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IP Indian Journal of Anatomy and Surgery of Head, Neck and Brain

Journal homepage: https://www.ijashnb.org/

Review Article

Intranasal drug delivery for brain tumors: Promise and challenges

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Abstract

Intranasal drug delivery represents a transformative strategy for targeting therapeutic agents to the central nervous system (CNS), offering a noninvasive route that bypasses the blood–brain barrier (BBB). This modality leverages the olfactory and trigeminal neural pathways to facilitate direct nosetobrain transport, providing enhanced drug bioavailability and rapid onset of action. Recent advances in nanocarrier technologies, including liposomes, polymeric nanoparticles, and mucoadhesive in situ gels, have further optimized intranasal delivery, enabling controlled release, improved stability, and tumorspecific targeting in brain malignancies. Despite its potential, several challenges hinder clinical translation, including mucociliary clearance, enzymatic degradation in the nasal cavity, formulation irritability, and variability in patient anatomy. Moreover, precise targeting of heterogeneous tumor microenvironments remains a critical hurdle. Strategies integrating bioadhesive polymers, permeability enhancers, and surface modified nanocarriers are under investigation to overcome these limitations. Preclinical studies demonstrate significant antitumor efficacy, yet comprehensive clinical validation is limited. Regulatory considerations, scalability, and reproducibility of formulation also demand careful attention. Future directions involve multimodal approaches that combine intranasal delivery with imagingguided precision therapy and immunomodulatory agents, aiming to maximize therapeutic index while minimizing systemic toxicity. Overall, intranasal drug delivery offers a promising, patientriendly alternative for brain tumor therapy, with ongoing research poised to address current limitations and unlock its full clinical potential.

Keywords: Intranasal delivery, Blood–brain barrier, Nanocarriers, Brain tumors, Mucoadhesive systems

Received: 05-09-2025; **Accepted:** 11-10-2025; **Available Online**: 27-10-2025

1. Introduction

Brain tumors constitute a heterogeneous group of CNS neoplasms that encompass both primary malignancies, such as gliomas, meningiomas, and medulloblastomas, and secondary metastatic lesions. Among these, glioblastoma multiforme (GBM) remains the most aggressive and lethal, with median survival rarely exceeding 15–18 months despite multimodal treatment. The epidemiological burden of brain tumors is steadily increasing worldwide, partly attributable to improved neuroimaging, aging populations, and changing environmental and genetic risk factors. From a clinical standpoint, brain tumors present not only as life-threatening conditions but also as diseases that profoundly compromise neurological function, leading to cognitive decline, seizures, focal deficits, and deterioration of quality of life. This dual burden of mortality and morbidity underscores the pressing need for therapeutic innovation.[1,2]

The conventional therapeutic triadmaximal safe surgical resection, adjuvant radiotherapy, and systemic chemotherapy offer limited long-term success. Surgical interventions are constrained by the infiltrative growth of malignant gliomas into eloquent brain regions, rendering complete excision nearly impossible without inducing severe neurological deficits. Radiotherapy, while useful in controlling residual disease, often fails due to radio resistant tumor subpopulations and cumulative neurotoxicity. Systemic chemotherapy, including temozolomide and nitrosoureas, is further hindered by the restrictive nature of the BBB. The BBB composed of tight endothelial junctions, efflux transporters, and metabolic enzymes, acts as a dynamic neuroprotective shield but simultaneously prevents the penetration of most hydrophilic and highmolecularweight drugs into the brain parenchyma.[3,4] Consequently, higher systemic doses are required to achieve therapeutic concentrations within the CNS, inevitably escalating off target toxicity and adverse systemic effects. These inherent

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https://doi:10.18231/j.ijashnb.13562.1760520564

limitations of conventional therapeutic modalities highlight the need for innovative strategies that can circumvent the BBB and enable efficient, localized drug delivery to intracranial tumors. Multiple approaches, including convection enhanced delivery, focused ultrasound mediated BBB disruption, and nanoparticle based carriers, have been investigated. However, many remain invasive, technically complex, or limited by heterogeneity in drug distribution.[5].

In this context, the intranasal route has emerged as an attractive non-invasive alternative for CNS drug delivery. The nasal cavity provides a unique anatomical gateway to the brain through the olfactory epithelium and trigeminal nerve pathways, allowing therapeutic agents to bypass the BBB and achieve direct nosetobrain transport. This route offers several advantages, including rapid onset of action, avoidance of first-pass hepatic metabolism, reduced systemic exposure, and improved patient compliance. Furthermore, intranasal delivery has shown potential for accommodating diverse drug modalities, ranging from small molecules to peptides, proteins, nanoparticles, and gene therapy vectors.[6]

Despite these advantages, translation of intranasal drug delivery into clinical oncology remains challenging. Variability in nasal physiology, mucociliary clearance, enzymatic degradation within the nasal mucosa, limited dosing volume, and the need for advanced mucoadhesive and nanocarrier systems pose significant barriers. Therefore, while intranasal delivery holds immense promise as a transformative strategy for brain tumor therapeutics, its optimization requires a multidisciplinary approach integrating pharmaceutical sciences, nanotechnology, and neurooncology.[7,8]

2. Discussion

2.1. Anatomy and physiology relevant to intranasal delivery

The nasal cavity constitutes a complex anatomical conduit with specialized subregions that directly influence drug transport to the CNS. It is broadly divided into the respiratory region and the olfactory region. The respiratory mucosa, lined with ciliated pseudo-stratified epithelium, accounts for the majority of nasal surface area and provides extensive vascularization that supports rapid systemic absorption. In contrast, the olfactory region, though spatially limited (~8–10% of the total cavity), offers a unique neural interface for direct access to the forebrain.[9,10]

The olfactory epithelium, localized at the roof of the nasal cavity, harbors bipolar sensory neurons whose axons traverse the cribriform plate and synapse in the olfactory bulb. This arrangement creates a direct nosetobrain conduit, bypassing the BBB. Such a neuroanatomical pathway provides a critical advantage for delivering chemotherapeutics and Nano carrier systems intended for brain tumor management.[11] Parallel to this, the trigeminal nerve pathway contributes an auxiliary but significant route. Its ophthalmic and maxillary branches innervate the respiratory and olfactory mucosa and extend projections to the brainstem and deeper parenchymal regions. This dual neural connectivity (olfactory and trigeminal) broadens the spatial reach of intranasally administered therapeutics, facilitating drug distribution into multiple brain compartments beyond the olfactory bulb. The **Figure 1** gives overview of nasal cavity.[12]

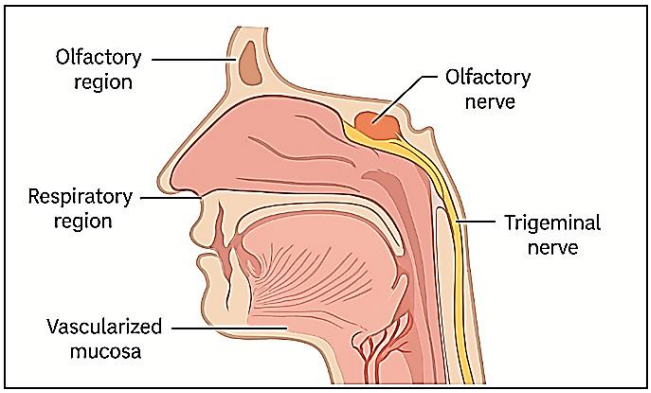

Figure 1: Overview of anatomy of nasal cavity[8-11]

The nasal mucosa itself exhibits high vascular density, rich lymphatic drainage, and relatively permeable epithelial barriers. The combination of a large absorptive surface area (~150 cm² in humans), thin epithelial lining, and fenestrated capillary network supports both systemic uptake and localized neural transport. These anatomical and physiological characteristics collectively underscore the nasal route as a privileged interface for noninvasive CNS drug targeting; particularly in the context of brain tumor therapeutics where bypassing the BBB remains a critical challenge.[13]

3. Blood–Brain Barrier (BBB) and Its Challenges

3.1. Structure and function of the BBB

The BBB represents one of the most formidable physiological defense systems of the human body. Structurally, it is formed by nonfenestrated endothelial cells connected by tight junction proteins (e.g., claudins, occludins, ZO1), which limit paracellular flux. The endothelial layer is reinforced by pericytes and enveloped by astrocyticendfeet, together forming the neurovascular unit (NVU). This highly orchestrated structure ensures controlled transport of glucose, amino acids, and essential ions through selective carrier systems while excluding potentially harmful agents. Furthermore, ATP binding cassette (ABC) efflux transporters such as Pglycoprotein (Pgp), BCRP, and multidrug resistance associated proteins (MRPs) actively pump xenobiotics and many therapeutic molecules back into circulation. The integrity of the BBB is crucial for neuroprotection and homeostasis, but it simultaneously acts as a barrier to CNS pharmacotherapy.[14-15]

3.2. Restriction of systemic drug delivery to the CNS

From a therapeutic standpoint, the restrictive properties of the BBB severely limit the success of systemic drug administration. Nearly all biologics and over 98% of small molecule compounds are excluded from the CNS. Lipophilic molecules under 400–500 Da may cross to some extent via passive diffusion, but most chemotherapeutics exceed these physicochemical thresholds. Moreover, the presence of active efflux pumps prevents sustained drug accumulation even for molecules that penetrate transiently. This result in a therapeutic paradox: high systemic doses are often required to achieve minimal brain concentrations, leading to significant offtarget toxicities without proportional improvement in CNS tumor control. For conditions like glioblastoma, where aggressive proliferation coexists with infiltrative spread, the inability of systemic drugs to reach infiltrating tumor cells significantly undermines treatment outcomes.[16]

3.3. Tumor microenvironment heterogeneity and its influence on drug penetration

Beyond the BBB, the tumor microenvironment itself introduces another layer of complexity. Malignant gliomas and metastatic brain tumors remodel the vascular architecture, creating what is referred to as the blood–tumor barrier (BTB). Unlike the classical BBB, the BTB exhibits spatially heterogeneous permeability. Some regions demonstrate leaky vasculature due to abnormal angiogenesis and fenestrated endothelium, while adjacent zones retain intact barrier properties. Consequently, drug penetration into tumor tissue is irregular, resulting in pockets of undertreated tumor cells that drive recurrence and resistance.[17-18]

Compounding this challenge, the tumor milieu is characterized by elevated interstitial fluid pressure, dense extracellular matrix deposition, and hypoxic zones. These features not only hinder convective transport of therapeutic molecules but also activate cellular resistance mechanisms, such as hypoxia inducible factor (HIF) mediated up regulation of efflux transporters. Thus, even when systemic drugs transiently breach compromised vasculature, their homogeneous distribution within tumor parenchyma remains highly inefficient.[19]

3.4. Implications for intranasal drug delivery

This dual challenge BBB mediated restriction and BTB induced heterogeneity has accelerated the exploration of alternative delivery routes that bypass systemic circulation. The intranasal pathway is particularly attractive because it provides direct neural conduits (olfactory and trigeminal pathways) to the CNS, thereby circumventing both the intact BBB and regions of heterogeneous BTB. Unlike systemic delivery, where tumor penetration is stochastic and limited, intranasal administration offers the potential for more uniform drug exposure across brain compartments, including infiltrative margins that are otherwise inaccessible. Moreover, intranasal delivery reduces systemic exposure and toxicity, enabling localized targeting of brain tumors with lower therapeutic doses.[6-8]

4. Mechanisms of Intranasal Drug Transport

Intranasal administration provides a multifaceted set of transport routes that enable therapeutic agents to circumvent the restrictive BBB and gain direct access to the CNS. The mechanisms of drug movement across the nasal mucosa involve paracellular, transcellular, and neuronal pathways, supported by both extracellular and intracellular processes that collectively dictate the pharmacokinetic fate of intranasally delivered therapeutics.[20,21]

4.1. Paracellular transport

Paracellular transport refers to the passage of molecules through the tight junctions located between adjacent epithelial cells. This pathway favors hydrophilic and low molecular weight drugs, though its efficiency is inherently limited by the restrictive nature of the intercellular junctional complexes. Modulation of these junctions, either by permeation enhancers or nanocarrierbased systems, has been explored to transiently improve drug penetration without compromising mucosal integrity.[22,23]

4.2. Transcellular transport

In contrast, transcellular transport entails the movement of drug molecules across the epithelial cell membrane and cytoplasm. This pathway is predominant for lipophilic, unionized, and small molecules that can readily diffuse through the phospholipid bilayer. Additionally, receptor mediated endocytosis and vesicular trafficking may facilitate the uptake of larger biomolecules, peptides, or engineered nanoparticles, thereby expanding the scope of drugs amenable to this route.[24]

Table 1: Comparative overview of intranasal drug transport mechanisms

Transport Mechanism	Pathway Description	Preferred Molecules/ Drugs	Advantages	Limitations	Relevance to Brain Tumor Therapy
Paracellular Transport	Movement between epithelial cells through tight junctions	Hydrophilic, low molecular weight drugs	Simple diffusion, nonenergy dependent	Restricted by tight junctions; limited permeability for macromolecules	Useful for small, water-soluble drugs if junction modulation is feasible
Transcellular Transport	Passage across epithelial cell membranes and cytoplasm	Lipophilic, small molecules; peptides via endocytosis	Bypasses paracellular restriction; allows carrier mediated transport	Dependent on lipophilicity and ionization; may require vesicular uptake	Applicable for lipophilic drugs, Nano carriers, and peptide based therapeutics
Neuronal Transport	Direct delivery via olfactory and trigeminal nerves	Small molecules, peptides, proteins, nanoparticles	Direct brain access; bypasses systemic circulation and BBB	Slower than vascular uptake; limited loading capacity	Highly promising for sitespecific delivery to forebrain, brainstem, and deep CNS regions
Extracellular & Intracellular Pathways	Extracellular: perineural/ perivascular diffusion; Intracellular: endocytosis, axonal transport, transcytosis	Both small molecules and bio macromolecules depending on route	Complementary transport; supports widespread distribution	Dependent on molecular properties and formulation	Enhances both rapid onset (extracellular) and sustained delivery (intracellular) for tumor th

Table 2: Comparative overview of formulation strategies for intranasal drug[28-34]

Formulation Strategy & Examples	Advantages	Limitations	Relevance for Brain Tumor Therapy
Nanocarriers (Liposomes, Polymeric nanoparticles, Solid lipid nanoparticles)	Protect labile drugs from degradation Enhance solubility of hydrophobic drugs Targeted and sustained release possible	Complex manufacturing Stability concerns during storage Potential toxicity at higher doses	Enable efficient delivery of chemotherapeutics and biologics across olfactory/trigeminal pathways with prolonged CNS exposure
Mucoadhesive Systems (Chitosan, Carbopol, Hyaluronic acid)	Prolong nasal residence time Improve paracellular transport Biocompatible and biodegradable	Possible nasal irritation Excessive viscosity may hinder diffusion	Enhance local retention of anticancer drugs, improving absorption and reducing dosing frequency
In Situ Gels (Thermosensitive: Poloxamer, pHsensitive polymers)	Ease of administration (liquidtogel transition) Sustained release depot formation Reduced clearance from nasal cavity	Limited drug loading capacity Gelation properties vary with formulation conditions	Provide controlled release of cytotoxic agents, reducing systemic toxicity while maintaining localized CNS delivery
Permeation Enhancers (Surfactants, Bile salts, Cyclodextrins)	Increase membrane permeability Improve solubility and stability of poorly soluble drugs	Risk of mucosal irritation and toxicity Need for precise concentration control	Facilitate delivery of large or poorly permeable anticancer molecules across nasal epithelium
Optimization Parameters (Particle size: 50–200 nm, Surface charge, Stability)	Smaller particles improve uptake Positive charge enhances mucoadhesion Stable systems prevent aggregation and drug loss	Excessive cationic charge may cause toxicity Scale-up and reproducibility issues	Critical for achieving consistent drug transport to brain parenchyma and maximizing therapeutic efficacy

4.3. Neuronal transport

A distinctive advantage of intranasal delivery lies in neuronal transport pathways, specifically via the olfactory and trigeminal nerves. The olfactory neurons provide a direct anatomical conduit to the olfactory bulb and forebrain, enabling rapid bypass of systemic circulation. Simultaneously, the trigeminal nerve innervates both respiratory and olfactory regions, projecting to the brainstem and deeper CNS structures. Transport along these neuronal routes occurs through intracellular axonal transport or extracellular diffusion along perineural channels, supporting widespread distribution into cortical and subcortical regions.[25]

4.4 Role of extracellular and intracellular pathways

Drug disposition within the nasal mucosa is governed by the interplay of extracellular and intracellular pathways. Extracellular transport includes bulk diffusion along perineural spaces, interstitial fluid dynamics, and movement through paracellular gaps. Intracellular routes, conversely, rely on endocytosis, transcytosis, and axonal transport mechanisms. The balance between these two processes is highly dependent on drug physicochemical properties, formulation design, and the presence of delivery enhancers. Together, they form a complementary system that determines the rate, extent, and regional distribution of intranasally delivered drugs within the CNS. The **Table 1** gives Comparative Overview of Intranasal Drug Transport Mechanisms.[26]

5. Formulation Strategies for Intranasal Delivery

The success of intranasal drug delivery for brain tumors is critically dependent on rational formulation design that maximizes transport across the nasal epithelium while ensuring therapeutic stability and safety. Diverse strategies have been developed to exploit the anatomical and physiological properties of the nasal route.[27]

5.1. Nanocarriers

Nanocarrierbased systems such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles (SLNs) have emerged as promising platforms for enhancing drug solubility, stability, and brain targeting. Liposomes, with their biocompatible phospholipid bilayers, can encapsulate both hydrophilic and lipophilic drugs, facilitating controlled release and improved residence in the nasal mucosa. Polymeric nanoparticles, often fabricated from biodegradable polymers such as PLGA or PEGylated derivatives, offer tunable size, surface functionality, and drugloading capacity. SLNs combine the advantages of lipidbased carriers with solid matrix stability, providing enhanced protection of labile drugs and prolonged release profiles.[28,29]

5.2. Mucoadhesive systems

To overcome rapid mucociliary clearance, mucoadhesive polymers are incorporated into nasal formulations to extend residence time. Chitosan, a cationic biopolymer, transiently opens tight junctions in the nasal epithelium, thereby improving paracellular transport of hydrophilic drugs. Carbopol, a polyacrylic acid derivative, swells in the nasal environment to form viscous gels that adhere to mucosal surfaces. Hyaluronic acid, beyond its biocompatibility, provides hydration and enhances local tissue permeation, making it a valuable excipient in nosetobrain formulations.[30]

5.3. In situ gels

In situ gelling systems that undergo sol–gel transition in response to physiological stimuli offer an advanced approach for controlled drug release. Thermosensitive polymers (e.g., poloxamers) remain liquid at room temperature for ease of administration but gel upon contact with nasal temperature, creating a depot effect. pH sensitive systems exploit the slight differences in nasal pH to trigger gelation, ensuring localized retention and gradual release of therapeutic payloads. Such platforms are particularly relevant for cytotoxic drugs, as they enable sustained delivery while minimizing systemic exposure.[31]

5.4. Permeation enhancers

To further improve drug flux across the nasal barrier, permeation enhancers are integrated into formulations. Surfactants modify membrane fluidity and enhance transcellular transport. Bile salts act by solubilizing lipophilic molecules and disrupting tight junctions, facilitating both paracellular and transcellular passage. Cyclodextrins form inclusion complexes with hydrophobic drugs, increasing aqueous solubility and stability while also modulating permeability. However, the choice and concentration of permeation enhancers must balance efficacy with potential mucosal irritation.[32]

5.5. Optimization of physicochemical parameters

The particle size, surface charge, and colloidal stability of formulations are pivotal for efficient nasal and neuronal uptake. Nanoparticles within the 50–200 nm range exhibit optimal penetration and distribution along olfactory and trigeminal pathways. Surface charge plays a dual role: positively charged systems enhance mucoadhesion and interaction with negatively charged mucin, while excessive cationic charge may induce toxicity. Ensuring physical and chemical stability during storage and administration is equally critical to prevent aggregation, drug leakage, or degradation, which could compromise therapeutic outcomes. Collectively, these formulation strategies provide a versatile toolkit for tailoring intranasal delivery systems. Their integration with emerging nanomedicine approaches holds promise for achieving effective, non-invasive therapy against brain tumors by circumventing the formidable BBB. The **Table 2** gives comparative overview of formulation strategies for intranasal drug.[33,34]

6. Therapeutic Agents Delivered Intranasally

6.1. Chemotherapeutic drugs

Traditional smallmolecule chemotherapeutics, such as temozolomide and paclitaxel, have been explored for intranasal administration to enhance brain bioavailability while minimizing systemic toxicity. Temozolomide, the gold standard in glioblastoma therapy, faces challenges of resistance and doselimiting toxicity; intranasal delivery can provide higher localized concentrations with reduced peripheral exposure. Similarly, intranasal paclitaxel has shown potential in preclinical models to achieve therapeutic CNS levels that are otherwise constrained by efflux transporters when delivered systemically.[35]

6.2. Immunotherapeutics

The intranasal pathway also supports the delivery of immunomodulatory agents, including cytokines (e.g., interleukin2, interferons) and monoclonal antibodies targeting tumorassociated receptors. This approach capitalizes on mucosal immunological priming and neural transport to elicit both local and systemic antitumor responses. Intranasal administration of immunotherapeutics holds potential to synergize with checkpoint inhibitors, enhancing immune cell infiltration into brain tumors without necessitating high systemic exposure.[36]

6.3. Gene and nucleic acid based therapies

Innovative genebased interventions such as siRNA, miRNA, antisense oligonucleotides, and CRISPRassociated systems are increasingly being evaluated via the nasal route. These molecules can silence oncogenic signaling, restore tumor suppressor pathways, or modulate tumor microenvironment dynamics. The nasal mucosa offers a favorable interface for nonviral and nanoparticlemediated gene delivery, avoiding systemic degradation and enabling sustained release in target neural tissues. The ability of intranasal carriers to shield nucleic acids from nuclease activity and direct them across the olfactory epithelium makes this strategy particularly appealing for brain tumor therapeutics.[37,38].

6.4. Combination therapies and personalized medicine approaches

Given the multifactorial nature of brain tumors, combination regimens integrating chemotherapeutics, immunotherapeutics, and genetic modulators are gaining attention. Intranasal codeliverysystemssuch as liposomal hybrids, polymeric nanoparticles, and mucoadhesive gelscan simultaneously transport multiple agents, enabling synergistic mechanisms against tumor heterogeneity. Furthermore, the evolution of personalized medicine, driven by molecular profiling of tumors, supports tailoring intranasal formulations to patientspecific genetic and immunological signatures. This convergence of nanotechnology, pharmacogenomics, and targeted drug delivery underscores the potential of intranasal therapy as a precision strategy for refractory brain tumors.[39]

7. Challenges and Limitations

7.1. Mucociliary clearance reducing drug residence time

The nasal epithelium possesses a highly efficient mucociliary clearance system, consisting of ciliated epithelial cells embedded in a mucus layer that is continuously propelled posteriorly toward the nasopharynx. This natural defense mechanism, while essential for maintaining airway sterility, significantly reduces the intranasal residence time of administered formulations to a matter of minutes. Such rapid elimination severely restricts drug absorption, particularly for hydrophilic or macromolecular agents. Advanced formulation strategies such as incorporation of mucoadhesive polymers (e.g., chitosan, carbopol), thermoresponsive in situ gels, and nanoparticle carriers are being investigated to enhance retention time and prolong local contact with the absorptive mucosa.[40]

7.2. Enzymatic degradation in nasal cavity

The nasal cavity expresses a diverse repertoire of metabolic enzymes, including cytochrome P450 isoforms, esterases, proteases, and peptidases. These enzymes catalyze extensive presystemic metabolism, particularly for peptides, proteins, and nucleic acid–based therapeutics. For brain tumor therapy, where many investigational agents are bio macromolecules, enzymatic degradation poses a critical barrier by not only lowering drug bioavailability but also generating truncated fragments with unpredictable pharmacodynamics or immunogenicity. Stabilization strategies such as PEGylation, prodrug synthesis, nanoparticle encapsulation, and co-administration of enzyme inhibitors have been explored to circumvent metabolic breakdown.[41]

7.3. Irritation and patient compliance issues

Intranasal formulations, especially those incorporating penetration enhancers (e.g., surfactants, bile salts, cyclodextrins), often induce epithelial irritation, nasal congestion, or microstructural disruption of tight junctions. Chronic administration may result in mucosal atrophy, impaired mucociliary clearance, or even olfactory dysfunction. For oncology patients—already subjected to multi-modal therapies with high side-effect burdens—treatment-related nasal discomfort can markedly compromise compliance and long-term adherence. Hence, safety profiling of excipients, optimization of pH and osmolarity, and development of minimally irritating carrier systems remain essential for clinical acceptance.[42]

7.4. Variability in anatomy and disease state affecting delivery

The nasal cavity exhibits significant interindividual anatomical variability in terms of surface area, mucosal thickness, and airflow patterns, all of which directly affect

deposition efficiency. In addition, pathological alterations such as chronic rhinosinusitis, allergic rhinitis, or tumor-induced anatomical distortion exacerbate variability in absorption. Tumor-related compression or invasion into nasal–cranial communication routes may further obstruct olfactory or trigeminal pathways, resulting in heterogeneous drug biodistribution. This anatomical and pathological variability complicates pharmacokinetic predictability and dose standardization in clinical populations.[43]

7.5. Difficulty in targeting heterogeneous tumor regions

Gliomas and other intracranial malignancies are characterized by profound spatial and molecular heterogeneity, encompassing proliferative tumor cores, necrotic centers, infiltrative margins, and highly vascularized peritumoral regions. Intranasally administered drugs, even if efficiently transported to the CNS, may preferentially accumulate in superficial or vascularized compartments while failing to achieve therapeutic concentrations in hypoxic or invasive tumor niches. This incomplete penetration reduces therapeutic efficacy and accelerates the risk of resistance. Multifunctional delivery systems such as receptor-targeted nanoparticles, stimuli-responsive carriers, and hybrid nanoplatforms capable of sustained releaseare being developed to address this distributional challenge.[44]

7.6. Regulatory and scale-up challenges

Translational progression of intranasal therapeutics encounters formidable regulatory hurdles. Safety assessments must account for chronic mucosal exposure, potential disruption of olfactory function, long-term immunogenicity of novel carriers, and variability in device performance. Furthermore, the lack of harmonized regulatory guidelines specific to intranasal brain-targeted therapies generates uncertainty in approval pathways. On the industrial side, scale-up of sophisticated nanosystems (e.g., lipid–polymer hybrids, dendrimers, exosomes) is constrained by batch-to-batch reproducibility, stability, and cost-efficiency concerns. The integration of Quality by Design (QbD) principles, standardized nasal deposition testing protocols, and rigorous long-term toxicology evaluations will be critical for advancing intranasal therapies from laboratory innovation to clinical adoption.[45]

8. Future Perspectives and Innovations

8.1. Multimodal therapy combining intranasal delivery with imaging

A promising frontier lies in integrating theranosticsthe simultaneous use of therapeutic and diagnostic modalitiesinto intranasal drug delivery. Coupling intranasal formulations with advanced imaging tools such as magnetic resonance imaging (MRI), positron emission tomography (PET), or fluorescence-based techniques can enable real-time tracking of drug distribution within the brain. This dual approach would not only enhance precision in targeting tumor microenvironments but also facilitate dynamic monitoring of therapeutic response, allowing timely optimization of dosage and delivery parameters.[46]

8.2. Smart nanocarriers with tumor-targeting ligands

Next-generation nanocarrier systems engineered for intranasal delivery are being designed with active targeting ligands including peptides, antibodies, and aptamers that recognize overexpressed receptors on glioblastoma and other brain tumor cells. Such ligand-functionalized carriers can significantly improve drug localization within tumor tissues, reduce systemic toxicity, and overcome heterogeneity in intratumoral penetration. Furthermore, the incorporation of stimuli-responsive mechanisms (e.g., pH, enzyme, or redox triggers) into these carriers can achieve on-demand drug release, thereby enhancing therapeutic precision and minimizing off-target effects.[47]

8.3. Personalized intranasal therapy based on tumor genomics

The era of precision oncology offers an opportunity to tailor intranasal therapies to the molecular landscape of individual tumors. Profiling genomic and transcriptomic signatures can guide the selection of chemotherapeutics, gene modulators, or RNA-based therapeutics best suited to a patient's tumor subtype. Intranasal delivery platforms may serve as customizable vehicles for such individualized regimens, allowing rapid adaptation of therapeutic payloads to evolving tumor resistance mechanisms. Personalized intranasal therapy thus has the potential to transform treatment outcomes by aligning delivery strategies with tumor biology.[16]

8.4. Combination with immunotherapy or gene therapy for enhanced efficacy

Intranasal administration also represents a strategic partner for synergistic therapeutic modalities such as immunotherapy and gene therapy. Delivering immune checkpoint inhibitors, oncolytic viruses, or CRISPR-based gene-editing systems via the nasal route could bypass systemic clearance barriers and facilitate direct CNS immunomodulation. In particular, co-delivery strategies that combine intranasal nanocarriers with immunotherapeutics or genetic payloads may overcome tumor immune evasion and induce durable antitumor responses. Such combination regimens hold promise for advancing intranasal delivery from a supportive adjunct to a core therapeutic pillar in brain tumor management.[48-51]

9. Animal Studies Evidence

Preclinical animal studies have provided convincing evidence supporting the potential of intranasal drug delivery for brain tumor therapy. Rodent models have demonstrated that intranasally administered anticancer drugs can effectively bypass the blood–brain barrier via olfactory and trigeminal pathways, leading to enhanced brain

accumulation. For example, temozolomide-loaded nanoparticles delivered intranasally showed improved brain bioavailability and prolonged survival in glioma-bearing rats, compared with conventional systemic routes. Similarly, doxorubicin-loaded nanocarriers administered intranasally achieved significant tumor regression with reduced systemic toxicity. These findings highlight the ability of the nasal route to achieve direct and sustained drug delivery to tumor sites within the central nervous system. Moreover, polymeric and lipid-based nanoparticle systems have shown promise in enhancing mucosal adhesion, permeability, and drug retention time in animal models. Overall, in vivo evidence strongly supports the translational potential of intranasal drug delivery as a noninvasive and efficient approach for managing brain tumors.[52-55]

10. Conclusion

Intranasal drug delivery has emerged as a promising, non-invasive strategy to overcome the formidable challenge of delivering therapeutic agents to brain tumors. By capitalizing on the unique anatomical and physiological features of the nasal cavity, particularly the olfactory and trigeminal neural pathways, this approach provides a direct route to the CNS while circumventing the restrictive BBB. Preclinical investigations have consistently demonstrated the capacity of intranasal administration to enhance drug bioavailability within brain tissues, reduce systemic exposure, and potentially improve therapeutic indices for chemotherapeutics, biologics, and nanomedicine formulations.Despite these compelling advantages, the translation of intranasal delivery into routine clinical practice remains in its infancy. Variability in nasal physiology, mucociliary clearance, enzymatic barriers, and patient-related factors such as dosing technique represent significant hurdles to consistent therapeutic outcomes. Moreover, while animal models have generated encouraging data, robust human trials validating efficacy, long-term safety, and reproducibility are urgently required. Integration of advanced delivery platformssuch as mucoadhesive systems, in situ gels, and targeted nanoparticlesmay further optimize residence time and drug distribution across relevant brain regions.Looking ahead, the future of intranasal drug delivery for brain tumors lies in multidisciplinary innovation. Collaborative efforts across pharmaceutical sciences, biomedical engineering, and clinical oncology will be essential to refine formulations, establish dosing regimens, and design patient-friendly devices that support adherence. With continued translational research and rigorous clinical validation, intranasal delivery has the potential to evolve into a transformative therapeutic modality, offering patients a safer, more effective, and accessible treatment paradigm for malignant brain tumors.

11. Source of Funding

None.

12. Conflict of Interest

None.

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Cite this article: Mane DV, Purohit R, Pawar T, Sutar A, Kurde R. Intranasal drug delivery for brain tumors: Promise and challenges. *IP Indian J Anat Surg Head, Neck Brain* 2025;11(1):61-70.