delivery systems that improve CNS exposure without causing unacceptable systemic or neurological toxicity remains an important area of pharmaceutical research.[1,4]

Several strategies have been investigated to address the BBB, including chemical modification of drugs, carrier-mediated transport, receptor-targeted systems, temporary barrier modulation, and direct administration into the CNS. Invasive approaches such as intracerebral or intrathecal injection can achieve local delivery but are associated with procedural risks, limited distribution, and practical difficulties for repeated treatment. It is not, however, a universal bypass route: nasal absorption into blood can also occur, and the relative contribution of direct and systemic pathways depends on the molecule, formulation, deposition site, and experimental model. [2,4,11]

Nanotechnology offers a means of modifying the behaviour of therapeutic molecules at this interface. Lipid-based systems may accommodate poorly water-soluble drugs and provide a matrix for controlled release; polymeric nanoparticles can be engineered for biodegradation,

surface functionalization, and mucoadhesion; and nanoemulsions can improve the apparent solubilization of lipophilic compounds. These functions are formulation-dependent and should not be interpreted as proof that every nanoparticle can enter olfactory neurons or cross the BBB. Particle size, surface charge, composition, morphology, drug loading, and release behaviour collectively influence performance.[6-10]

Recent research has explored nanocarrier-based intranasal delivery for neurodegenerative diseases, epilepsy, glioblastoma, and ischemic injury. Examples include rivastigmine-loaded liposomes and nanoparticles, dopamine-loaded lipid carriers, insulin-loaded chitosan-coated polymeric nanoparticles, liposomal drug and siRNA combinations, and lipid nanoparticles carrying therapeutic RNA. discuss formulation and safety requirements, and critically summarize representative therapeutic applications while distinguishing experimental promise from demonstrated clinical benefit. [8-24]

MATERIALS AND METHODS

This manuscript was prepared as a narrative review of published literature on intranasal and nanocarrier-mediated drug delivery to the brain. Literature discovery focused on PubMed/MEDLINE-indexed records, targeted searches of journal and publisher platforms (including ScienceDirect, SpringerLink, RSC and relevant journal websites), and reference lists of major reviews and primary studies. Searches were updated on 19 November 2026. Google Scholar was not independently searched through a structured, exportable workflow; no claim is made that retrieval was exhaustive. Search phrases were used in different combinations and included “nose-to-brain drug delivery”, “intranasal nanocarriers”, “blood-brain barrier”, “olfactory pathway”, “trigeminal pathway”and terms for Alzheimer’s disease, Parkinson’s disease, epilepsy, glioma, and ischemic stroke. The approach was designed to identify mechanistic studies, formulation papers, preclinical therapeutic investigations, clinical-translational reviews, and authoritative discussions of BBB biology; it was not designed as a systematic review or meta-analysis.[1,4-11]

Peer-reviewed original research, experimental formulation studies, relevant clinical or translational reports, and authoritative narrative reviews were considered when they directly addressed nasal anatomy, transport mechanisms, nanocarrier composition, brain pharmacokinetics, neurological applications, or local safety. Studies were prioritized when their carrier type, therapeutic payload, route of administration, and evidence model could be identified. Publications were not used to support claims when their bibliographic details could not be verified or when the reported findings could not be distinguished from broader

claims in a secondary review. No article counts, formal risk-of-bias scores, or exhaustive database-screening totals are reported because a reproducible systematic screening and extraction workflow was not undertaken. Retrieved literature was organized into themes covering nasal physiology, BBB structure, transport pathways, carrier platforms, formulation characterization, therapeutic applications, limitations, and safety.[5-24]

RESULTS AND DISCUSSION

1. OVERVIEW OF NOSE-TO-BRAIN DRUG DELIVERY

Nose-to-brain (N2B) delivery refers to the administration of a drug into the nasal cavity with the intention of achieving exposure in the CNS through anatomical connections associated mainly with the olfactory and trigeminal nerves. It is distinct from conventional intranasal systemic delivery, in which a drug is absorbed across the respiratory mucosa into the circulation and subsequently distributes to the brain only to the extent permitted by the BBB. The proposed advantage of N2B delivery is that some fraction of the dose may reach the olfactory bulb, brainstem, cerebrospinal-fluid spaces, or connected CNS regions without first undergoing vascular passage across the BBB. The magnitude and distribution of this direct component vary across drugs and experimental conditions, and should be established through appropriate pharmacokinetic and biodistribution studies rather than inferred from intranasal administration alone.[1,2,4,11]

2. ANATOMY AND PHYSIOLOGY OF THE NASAL CAVITY

The nasal cavity is divided functionally into the vestibular, respiratory, and olfactory regions. The nasal vestibule is the entrance portion, lined predominantly by keratinized stratified squamous epithelium and containing vibrissae that filter larger particles. Behind it, the respiratory region occupies most of the nasal cavity and is lined by a vascular, ciliated pseudostratified columnar epithelium containing goblet cells and mucus-producing glands. Its rich blood supply supports systemic absorption, but the ciliated epithelial surface and mucus layer can also remove deposited materials. The olfactory neurons project through the cribriform plate towards the olfactory bulb, providing an anatomical connection relevant to direct CNS transport.[2,4,11]

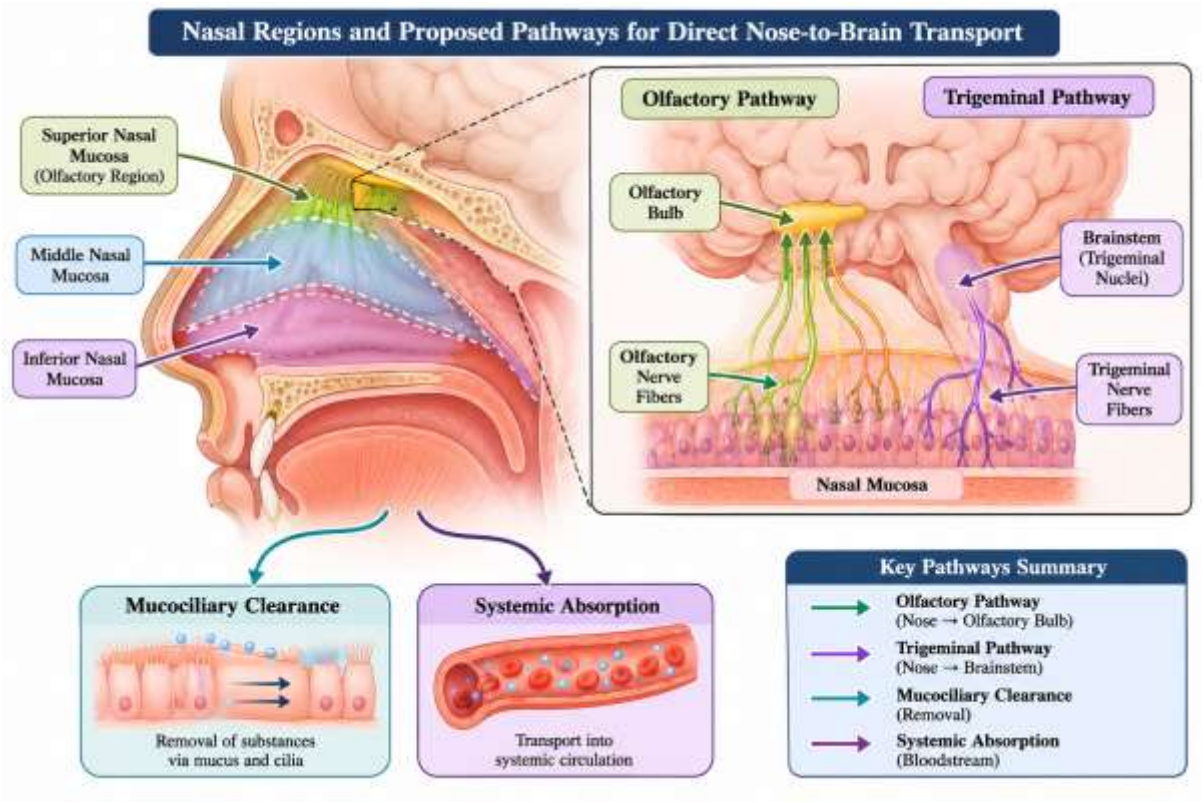

FIGURE 1. ANATOMY OF THE NASAL CAVITY AND ANATOMICAL PATHWAYS INVOLVED IN NOSE-TO-BRAIN TRANSPORT.

3. BLOOD-BRAIN BARRIER AND ITS ROLE IN DRUG DELIVERY

The BBB is formed by specialized brain endothelial cells connected by tight junctions that restrict paracellular diffusion. The endothelial cells show low nonspecific vesicular transport compared with many peripheral vascular beds and express transport proteins that regulate the movement of nutrients, metabolites, and xenobiotics. Pericytes contribute to vascular stability and endothelial regulation, while astrocytic end-feet and basement membranes support the neurovascular unit. Neurons, microglia, and other cells also participate in signalling that maintains barrier properties. The BBB is dynamic rather than an inert wall, and its permeability can change in disease; however, pathological disruption is spatially and temporally variable and cannot be assumed to provide reliable therapeutic access.[5]

Nanocarriers are being explored to address selected BBB limitations by changing the form in which a drug circulates or reaches the CNS interface. Surface ligands can be designed to interact with receptors or transport systems, while lipid or polymer matrices can protect a payload and influence cellular uptake. For intranasal use, the most relevant benefit may be transport along olfactory or trigeminal-associated pathways before the formulation encounters the vascular BBB. These concepts should not be conflated: a formulation that

enters the brain through a direct nasal route has not necessarily crossed the BBB, and a nanoparticle that is detected in brain homogenate has not necessarily delivered intact carrier or active drug to neurons. Distinguishing free drug, encapsulated drug, vascular contamination, and true parenchymal distribution is essential when interpreting results.[5,6,10,11]

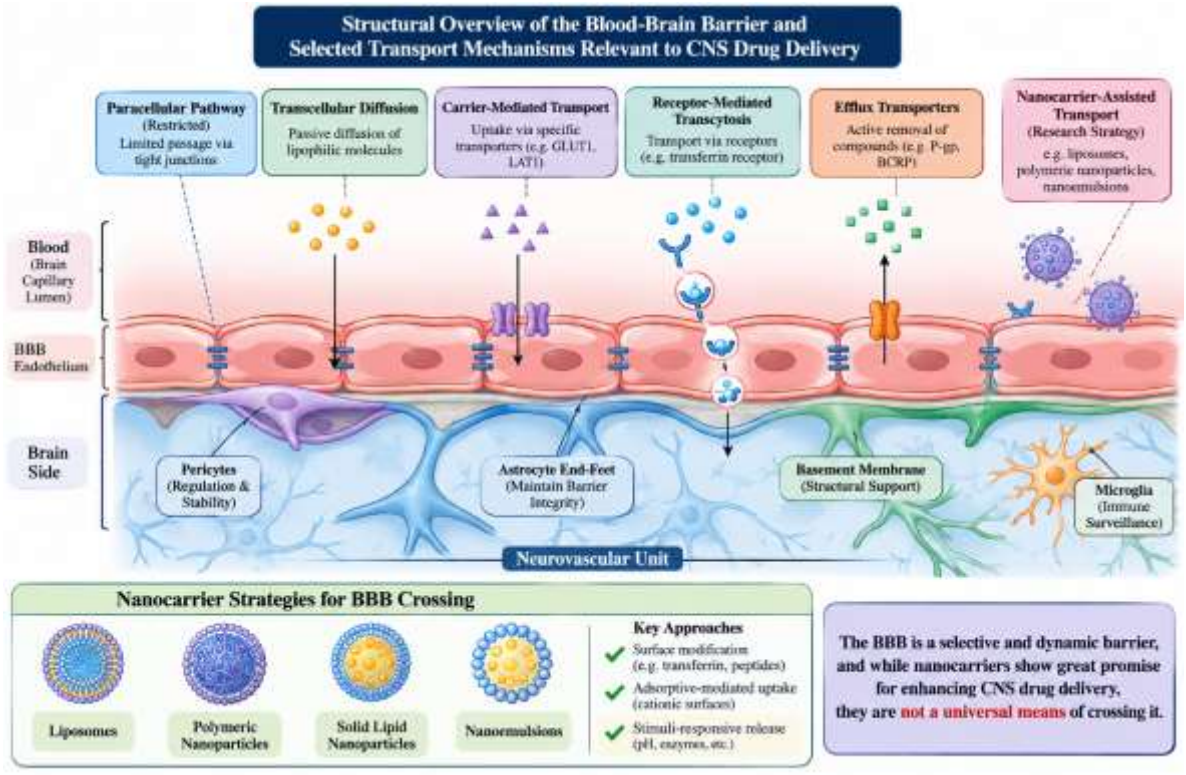

FIGURE 2. STRUCTURE OF THE BLOOD-BRAIN BARRIER AND POTENTIAL NANOCARRIER-ASSISTED TRANSPORT MECHANISMS

4. MECHANISMS OF NOSE-TO-BRAIN DRUG TRANSPORT

The olfactory pathway is associated with the superior nasal cavity and olfactory neuroepithelium. Following deposition, a drug may move extracellularly along spaces surrounding olfactory neurons and their axonal bundles, or it may be internalized by neuronal or supporting cells and undergo intracellular trafficking. Olfactory axons pass through the cribriform plate and terminate in the olfactory bulb. From this region, material may distribute to connected CNS structures or to cerebrospinal-fluid compartments. The relative contributions of extracellular movement, endocytosis, axonal transport, and perineural flow remain under investigation; these routes may operate in parallel rather than as mutually exclusive mechanisms.[2,4,11]

Extracellular transport describes movement through spaces surrounding nerves, between cells, or along perivascular and perineural interfaces; intracellular transport involves endocytosis and subsequent movement within cells or neuronal processes. These mechanisms are supported by experimental observations, but the exact routes and quantitative contribution in humans are not fully resolved. Studies using brain-to-plasma exposure ratios, vascular perfusion, imaging, and appropriate intravenous comparators provide stronger evidence of direct targeting than brain concentration alone.[6,8,11]

TABLE 1. MAJOR NASAL TRANSPORT PATHWAYS AND THEIR PHARMACEUTICAL CHARACTERISTICS.

Pathway	Anatomical basis	Potential contribution	Important limitation
Olfactory	Olfactory epithelium; olfactory neurons and axons pass through the cribriform plate to the olfactory bulb.	May support extracellular perineural movement and intracellular/axonal transport towards the olfactory bulb and connected CNS regions.	Small superior target region; deposition is difficult to reproduce; mechanism and magnitude in humans remain uncertain. [2,4,11]
Trigeminal	Trigeminal sensory branches innervate nasal mucosa and project centrally to brainstem structures.	May provide nerve-associated access from respiratory/posterior nasal regions towards brainstem and connected areas.	Route contribution varies with deposition site; direct transport is difficult to separate from systemic absorption. [2,8,11]
Extracellular / perineural	Spaces around olfactory and trigeminal nerves, associated connective tissues and fluid pathways.	May permit relatively rapid movement without requiring intact particles to enter neurons.	Size, surface chemistry, mucus interaction and local anatomy may limit movement; evidence is model-dependent. [4,6,11]
Intracellular / neuronal	Cellular uptake by olfactory or trigeminal-associated cells, followed by intracellular trafficking.	Could transport selected molecules or nanocarrier-associated payloads along neuronal pathways.	Endosomal trapping, degradation and slow transport may reduce delivery of active payload. [4,10,11]

Pathway	Anatomical basis	Potential contribution	Important limitation
Systemic absorption	Uptake through vascular respiratory mucosa into the circulation.	Can increase systemic bioavailability and may contribute to brain exposure for BBB-permeable drugs.	Not direct N2B delivery; systemic exposure may increase without proportional brain targeting. [1,6,11]

5. NANOCARRIER SYSTEMS USED IN NOSE-TO-BRAIN DRUG DELIVERY

5.1. Liposomes

Liposomes are vesicular carriers composed of one or more phospholipid bilayers surrounding an aqueous compartment. Hydrophilic drugs can be incorporated into the aqueous core, whereas lipophilic drugs partition into the lipid bilayer. Their composition resembles biological membranes, which supports biocompatibility, but conventional liposomes may undergo aggregation, fusion, oxidation, hydrolysis, or payload leakage during storage. For nasal use, the formulation must also resist dilution by mucus and avoid disrupting epithelial integrity.[6,8,15]

5.2. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal carriers in which the matrix is composed mainly of lipids that remain solid at room and body temperature. Common lipid materials include physiological or biodegradable lipids, combined with surfactants to stabilize the dispersion. The solid matrix can protect the drug from degradation and provide modified release. SLNs are especially useful for lipophilic molecules, although hydrophilic drugs may also be incorporated using suitable preparation methods. [6,9]

5.3. Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are commonly described as a second-generation lipid nanoparticle system. They combine solid lipids with liquid lipids, creating a less ordered matrix than the highly crystalline structure of an SLN. The ratio of solid to liquid lipid, the surfactant system, and the preparation method influence particle size, entrapment efficiency, release behaviour, and stability. NLCs may be particularly useful for hydrophobic drugs, though the selection of liquid lipid can influence oxidation susceptibility and long-term physical stability.[6,9]

5.4. Polymeric Nanoparticles

Polymeric nanoparticles are solid or matrix-like colloidal systems prepared from natural or synthetic polymers. Poly(lactic-co-glycolic acid) (PLGA) is widely used because it is biodegradable and its degradation rate can be influenced by polymer composition and molecular

weight. Depending on the process, the drug may be dispersed within the polymer matrix or associated with the particle surface. Polymer degradation, diffusion, and matrix swelling can influence release, while residual solvents, burst release, polymer degradation products, and scale-up reproducibility require attention.[7,10]

5.5. Nanoemulsions

Nanoemulsions are dispersions of oil and water stabilized by surfactants, with droplet dimensions commonly in the nanometre range. Oil-in-water nanoemulsions are frequently considered for intranasal delivery of poorly water-soluble drugs because the oil phase can improve solubilization and the small droplets provide a large interfacial area. Their apparent fluidity may assist nasal spreading, but surfactant concentration, droplet size, osmolarity, pH, and oil selection are important to mucosal compatibility. Excess surfactant or aggressive permeation enhancers may cause epithelial irritation or ciliary impairment.[6,18]

5.6. Dendrimers and Other Branched Polymeric Carriers

Dendrimers are highly branched macromolecules with a defined central core, repeating branching units, and multiple terminal surface groups. Cationic dendrimers can interact with cell membranes and nucleic acids, but the same positive charge may contribute to membrane disruption, cytotoxicity, or mucosal irritation. Their use in N2B delivery remains less mature than the evidence base for lipid and conventional polymeric nanoparticles. Dendrimers should therefore be regarded as a designable platform with a need for rigorous local and neurological safety assessment, not as a routinely validated intranasal carrier.[7,10]

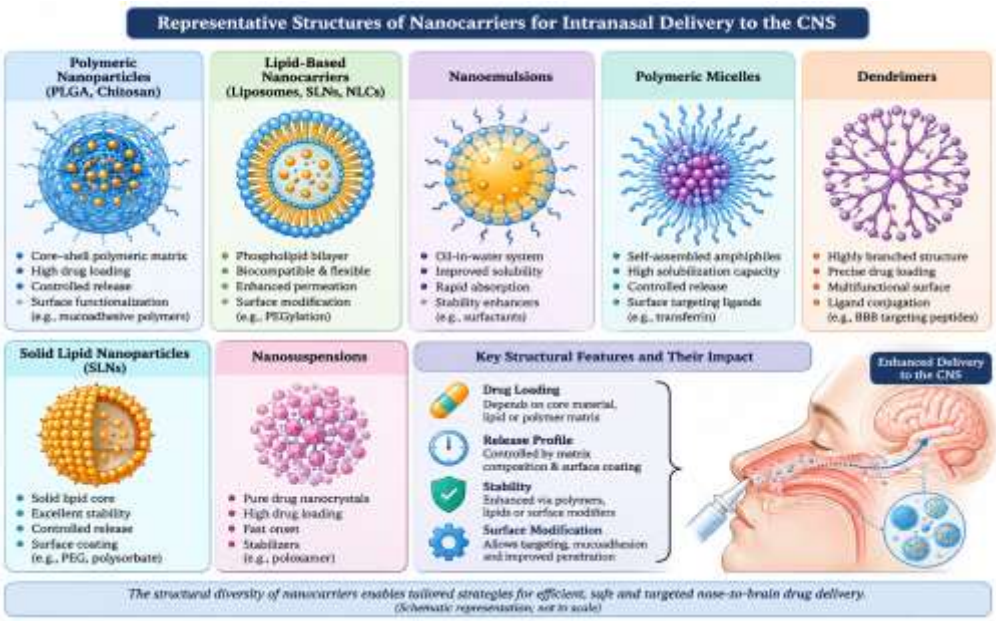

FIGURE 3. MAJOR NANOCARRIER SYSTEMS INVESTIGATED FOR INTRANASAL BRAIN DELIVERY.

6. FORMULATION DEVELOPMENT AND PHARMACEUTICAL CHARACTERIZATION

Formulation development begins with the physicochemical profile of the drug, including aqueous solubility, lipophilicity, molecular weight, ionization behaviour, chemical stability, and the intended therapeutic dose. The carrier material should be selected according to payload compatibility, biodegradability, route-specific safety, and the required release period. For lipid systems, the solid and liquid lipid composition, surfactant type, and lipid-to-drug ratio influence entrapment and crystallinity. For polymeric systems, polymer molecular weight, lactide-to-glycolide ratio, polymer concentration, solvent, and stabilizer affect particle formation and degradation. For nanoemulsions, oil phase, surfactant/co-surfactant ratio, and aqueous phase determine droplet formation and physical stability.[6,9,10]

Characterization should include particle size and polydispersity index (PDI), commonly measured by dynamic light scattering; zeta potential to estimate surface charge; morphology using transmission or scanning electron microscopy; and drug content, encapsulation efficiency, and loading capacity using validated analytical methods. Differential scanning calorimetry and X-ray diffraction can evaluate lipid or polymer solid-state behaviour, while Fourier-transform infrared spectroscopy may help investigate drug-excipient compatibility. In-vitro release tests should use conditions that avoid misleading sink or membrane effects. Ex-vivo nasal permeation, mucoadhesion, mucosal retention, and ciliary-function testing provide route-specific information that conventional particle characterization cannot supply.[6,9,10,13,16]

For in-vivo evaluation, plasma and brain concentrations should be measured over time using a validated analytical method. Studies should report the formulation dose, nasal volume, administration device, anaesthesia conditions where relevant, sampling times, and whether the animals underwent vascular perfusion before brain collection. Brain-to-plasma exposure ratios, drug-targeting efficiency, and drug-targeting percentage may be used, but their calculation and assumptions must be stated. Imaging or tissue distribution can add useful evidence, although fluorescent labels may separate from the intact carrier and should not automatically be treated as proof that the drug and nanoparticle remain associated. Appropriate intravenous and intranasal solution controls strengthen interpretation of direct targeting.[6,8,11]

TABLE 2. IMPORTANT CHARACTERIZATION PARAMETERS AND THEIR PHARMACEUTICAL SIGNIFICANCE.

Parameter / test	Typical method	Why it matters for intranasal nanocarriers
Mean particle size and PDI	Dynamic light scattering; report mean, distribution and measurement conditions.	Influence dispersion uniformity, physical stability, mucus interaction and possible cellular uptake. PDI indicates breadth of size distribution. [6,9,10]
Zeta potential	Electrophoretic light scattering.	Provides an estimate of surface charge and colloidal stability; strongly charged particles may interact with mucin and cell membranes. [6,10]
Morphology	TEM or SEM; cryo-TEM where available.	Confirms shape and structural features; helps identify aggregation or irregular particles. [9,13]
Drug content / entrapment efficiency	Validated HPLC, UV or other suitable assay after separating free drug.	Determines how much drug is present and what proportion is associated with the carrier. [9,13,16]
Drug loading	Drug mass relative to total carrier mass.	Supports dose calculation and comparison of carrier efficiency. [6,10]
Solid-state / compatibility	DSC, XRD and FTIR.	Assesses crystallinity, polymorphic transitions and possible drug-excipient interactions. [9,13]
In-vitro release	Dialysis, diffusion-cell or validated sample-and-separate method.	Describes burst and sustained release; method should minimize artefacts from membrane limitation. [6,10]
Nasal permeation / retention	Ex-vivo nasal tissue, diffusion cell, mucin interaction and retention assays.	Estimates mucosal transport and contact time but cannot by itself prove brain targeting. [6,16,18]
Local tolerability / ciliary function	Histology, ciliary beat frequency, epithelial integrity and inflammatory markers.	Detects mucosal injury or functional disturbance that could make repeated dosing unsuitable. [3,11,18]
Brain pharmacokinetics	Brain and plasma concentration-time profiles; validated analytical assay.	Distinguishes direct targeting from systemic exposure when suitable comparators and calculations are included. [6,8,11]

7. STRATEGIES TO IMPROVE NOSE-TO-BRAIN DELIVERY

Mucoadhesive polymers such as chitosan, hyaluronic acid, hydroxypropyl methylcellulose, carbomers, and selected poloxamers can increase the time a formulation remains in contact

with nasal mucus. Chitosan is especially studied because its cationic character can promote interaction with negatively charged mucins and may transiently influence epithelial permeability. However, prolonged retention is not always beneficial: strong adhesion can trap a formulation in mucus that is subsequently cleared, and a polymer that alters tight junctions may increase local irritation. Mucoadhesion should therefore be optimized together with ciliary compatibility, mucus turnover, and actual deposition in the olfactory or trigeminal region.[3,6,10,16]

TABLE 3. FORMULATION STRATEGIES, RATIONALE AND DEVELOPMENTAL CAUTIONS

Strategy	Pharmaceutical rationale	Caution / evaluation need
Mucoadhesive coating (e.g., chitosan, HPMC, hyaluronic acid)	Increases contact with mucus and may prolong local residence or support epithelial interaction.	Assess ciliary function, mucus transport, irritation and whether retained drug reaches the intended region. [3,6,16]
PEG or hydrophilic surface modification	May reduce aggregation and modify protein/mucus interactions.	Can change cell uptake and release; verify surface coverage, stability and nasal compatibility. [10,17]
Ligand functionalization	May promote receptor-associated uptake or cell-type interaction.	Receptor expression and ligand density vary; confirm specificity rather than infer targeting from design alone. [7,10,17,23]
Cell-penetrating peptides	May facilitate uptake of macromolecules or carrier-associated payloads.	Potential membrane toxicity, proteolysis, immunogenicity and non-specific uptake. [10,17]
Permeation enhancers	Can increase solubilization or transiently alter epithelial permeability.	Repeated exposure may injure epithelium or cilia; select concentration based on safety data. [1,3,18]

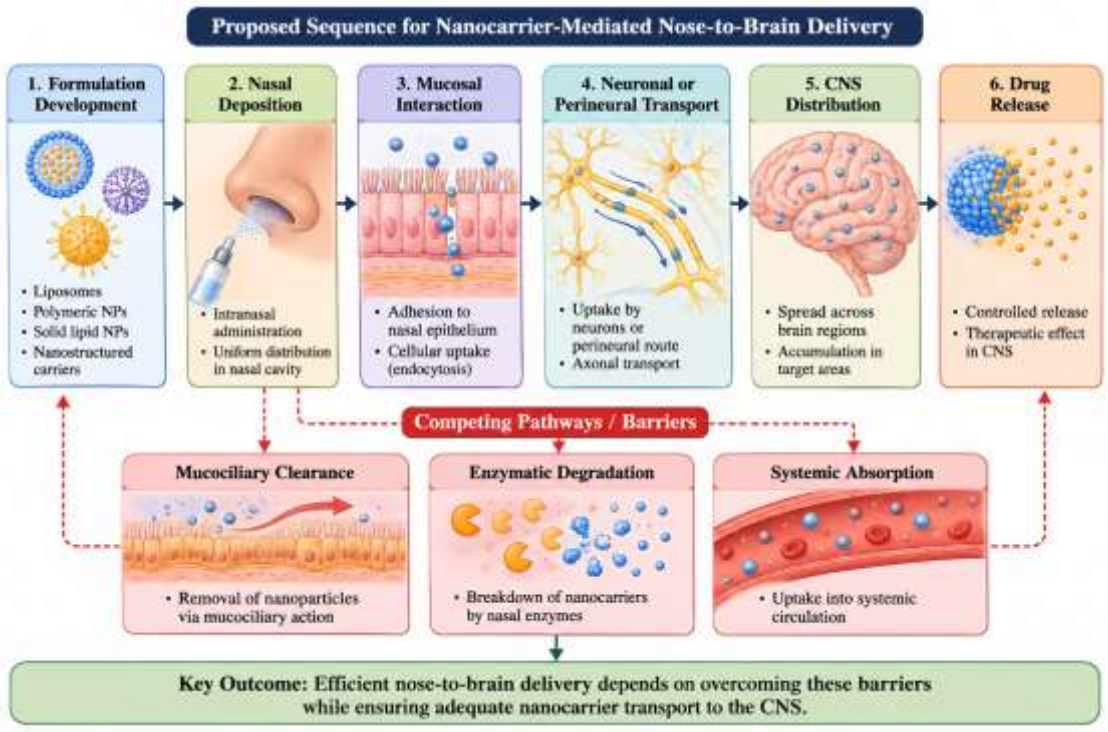

FIGURE 4. CONCEPTUAL WORKFLOW OF NANOCARRIER-MEDIATED NOSE-TO-BRAIN DRUG DELIVERY

8. THERAPEUTIC APPLICATIONS IN NEUROLOGICAL DISORDERS

8.1. Alzheimer's Disease

Alzheimer's disease is characterized by progressive cognitive impairment and pathological processes involving amyloid-beta, tau, synaptic dysfunction, neuroinflammation, and neuronal loss. Rivastigmine-loaded nasal liposomes and nanoparticles have been assessed in acute and chronic animal models, while liposomal formulations containing donepezil, memantine, and BACE1 siRNA have been evaluated in cellular systems. These studies support continued investigation but do not show that intranasal nanocarriers modify Alzheimer's disease progression in humans.[12,15]

8.2. Parkinson's Disease

Parkinson's disease involves degeneration of dopaminergic neurons in the substantia nigra and a resulting disturbance of basal-ganglia motor circuitry. Dopamine itself has poor suitability for conventional systemic brain delivery because it is polar and does not readily cross the BBB. N2B delivery therefore offers a rational route for investigating dopamine replacement, although dopamine oxidation, rapid metabolism, nasal enzymatic activity, and the need for sustained and regionally relevant exposure remain challenges. NLCs containing

dopamine hydrochloride and SLNs co-loaded with dopamine and citicoline have been developed for intranasal administration in experimental settings. [7,8,13,14]

8.3. Epilepsy

Epilepsy is characterized by recurrent seizures arising from abnormal neuronal network activity. For acute seizure management, rapid administration and reliable absorption are important, and intranasal delivery is already clinically relevant for selected conventional formulations. Nanocarrier research addresses a different question: whether encapsulation can improve the delivery or duration of action of specific antiepileptic candidates while maintaining nasal tolerability. The reported work provides early formulation and safety observations; additional evidence is required to establish seizure control, pharmacokinetic benefit, and safety after repeated exposure.[11,18]

8.4. Brain Tumours and Gliomas

Glioblastoma and other malignant gliomas are difficult to treat because of tumour invasiveness, heterogeneous BBB integrity, limited drug penetration, and dose-limiting systemic toxicity. Although some regions of a tumour may have a disrupted blood-tumour barrier, infiltrating cells can remain behind relatively intact vasculature. The biomimetic study reported nasal mucosal permeation, cellular effects, tumour-related assay findings, and brain biodistribution in animals, but clinical antitumour efficacy has not been established.[19,20,24]

8.5. Ischemic Stroke and Other CNS Disorders

Ischemic stroke produces acute vascular obstruction followed by excitotoxicity, oxidative stress, neuroinflammation, and secondary tissue injury. A recent preclinical study used intranasal lipid nanoparticles to deliver circular RNA SCMH1 in stroke models and reported increased delivery to peri-infarct regions with improvements in selected functional and tissue-repair outcomes in animals. Reviews of nanoparticle-mediated N2B delivery in stroke describe a growing experimental field, but the effectiveness, dosing window, and safety of these RNA nanocarriers in human stroke remain unknown.[21,22]

9. ADVANTAGES OF NANOCARRIER-MEDIATED NOSE-TO-BRAIN DELIVERY

The major potential advantage of N2B nanocarriers is the possibility of increasing CNS exposure while reducing dependence on systemic circulation. For drugs that are poorly absorbed orally, unstable in gastrointestinal fluids, or restricted by the BBB, intranasal delivery may provide a complementary route. These effects can be particularly relevant for

peptides, proteins, nucleic acids, and poorly soluble drugs that are difficult to formulate as simple nasal solutions. [4,6,10,11]

Nanocarriers may also provide controlled or sustained release, which could reduce rapid loss through mucociliary clearance and potentially decrease the need for frequent administration. A non-invasive route may be more acceptable than repeated injections for chronic neurological conditions, although patient acceptability depends on device design, nasal tolerability, and dosing frequency. Reduced systemic exposure is possible in selected formulations when direct transport is substantial, but it cannot be assumed for every drug. A meaningful advantage should be demonstrated through comparative exposure and safety data rather than claimed solely from nanometre-scale particle size or encapsulation efficiency.[6,8,11]

10. FUTURE PERSPECTIVES

Future development is likely to focus on more reproducible upper-nasal deposition, rational surface engineering, and responsive systems that adjust release to local conditions. Ligand-functionalized particles, cell-penetrating peptides, hybrid lipid-polymer carriers, and RNA-loaded lipid nanoparticles provide opportunities for delivering complex payloads. Thermoresponsive gels and device-assisted administration may improve residence or direct deposition, but should be integrated with human-relevant nasal anatomy and user factors. Personalized approaches could eventually account for nasal anatomy, disease status, age, and mucosal condition, although current evidence is not sufficient to define patient-selection algorithms.[8-11,20-22]

A stronger translational pathway requires standardized preclinical methods and well-designed early clinical studies. Animal studies should report the species, nasal anatomy, dose volume, delivery device, anaesthesia, formulation deposition, pharmacokinetic sampling, and safety endpoints. Human studies will need a clear distinction between systemic absorption and direct CNS delivery, potentially using suitable imaging, biomarker, or pharmacokinetic approaches. Manufacturing work must demonstrate batch reproducibility, stability, compatibility with the delivery device, and practical storage conditions. Ultimately, nanocarrier-mediated N2B delivery should advance only when improved brain exposure is linked to a meaningful clinical outcome and a favourable benefit-risk balance.[6,8,11,22]

CONCLUSION

Nanocarrier-mediated nose-to-brain drug delivery is a promising pharmaceutical strategy for improving the delivery of selected therapeutic agents to the CNS. The anatomical connections associated with the olfactory and trigeminal pathways provide a rationale for direct transport from the nasal cavity, while nanocarriers can protect drugs, improve solubilization, modify release, and influence mucosal residence and cellular uptake. Liposomes, SLNs, NLCs, polymeric nanoparticles, nanoemulsions, and dendrimers each offer distinct formulation advantages, but their performance depends on the drug, carrier composition, nasal deposition, and intended therapeutic application.

Experimental studies in Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, and ischemic stroke demonstrate a range of possible applications; however, most nanocarrier-specific evidence remains in-vitro or preclinical. Important barriers include mucociliary clearance, limited olfactory deposition, differences between animal and human nasal anatomy, uncertainty in quantifying direct brain transport, local mucosal toxicity, and manufacturing reproducibility. Progress towards clinical use will require standardized pharmacokinetic assessment, clinically relevant devices, repeated-dose safety studies, robust quality control, and controlled human trials. The approach should therefore be viewed as a developing drug-delivery platform with significant research potential rather than an established replacement for conventional neurological therapy.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to **Ms. Prajakta Gaikwad** Assistant Professor, Department of Pharmaceutics for their valuable guidance, constructive suggestions, and continuous support throughout the preparation of this review article. The authors also gratefully acknowledge **Dr. Ganesh shankar mhaske** Principal, for providing the necessary institutional support, encouragement, and facilities required for the completion of this work. The authors sincerely appreciate their valuable contributions and support.

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