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INTRANASAL DRUG DELIVERY FOR GLIOBLASTOMA THERAPY: A COMPREHENSIVE REVIEW

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ABSTRACT

Glioblastoma (GBM) is the most aggressive primary brain malignancy, characterized by rapid proliferation, diffuse infiltration, and poor clinical outcomes despite multimodal treatment strategies. A major limitation in GBM therapy is the presence of the blood–brain barrier (BBB) and the blood–brain tumor barrier, which severely restrict the penetration of therapeutic agents into the brain. Intranasal drug delivery has emerged as a promising non-invasive approach that enables direct transport of drugs from the nasal cavity to the central nervous system via olfactory and trigeminal nerve pathways, thereby bypassing the BBB. This route offers several advantages, including rapid onset of action, reduced systemic exposure, and improved brain targeting. Recent advancements in nanotechnology have significantly enhanced the efficiency of intranasal delivery systems. Polymeric nanoparticles, lipid-based carriers, in situ gels, and biomimetic nanocarriers have been developed to improve drug stability, prolong nasal residence time, and facilitate targeted delivery to glioblastoma cells. In addition to conventional chemotherapeutics such as temozolomide, emerging therapeutic modalities including gene therapy, immunotherapy, and stem cell-based approaches are being explored via the intranasal route. These strategies have demonstrated promising results in preclinical studies, with improved tumor targeting and therapeutic efficacy. Clinical translation of intranasal therapies is currently underway, with agents such as intranasal perillyl alcohol (NEO100) showing encouraging safety and efficacy profiles in early-phase trials. However, challenges including mucociliary clearance, limited dosing volume, and anatomical variability remain significant barriers. Overall, intranasal drug delivery represents a transformative strategy for GBM therapy, with the potential to improve patient outcomes through targeted, non-invasive treatment approaches.

KEYWORDS: Intranasal drug delivery; Glioblastoma; Nose-to-brain transport; Nanocarriers; Blood–brain barrier; Targeted therapy.

1. INTRODUCTION

Glioblastoma (GBM) is a highly malignant Grade IV astrocytoma associated with poor prognosis and a median survival of approximately 12–15 months despite aggressive treatment involving surgical resection, radiotherapy, and chemotherapy.[1] The limited success of current therapeutic approaches is primarily attributed to the presence of the blood–brain barrier (BBB), which restricts the entry of most therapeutic agents into the central nervous system. It is estimated that nearly 98% of small-molecule drugs and almost all macromolecular therapeutics fail to cross the BBB in therapeutically relevant concentrations.[2] This has prompted the exploration of alternative drug delivery strategies capable of bypassing this physiological barrier.

Intranasal drug delivery has gained considerable attention as a non-invasive and efficient route for brain targeting. By utilizing direct nose-to-brain pathways, drugs administered intranasally can reach the brain via

olfactory and trigeminal nerves, thereby circumventing the BBB and enhancing therapeutic efficacy.[3] This approach offers significant advantages, including improved patient compliance, reduced systemic toxicity, and rapid drug absorption, making it particularly attractive for the treatment of central nervous system disorders such as glioblastoma.

2. Anatomical and Physiological Basis of Intranasal Delivery

The nasal cavity serves as a unique interface between the external environment and the central nervous system, offering direct access to the brain through neural pathways. The olfactory region, located in the upper part of the nasal cavity, plays a critical role in nose-to-brain drug transport. Drugs administered intranasally can traverse the olfactory epithelium and reach the olfactory bulb through the cribriform plate. This transport occurs via both intracellular mechanisms, involving endocytosis and axonal transport, and extracellular pathways, where molecules diffuse through perineural channels into the cerebrospinal fluid.[5] In addition to the olfactory pathway, the trigeminal nerve provides another important route for drug delivery to the brain. This nerve innervates both the olfactory and respiratory regions of the nasal cavity and facilitates the transport of therapeutic agents to deeper brain structures, including the brainstem.[5]

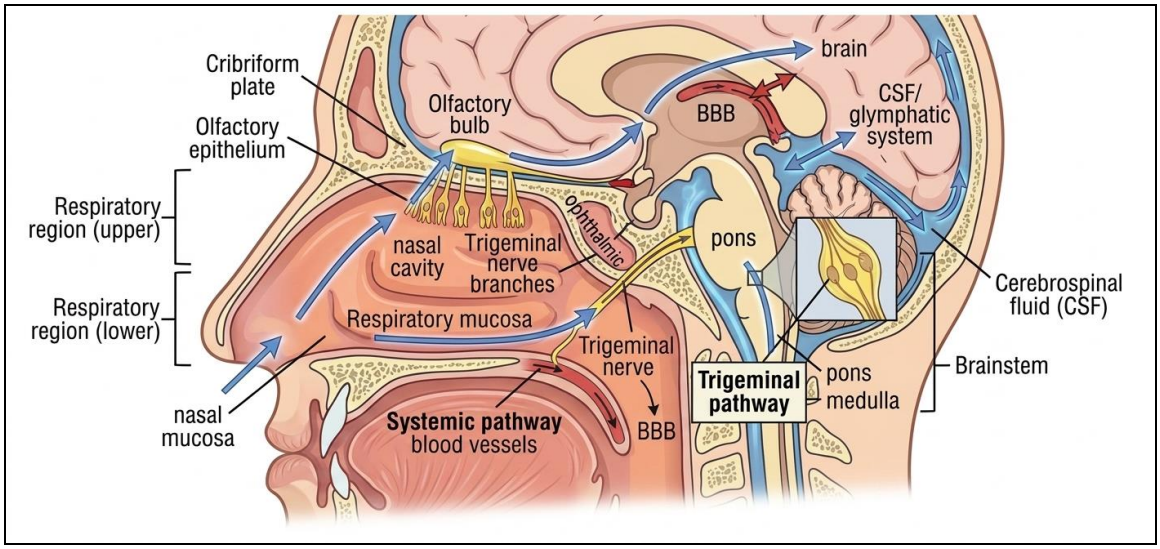

Figure 1: Nose-to-Brain Pathways for Intranasal Drug Delivery.

Once drugs enter the cerebrospinal fluid, they can be distributed throughout the brain via the glymphatic system, a network of perivascular channels that facilitates the exchange of cerebrospinal fluid and interstitial fluid.[7] Although a portion of the drug may be absorbed into systemic circulation through the highly vascularized nasal mucosa, this pathway is less advantageous for brain targeting, as it still requires crossing the BBB.[6] The efficiency of intranasal delivery is influenced by several physiological factors, including mucociliary clearance, enzymatic activity, and the limited surface area of the olfactory region.

3. Challenges in Intranasal Drug Delivery

Despite its potential advantages, intranasal drug delivery faces several challenges that can limit its effectiveness. One of the primary obstacles is mucociliary clearance, a natural defense mechanism that rapidly removes foreign particles from the nasal cavity, thereby reducing drug residence time and absorption. Additionally, the presence of metabolic enzymes in the nasal mucosa can lead to the degradation of drugs before they reach the brain. The limited dosing volume that can be administered intranasally, typically ranging from 0.2 to 0.4 mL, also restricts the amount of drug that can be delivered. Furthermore, anatomical variations among individuals can result in inconsistent drug deposition and absorption, complicating dose standardization and therapeutic outcomes.[8]

Table 1: Physiological and Formulation Barriers in Intranasal Drug Delivery and Their Strategic Solutions for Glioblastoma Therapy.

Barrier	Description	Impact on Drug Delivery	Strategies / Solutions
Mucociliary Clearance	Continuous movement of mucus by cilia toward the nasopharynx	Rapid elimination of drug from nasal cavity, reducing residence time and absorption	Use of mucoadhesive polymers (e.g., chitosan), in situ gels, viscosity enhancers
Enzymatic Degradation	Presence of proteases and peptidases in nasal mucosa	Degradation of peptides, proteins, and nucleic acids	Enzyme inhibitors, protective nanocarriers (polymeric

		before reaching the brain	nanoparticles, liposomes)
Limited Dose Volume	Nasal cavity can accommodate only ~0.2–0.4 mL	Restricts drug loading and therapeutic dose delivery	Use of highly potent drugs, concentrated formulations, nanocarrier systems for improved efficiency
Poor Permeability	Tight junctions in nasal epithelium restrict drug transport	Reduced absorption of hydrophilic and large molecules	Permeation enhancers (e.g., surfactants), tight junction modulators, lipid-based carriers
Low Retention Time	Drug is quickly cleared due to nasal secretions and airflow	Insufficient contact time with absorption sites	In situ gels, bioadhesive formulations, nanoparticle surface modification
Blood–Brain Barrier (BBB)	Protective barrier preventing drug entry into CNS (for systemic absorption route)	Limits effectiveness of drugs entering via systemic circulation	Direct nose-to-brain delivery via olfactory and trigeminal pathways, targeted nanocarriers
Nasal Irritation and Toxicity	Some formulations may damage nasal mucosa	Reduced patient compliance and long-term safety concerns	Use of biocompatible excipients, toxicity screening, optimized pH and osmolarity
Anatomical Variability	Differences in nasal cavity structure among individuals	Inconsistent drug deposition and absorption	Advanced delivery devices (metered-dose sprays, nebulizers), personalized dosing strategies
Drug Solubility Issues	Poor aqueous solubility of many therapeutic agents	Reduced bioavailability and absorption	Use of solubilizers, nanoemulsions, lipid carriers, cyclodextrin complexes
Drug Efflux Mechanisms	Presence of efflux transporters (e.g., P-gp)	Reduced intracellular drug concentration	Efflux transporter inhibitors, nanoparticle encapsulation

4. Nanocarrier-Based Strategies for Enhanced Delivery

To overcome the limitations associated with intranasal delivery, various nanocarrier systems have been developed to improve drug stability, permeability, and targeting efficiency. Polymeric nanoparticles, particularly those composed of materials such as poly(lactic-co-glycolic acid) (PLGA) and chitosan, have been widely investigated for their ability to provide controlled drug release and protect therapeutic agents from enzymatic degradation. Surface modification of these nanoparticles with targeting ligands, such as RGD peptides, has been shown to enhance their accumulation in glioblastoma tissues by facilitating receptor-mediated uptake.[9]

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, offer additional advantages due to their biocompatibility and ability to encapsulate both hydrophilic and lipophilic drugs. These systems have demonstrated improved brain delivery of chemotherapeutic agents such as temozolomide when administered via the intranasal route.[10] In situ gel systems represent another promising approach, as they undergo a sol-to-gel transition upon contact with nasal mucosa, thereby increasing drug residence time and reducing clearance. These systems can be designed to respond to physiological stimuli such as temperature or ionic strength, enabling sustained drug release.[11]

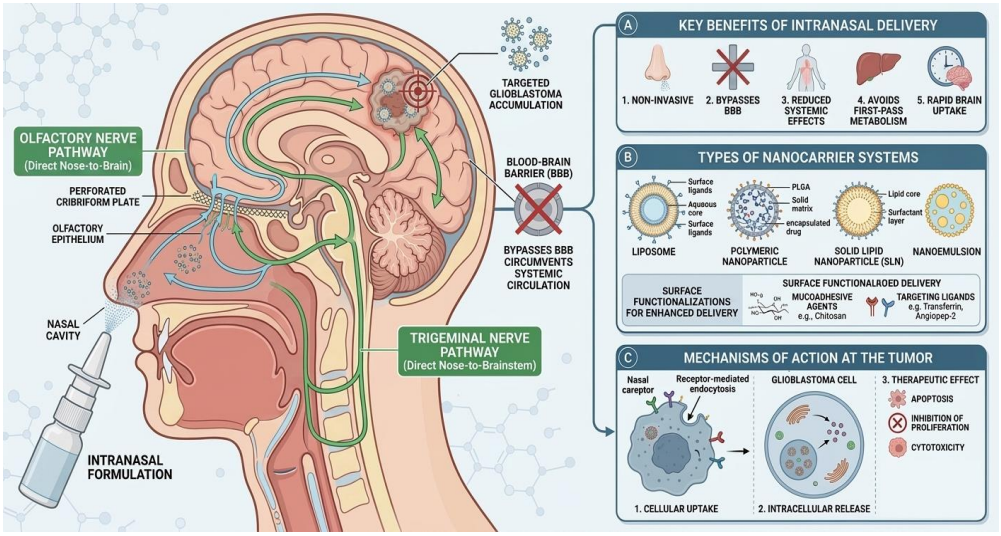

Figure 2: Nanocarrier Systems for Intranasal Glioblastoma Therapy.

Inorganic nanoparticles, including gold and magnetic nanoparticles, have also been explored for their potential in targeted drug delivery and imaging applications. However, concerns regarding their long-term safety and potential toxicity remain a significant barrier to clinical translation.[12] More recently, biomimetic nanocarriers, such as cell membrane-coated nanoparticles, have gained attention due to their ability to mimic natural cellular interactions and exhibit homotypic targeting toward glioblastoma cells.[13]

5. Targeting Approaches for Glioblastoma Therapy

Targeted drug delivery is essential for improving therapeutic outcomes in glioblastoma treatment. Ligand-mediated targeting strategies have been extensively studied, wherein nanoparticles are functionalized with molecules that bind to specific receptors overexpressed on tumor cells. For instance, transferrin targets transferrin receptors, which are highly expressed in glioblastoma cells, while angiopep-2 facilitates transport across the BBB by interacting with low-density lipoprotein receptor-related protein 1. Similarly, RGD peptides target integrins that are involved in tumor angiogenesis, thereby enhancing drug accumulation in tumor vasculature.[14] Cell-penetrating peptides have also been employed to improve intracellular delivery of therapeutic agents, further increasing their efficacy.[15]

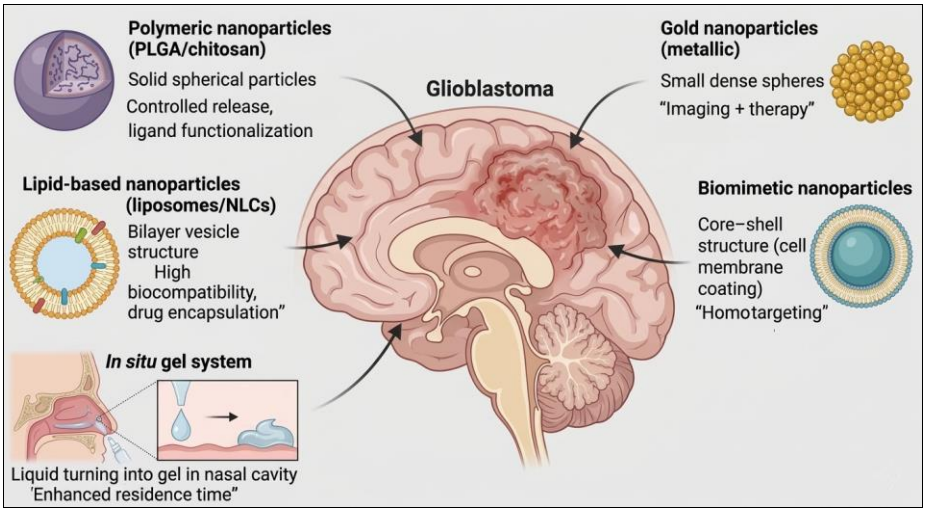

Figure 3: Nanocarrier-based strategies for enhanced intranasal delivery in glioblastoma.

6. Therapeutic Applications of Intranasal Delivery

Intranasal drug delivery has been investigated for a wide range of therapeutic modalities in glioblastoma treatment. Chemotherapeutic agents, particularly temozolomide, remain the cornerstone of GBM therapy, and their intranasal administration has been shown to enhance drug concentration in the brain while reducing systemic toxicity.[16] Gene therapy approaches, including the delivery of small interfering RNA and microRNA, have demonstrated the ability to silence oncogenes and inhibit tumor growth in preclinical models.[17] Immunotherapeutic strategies, such as the use of spherical nucleic acids, have shown promise in activating immune responses against tumor cells and improving survival outcomes.[18]

Stem cell-based therapies represent another innovative approach, as neural and mesenchymal stem cells possess an inherent ability to migrate toward tumor sites. These cells can be engineered to carry therapeutic agents, thereby enabling targeted delivery to infiltrative tumor regions.[19] Combination therapies, involving the co-delivery of multiple drugs or therapeutic modalities, have also shown synergistic effects and improved efficacy in glioblastoma treatment.[20]

Table 2: Therapeutic Applications of Intranasal Delivery in Glioblastoma.

Therapeutic Modality	Examples	Mechanism of Action	Advantages of Intranasal Delivery	Key Findings
Chemotherapy	Temozolomide, Paclitaxel	DNA alkylation, inhibition of cell division	Enhanced brain targeting, reduced systemic toxicity	Increased brain drug concentration and improved tumor suppression.[16]
Gene Therapy	siRNA, miRNA, mRNA	Gene silencing, modulation of oncogenic pathways	Targeted molecular therapy, precision medicine	Effective suppression of tumor growth in preclinical models.[17]
Immunotherapy	Spherical nucleic acids, STING agonists	Activation of immune response, T-cell recruitment	Local immune activation, reduced systemic side effects	Enhanced immune-mediated tumor regression.[18]

Stem Cell Therapy	Neural stem cells, mesenchymal stem cells	Tumor-tropic migration, targeted drug delivery	Targeting infiltrative tumor regions	Significant tumor reduction and improved targeting.[19]
Combination Therapy	TMZ + disulfiram, chemo + gene therapy	Synergistic anticancer effects	Enhanced efficacy, reduced resistance	Improved survival and therapeutic outcomes.[20]

7. Clinical Progress and Translational Potential

The clinical translation of intranasal drug delivery for Glioblastoma therapy remains in a relatively early but steadily advancing phase, driven by the urgent need to overcome the limitations imposed by the blood–brain barrier and the poor prognosis associated with conventional treatment modalities. Among the most prominent clinical candidates, NEO100, a highly purified pharmaceutical-grade formulation of perillyl alcohol, has emerged as a pioneering agent in this domain. Perillyl alcohol, a naturally occurring monoterpene, has demonstrated antitumor activity through mechanisms involving inhibition of oncogenic signaling pathways, induction of apoptosis, and disruption of tumor cell metabolism. Its intranasal administration has been specifically designed to exploit direct nose-to-brain transport pathways, thereby enhancing drug delivery to the tumor site while minimizing systemic exposure. Clinical investigations, including Phase I and Phase IIa trials in patients with recurrent glioblastoma, have reported that repeated intranasal dosing of NEO100 is generally well tolerated, with minimal systemic toxicity and encouraging signals of therapeutic efficacy, including prolonged survival in a subset of patients.[21]

Beyond small-molecule therapeutics such as NEO100, the translational landscape is increasingly expanding to include advanced nanomedicine platforms and gene-based interventions. Nanoparticle-based delivery systems, including lipid nanoparticles and polymeric carriers, are being actively explored in early-phase clinical studies for their ability to encapsulate chemotherapeutic agents, nucleic acids, and biologics while protecting them from degradation and facilitating targeted delivery to tumor tissues. These systems offer the additional advantage of surface functionalization with ligands that enable receptor-mediated uptake, thereby enhancing specificity toward glioblastoma cells. Parallel to these developments, gene therapy approaches utilizing small interfering RNA, microRNA, and messenger RNA are being investigated for their capacity to modulate oncogenic pathways at the molecular level. Although most of these strategies remain at the preclinical or early clinical stage, their successful translation will depend on overcoming critical challenges related to delivery efficiency, immunogenicity, and long-term safety.[22]

Despite these promising advances, several barriers continue to hinder the widespread clinical adoption of intranasal delivery systems. Variability in nasal anatomy among patients, limited dosing capacity, and the lack of standardized delivery devices pose significant challenges for dose optimization and reproducibility. Furthermore, the long-term safety of repeated intranasal administration, particularly for nanocarrier-based and gene therapies, requires comprehensive evaluation through large-scale clinical trials. Nevertheless, ongoing research efforts, coupled with technological innovations in formulation design and delivery devices, are expected to accelerate the clinical translation of intranasal therapies. Collectively, these developments underscore the potential of intranasal drug delivery as a transformative approach in glioblastoma management, offering a non-invasive, patient-friendly, and targeted alternative to conventional therapeutic strategies.

8. Limitations and Future Perspectives

Despite significant advancements, several challenges must be addressed to fully realize the potential of intranasal drug delivery for glioblastoma therapy. These include the limited drug loading capacity, variability in nasal anatomy, and the need for standardized delivery devices. Additionally, the long-term safety of nanocarrier systems must be thoroughly evaluated, particularly for inorganic nanoparticles that may accumulate in tissues. Future research should focus on the development of advanced targeting strategies, personalized treatment approaches, and the integration of imaging techniques to monitor drug distribution and therapeutic response. Large-scale clinical trials will be essential to validate the efficacy of intranasal delivery systems and facilitate their adoption in clinical practice.[23]

9. CONCLUSION

Intranasal drug delivery represents a promising and innovative approach for overcoming the challenges associated with glioblastoma therapy. By enabling direct transport of therapeutic agents to the brain, this strategy has the potential to improve drug efficacy while minimizing systemic side effects. Advances in nanotechnology, targeted delivery, and combination therapies have further enhanced the potential of this approach. However, continued research and clinical validation are necessary to address existing limitations and establish intranasal delivery as a standard treatment modality for glioblastoma.

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