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RECENT TRENDS IN NANO- AND MICRO-PARTICULATE SYSTEMS FOR TARGETED DRUG DELIVERY TO GLIOBLASTOMA: A COMPREHENSIVE REVIEW

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive and fatal primary brain tumour, characterized by rapid progression, high invasiveness, and poor prognosis. The effectiveness of conventional therapeutic approaches, including surgical resection, radiotherapy, and chemotherapy (temozolomide), is significantly limited by challenges such as the blood–brain barrier (BBB), tumour heterogeneity, multidrug resistance, and systemic toxicity. Recent advancements in nano- and micro-particulate drug delivery systems have emerged as promising strategies to overcome these limitations and enhance therapeutic efficacy. Nanoparticulate systems, including lipid-based, polymeric, inorganic, and carbon-based nanocarriers, offer improved drug solubility, prolonged circulation, targeted delivery, and the ability to cross or bypass the BBB via passive and active targeting mechanisms. Additionally, stimuli-responsive systems enable controlled drug release in response to tumour-specific conditions such as pH, temperature, or external magnetic fields. In parallel, microparticulate systems such as microspheres and in-situ forming implants provide localized drug delivery, bypassing the BBB and ensuring sustained drug release at the tumour site, particularly in post-surgical conditions. Furthermore, advanced administration routes such as intranasal delivery and convection-enhanced delivery (CED) have shown potential in improving drug distribution within the brain. Despite significant progress, challenges related to toxicity, immunogenicity, large-scale manufacturing, and regulatory approval remain critical barriers to clinical translation. Future perspectives emphasize the integration of personalized nanomedicine, multifunctional therapeutic platforms, and artificial intelligence-driven design to optimize treatment outcomes. This review highlights recent trends, challenges, and future directions in nano- and micro-particulate drug delivery systems for targeted GBM therapy, offering insights into their potential to transform current treatment paradigms.

KEYWORDS: Glioblastoma multiforme (GBM); Blood–brain barrier (BBB); Nanoparticles; Microparticles; Targeted drug delivery; Liposomes; Polymeric nanoparticles; PLGA; Drug resistance; Intranasal delivery; Convection-enhanced delivery (CED); Theragnostic; Stimuli-responsive systems; Cancer nanotechnology.

1. INTRODUCTION

1.1. Overview of Glioblastoma Multiforme (GBM)

Glioblastoma Multiforme (GBM) is recognized as the most prevalent and aggressive primary malignancy of the central nervous system in adults. It is characterized by its rapid progression and a notoriously poor clinical prognosis. Despite significant medical advancements, the survival rate for GBM patients remains exceptionally low, making it one of the most challenging cancers to treat in modern oncology.

1.2. Pathophysiology and why it is the Most Aggressive Brain Tumour

The aggressive nature of GBM is a result of several complex biological factors:

- **Highly Infiltrative Growth**: GBM cells possess an innate ability to invade surrounding healthy brain tissues, making complete surgical removal nearly impossible.
- **The Blood-Brain Barrier (BBB)**: This physiological barrier restricts the entry of over 98%

of small-molecule drugs and nearly 100% of large-molecule therapeutics into the brain.

- **Tumour Heterogeneity**: The presence of diverse cell subpopulations within a single tumour allows some cells to survive even when others are killed by treatment.
- **Microenvironmental Factors**: Hypoxia and rapid angiogenesis (the formation of new blood vessels) within the tumour promote aggressive behaviour and therapeutic resistance.

1.3. Current Standard of Care

The standard clinical management for newly diagnosed GBM involves a multimodal approach:

- **Surgical Resection**: The primary goal is the maximal safe removal of the tumour mass to reduce intracranial pressure.
- **Radiotherapy:** Post-operative radiation is employed to target the remaining microscopic infiltrative cells.
- **Chemotherapy (Temozolomide):** Temozolomide (TMZ), an oral alkylating agent, is administered concurrently with and following radiotherapy to inhibit DNA replication in cancer cells.

1.4. Limitations of Conventional Therapy

Standard treatments frequently fail due to several critical limitations:

- Poor Solubility and Bioavailability: Many potent anticancer agents are hydrophobic, leading to poor water solubility and insufficient absorption into the bloodstream.
- Multidrug Resistance (MDR): Cancer cells often overexpress efflux transporters, such as P-glycoprotein (P-gp), which actively pump chemotherapeutic drugs out of the cell before they can take effect.
- Lack of Specificity: Conventional drugs do not distinguish between cancerous and healthy cells, leading to systemic toxicity and severe side effects for the patient.
- Short Half-life: Many drugs are rapidly cleared from the body or degraded before they can reach the brain tumour site in therapeutic concentrations.

Table 1: Comparative Challenges of Conventional GBM Therapeutics.

Challenge	Impact on Treatment	Scientific Mechanism +1
Blood-Brain Barrier (BBB)	Extremely low drug reach.	Restricts >98% of small-molecule drugs from entering the brain parenchyma.
P-gp Efflux	Multidrug Resistance (MDR).	Transporters actively pump chemotherapeutic agents out of the tumour cells.
Hydrophobicity	Poor bioavailability.	Low water solubility prevents effective drug absorption and circulation.
Non-Specific Toxicity	Severe side effects.	Lack of targeting leads to damage in healthy tissues and systemic organs.
Tumour Hypoxia	Aggressive growth.	Oxygen-deprived regions promote resistance and prevent drug penetration.

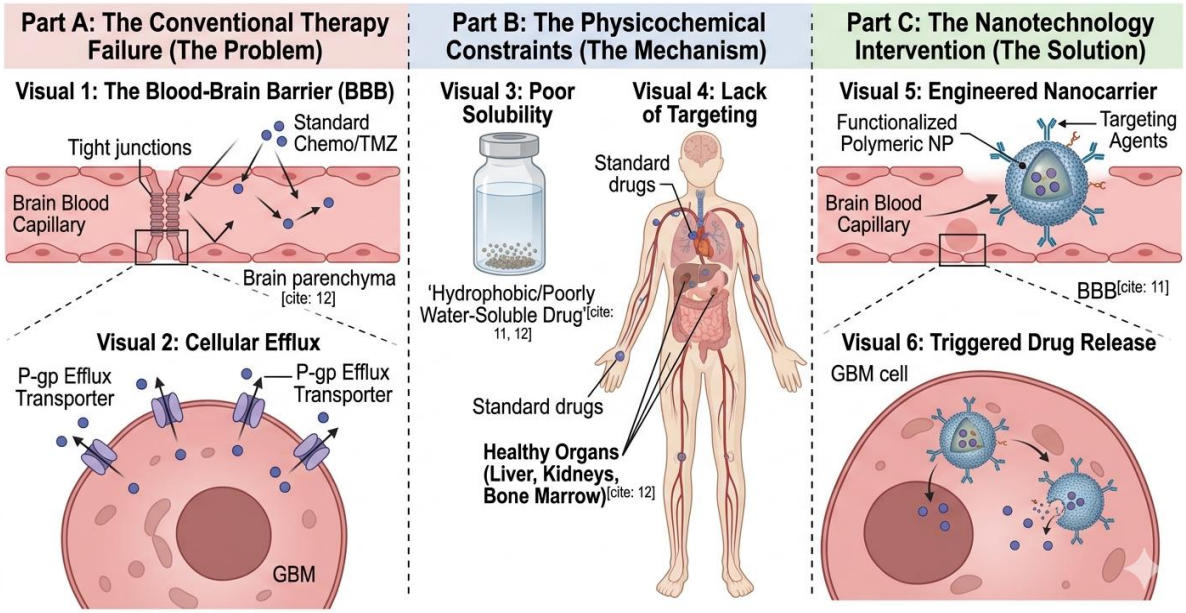

Figure 1: Overcoming Barriers in GBM Therapy.

2. THE MAJOR BARRIER: BLOOD-BRAIN BARRIER (BBB)

2.1. Structure and Function of the BBB

The Blood-Brain Barrier (BBB) is a highly selective semipermeable border that separates the circulating blood from the brain extracellular fluid in the central nervous system.

- **Endothelial Cells and Tight Junctions:** Unlike peripheral capillaries, brain capillaries are lined with endothelial cells connected by extremely tight junctions that lack fenestrations, creating a high-resistance physical barrier.
- **Supporting Architecture**: The barrier is further reinforced by a basement membrane, pericytes, and the end-feet of astrocytes, which collectively maintain the brain's microenvironment and protect it from neurotoxins.
- **Regulatory Role:** Its primary function is to maintain homeostasis by allowing the entry of essential nutrients while strictly excluding harmful substances and most therapeutic agents.

2.2. Why 98% of Small Molecule Drugs Fail to Cross the BBB

Despite being designed for therapeutic use, the vast majority of small-molecule drugs are unable to penetrate the BBB due to several physiological and biochemical constraints:

- **Size and Hydrophobicity**: Only very small, lipid-soluble molecules (typically <400–500 Daltons) can passively diffuse across the BBB. Most conventional drugs do not meet these specific physicochemical criteria.
- **Efflux Transporters**: The BBB is equipped with powerful ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp), which actively recognize and pump foreign molecules out of the brain even if they manage to enter.
- **Metabolic Barrier:** Enzymes present within the endothelial cells can metabolize drugs during their passage, further reducing their concentration before they reach the brain tissue.
- **Bioavailability Issues**: Poor water solubility often leads to rapid clearance from the bloodstream, preventing drugs from reaching the brain at therapeutic levels.

2.3. The Role of Blood-Brain Tumour Barrier (BBTB)

As a brain tumour like GBM grows, the standard BBB is modified into what is known as the Blood-Brain Tumour Barrier (BBTB).

- Increased Permeability but Heterogeneity: While the BBTB is generally more permeable than the healthy BBB due to disrupted tight junctions and abnormal vessel growth, this permeability is highly inconsistent and heterogeneous across the tumour mass.
- High Interstitial Fluid Pressure: The BBTB often exhibits high interstitial pressure, which creates an outward flow that prevents drugs from effectively penetrating deep into the tumour core.
- **Hypoxic Niches:** The chaotic vascularization of the BBTB leads to oxygen-deprived (hypoxic) areas where drugs cannot reach, providing a sanctuary for treatment-resistant cancer stem cells.
- **Continued Efflux Activity:** Despite the structural damage to the barrier, efflux pumps remain highly active in the BBTB, continuing to exclude chemotherapeutic agents from the tumour microenvironment.

3. NANOPARTICULATE DRUG DELIVERY SYSTEMS FOR GBM

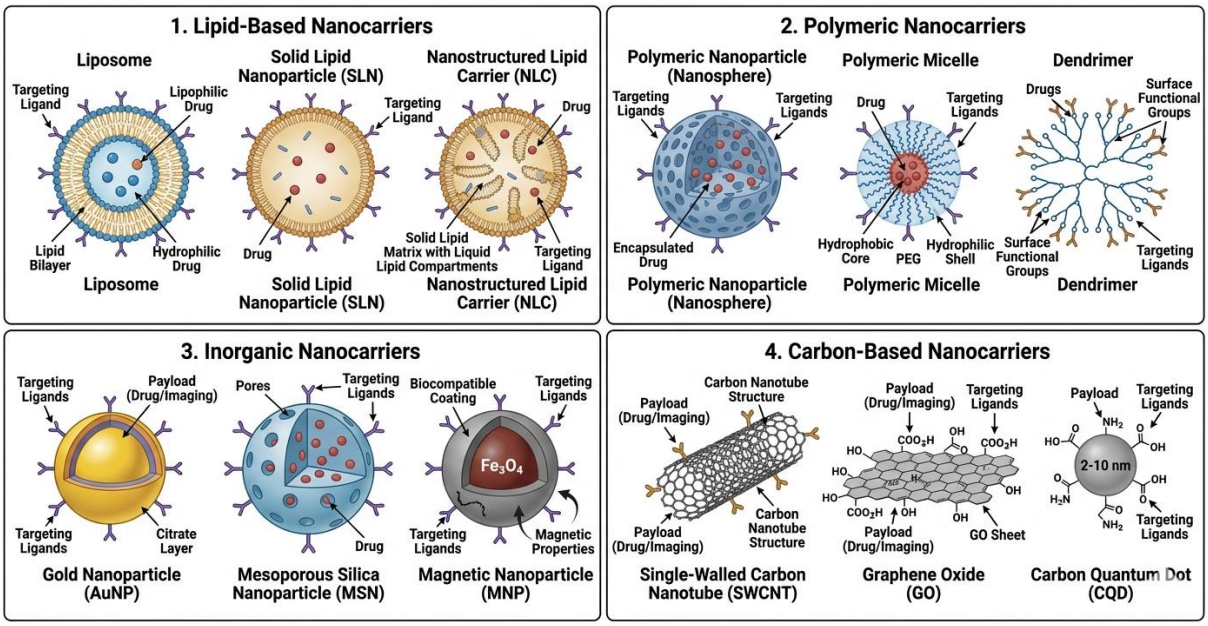

Figure 2: Diversity of Nanoparticulate Platforms for Brain Tumour Targeting.

3.1. Lipid-based Nanoparticles

Lipid-based systems are highly favoured for GBM due to their biomimetic properties and ability to carry diverse drug payloads.

- **Liposomes:** These spherical vesicles consist of lipid bilayers that can encapsulate both hydrophilic drugs in the aqueous core and lipophilic drugs within the bilayer. They are frequently modified with PEG (PEGylation) to increase circulation time and avoid immune detection.
- **Solid Lipid Nanoparticles (SLNs):** SLNs are composed of biocompatible lipids that remain solid at body temperature, offering better drug stability and controlled release compared to traditional liposomes. Their small size facilitates improved uptake through the leaky vasculature of the Blood-Brain Tumour Barrier (BBTB).

3.2. Polymeric Nanoparticles

Polymeric platforms offer a high degree of chemical flexibility for targeting and drug release.

- **PLGA (Poly lactic-co-glycolic acid):** This FDA-approved biodegradable polymer is widely used to create nanocarriers that provide sustained drug release, significantly reducing the systemic toxicity associated with conventional chemotherapy.
- **Chitosan:** As a natural cationic polymer, chitosan is valued for its mucoadhesive properties and its ability to open tight junctions in biological barriers, potentially aiding in BBB penetration.
- **Dendrimers:** These are highly branched, symmetrical macromolecules. Their unique structure allows for a high density of surface functional groups, which can be used to attach multiple targeting ligands (like transferrin) simultaneously to maximize brain delivery.

3.3. Inorganic Nanoparticles

Inorganic materials introduce unique physical properties that allow for combined therapy and imaging (theragnostic).

- **Gold Nanoparticles (AuNPs):** Due to their unique surface plasmon resonance, AuNPs are used for photothermal therapy, where they convert light into heat to destroy cancer cells locally.
- **Magnetic Iron Oxide Nanoparticles (SPIONs**): These nanoparticles can be guided to the tumour site using external magnetic fields. Additionally, they are used for magnetic hyperthermia heating the tumour to sensitize it to radiation and as contrast agents for high resolution MRI.

3.4. Carbon-based Nanomaterials

Carbon-based systems offer exceptional surface area and mechanical strength.

- **Carbon Nanotubes (CNTs):** CNTs can penetrate cellular membranes like nanoneedles, delivering drugs directly into the cytoplasm of GBM cells. However, their long-term biocompatibility remains a subject of intense research.
- **Graphene and Graphene Oxide**: These 2D nanomaterials provide a vast surface area for the high-capacity loading of aromatic anticancer drugs via pi-pi stacking interactions.

Table 2: Comparison of Nanoparticulate Systems for GBM Therapy.

Nanoparticle Type	Materials	Primary Advantage	Limitation
Lipid-based	Phospholipids, Cholesterol	High biocompatibility, biomimetic	Potential for drug leakage
Polymeric	PLGA, Chitosan, PEG	Controlled/sustained release	Complex scale-up manufacturing
Inorganic	Gold, Iron Oxide	Theragnostic (imaging + therapy)	Long-term toxicity concerns
Carbon-based	CNTs, Graphene	Ultra-high drug loading	High risk of immunogenicity

4. MICROPARTICULATE DELIVERY SYSTEMS

Table 3: Comparison of Nano-scale vs. Micro-scale Systems for GBM.

Feature	Nanoparticles (NPs)	Microparticles/Implants
Typical Size	10–200 nm	1–500 µm
Route of Admin	Intravenous (IV)	Local/Intracranial
BBB Barrier	Must cross the BBB	Bypasses the BBB
Clinical Goal	Target primary and distant cells	Prevent post-surgical recurrence

4.1. Microspheres

Microspheres are solid, spherical particles ranging from 1 to 1000 micro meter in diameter, typically composed of biodegradable polymers.

- Encapsulation and Protection: These systems protect unstable drugs from enzymatic degradation in the brain environment and provide a high payload capacity.
- Release Kinetics: By adjusting the polymer ratio (e.g., PLGA 50:50 vs. 75:25), the drug release can be tuned from several days to multiple months, ensuring a constant therapeutic concentration at the tumour site without the peaks and troughs of oral dosing.

4.2. In-situ Forming Implants

One of the most promising applications for micro-scale systems is the management of the surgical resection cavity after a tumour is removed.

- Gelation Mechanism: These systems are injected as a liquid and undergo a phase transition (e.g., temperature-sensitive or solvent-exchange) to form a solid or semi-solid depot inside the brain.
- Prevention of Recurrence: By filling the resection cavity, these implants deliver high doses of chemotherapy directly to the infiltrative "margin" cells that surgery cannot reach, bypassing the BBB entirely.

4.3. Advantages of Micro-scale Systems in Local Delivery

While nanoparticles are ideal for systemic circulation, micro-scale systems offer unique benefits for local administration:

- Reduced Systemic Toxicity: Since the drug is confined to the brain, the risk of damage to the liver, kidneys, and bone marrow is virtually eliminated.
- Bypassing the BBB: Direct intracranial injection or implantation removes the BBB as a factor, allowing the use of potent drugs that would otherwise never reach the brain.
- High Local Concentration: These systems achieve a drug concentration in the tumour area that is several times higher than what can be achieved through intravenous infusion.

5. TARGETING STRATEGIES

Table 4: Summary of Targeting Ligands and Their Receptors

Ligand	Target Receptor	Mechanism
Transferrin	Tf Receptor	Receptor mediated transcytosis
Lactoferrin	Lf Receptor	Dual-targeting (BBB + Tumour)
Folic Acid	Folate Receptor	Endocytosis-mediated uptake
Antibodies	Specific Antigens (e.g., EGFRvIII)	High-affinity molecular recognition

5.1. Passive Targeting: Enhanced Permeability and Retention (EPR) Effect

Passive targeting relies on the physiological characteristics of the tumour vasculature rather than specific molecular recognition.

- Leaky Vasculature: GBM tumours exhibit rapid and chaotic angiogenesis, resulting in "leaky" blood vessels with large gaps between endothelial cells.
- Accumulation: Nanoparticles within the 10–200 nm size range can extravasate through these gaps and accumulate preferentially within the tumour mass.
- Poor Lymphatic Drainage: The lack of functional lymphatic drainage in tumours further ensures that nanoparticles remain trapped in the tumour environment for an extended period, increasing drug exposure.

5.2. Active Targeting: Using Ligands

Active targeting involves decorating the surface of nanocarriers with specific ligands that bind to receptors overexpressed on the BBB or GBM cells.

- Transferrin (Tf) Receptors: Since brain tumour cells require high amounts of iron for rapid growth, they overexpress transferrin receptors; targeting these allows nanocarriers to cross the BBB via receptor-mediated transcytosis.
- Lactoferrin: This ligand is highly effective because its receptors are expressed on both the BBB endothelial cells and the glioma cells, providing a dual-targeting approach.
- Folic Acid: Many cancer cells overexpress folate receptors. Attaching folic acid to nanoparticles ensures high affinity and selective internalisation into the tumour cells, sparing healthy brain tissue.

5.3. Stimuli Responsive Delivery

These smart delivery systems release their drug payload only when triggered by specific internal or external signals.

- pH-Sensitive Delivery: The tumour microenvironment is typically more acidic (6.5–6.8 pH) than healthy tissue (pH 7.4). Nanocarriers can be engineered to degrade and release drugs only under these acidic conditions.
- Thermo-responsive Systems: Using external heat (hyperthermia), specific polymers can undergo a phase transition, opening the nanocarrier to release the drug exactly at the tumour site.
- Magnetic-field-guided Delivery: Magnetic nanoparticles (like Iron Oxide) can be physically pulled toward the tumour using an external magnetic field, increasing the concentration of the drug in the brain while reducing systemic exposure.

6. ROUTES OF ADMINISTRATION FOR GBM

Table 5: Comparison of Administration Routes for GBM.

Route	Mechanism	BBB Bypass	Advantage
Systemic (IV)	Circulation / Diffusion	No (Requires targeting)	Non-invasive, patient-friendly
Intranasal	Olfactory/Trigeminal nerves	Yes (Direct)	Non-invasive, rapid brain entry
CED	Bulk flow / Pressure	Yes (Direct)	High local concentration, large coverage

6.1. Systemic (Intravenous) Route

The intravenous (IV) route remains the most common clinical approach for administering chemotherapeutic agents due to its non-invasive nature and ease of administration.

- Challenges: Drugs administered systemically face rapid clearance by the Reticuloendothelial System (RES) and significant dilution in the blood volume.
- The Nanotech Solution: Utilizing PEGylated nanoparticles prevents "opsonization," allowing the drug to remain in circulation long enough to utilize the EPR effect for tumour accumulation.
- Limitation: Despite long circulation times, only a small fraction of the injected dose typically crosses the BBB, necessitating higher doses that can cause systemic side effects.

6.2. Intranasal Delivery (Nose-to-Brain Bypass)

Intranasal administration is a revolutionary non-invasive route that allows drugs to bypass the BBB and enter the brain directly.

- Anatomical Pathway: Drugs travel along the olfactory and trigeminal nerve pathways, moving from the nasal cavity directly into the cerebrospinal fluid (CSF) and brain parenchyma.
- Rapid Action: This route provides a faster onset of action and avoids first-pass metabolism in the liver.
- Nano-enhancement: Mucoadhesive nanoparticles (like Chitosan) are often used to increase the residence time of the drug in the nasal mucosa, preventing it from being washed away by ciliary clearance.

6.3. Convection-Enhanced Delivery (CED)

CED is a local delivery technique that involves the surgical insertion of small catheters directly into the tumour or the surrounding brain tissue.

- Pressure-Driven Flow: Unlike simple diffusion, CED uses a continuous low-pressure infusion to create a pressure gradient that pushes the drug through the interstitial spaces of the brain.
- Large Distribution Volume: This method allows for the uniform distribution of large molecules and nanoparticles over a much larger area than diffusion alone could achieve.
- Bypassing Barriers: Since the drug is infused directly into the brain, the BBB is not a factor, allowing for high local concentrations with minimal systemic exposure.

7. CLINICAL STATUS AND MARKETED FORMULATIONS

7.1. FDA-approved Nano-formulations for Brain Cancer

The transition of nanotechnology from laboratory research to clinical practice for Glioblastoma Multiforme (GBM) has been a rigorous process, with only a few formulations successfully navigating the FDA approval pipeline for neurological applications. Currently, while several nano-formulations such as Abraxane (albumin-bound paclitaxel) and Doxil/Caelyx (liposomal doxorubicin) have revolutionized the treatment of systemic cancers like breast and ovarian cancer, their use in GBM remains primarily focused on off-label applications or investigational studies. The most significant hurdle for these approved agents is their limited ability to achieve therapeutic concentrations across the intact portions of the Blood-Brain Barrier (BBB). However, the success of Gliadel Wafer (a carmustine-loaded biodegradable polymer) serves as a critical clinical precedent, proving that local microparticulate delivery systems can successfully bypass the BBB to provide sustained therapeutic release within the post-surgical cavity.

7.2. Case Studies of Recent Clinical Trials

Recent clinical trials are shifting focus toward "Smart" nanocarriers that utilize active targeting and stimuli-responsive mechanisms to improve efficacy. Case studies of Phase I and Phase II trials have highlighted the potential of Targeted Polymeric Nanoparticles decorated with ligands like Transferrin, which aim to exploit the overexpression of iron-transport receptors on both the BBB and glioma cells to facilitate receptor-mediated transcytosis. Additionally, trials involving Magnetic Iron-Oxide Nanoparticles have explored the dual role of Theragnostic, where the particles act as both MRI contrast agents and mediators for magnetic hyperthermia; by applying an alternating magnetic field, these particles generate localized heat to thermally ablate tumour cells. Other notable trials are investigating Liposomal Irinotecan and Gold Nanoparticles for photothermal therapy, reflecting a broader trend toward personalized medicine where the nanocarrier is tailored to the specific genetic and physiological profile of the patient's tumour.

8. TOXICITY AND REGULATORY CHALLENGES

Despite the immense potential of nanotechnology in treating Glioblastoma, several safety and regulatory hurdles must be addressed before these systems become standard clinical practice.

- Nanotoxicity and Biocompatibility: Many inorganic nanoparticles, such as carbon nanotubes and certain metal-based carriers, raise concerns regarding long-term accumulation in the liver, spleen, and brain tissue, potentially leading to chronic inflammation or oxidative stress.
- Immunogenicity: The body’s immune system often recognizes synthetic nanocarriers as foreign entities, leading to rapid clearance by the reticuloendothelial system (RES), which necessitates the use of PEGylation to "cloak" the particles.
- Manufacturing Scalability: Moving from small-scale laboratory synthesis to large-scale pharmaceutical manufacturing is complex, as maintaining consistent particle size, drug loading, and surface functionalization across batches is technically demanding.

- Regulatory Complexity: Current regulatory frameworks often struggle to categorize nanomedicines because they function as a combination of a drug and a medical device, leading to prolonged approval times and the need for more specialized safety protocols.

9. FUTURE PERSPECTIVES

The future of GBM therapy lies in the integration of "Smart" nanotechnology with personalized medicine.

- Personalized Nanomedicine: Future strategies will likely involve tailoring the surface ligands of nanoparticles to match the specific genetic mutations or receptor expressions found in an individual patient's biopsy.
- Combined Modalities: We expect to see a rise in multi-functional platforms that combine chemotherapy with photothermal therapy, gene silencing (siRNA), or immunotherapy within a single nanocarrier.
- Artificial Intelligence: AI is beginning to play a role in predicting how specific nanostructures will interact with the Blood-Brain Barrier, allowing researchers to design more efficient carriers before entering the clinical phase.

10. CONCLUSION

The treatment of Glioblastoma remains one of the most formidable challenges in oncology due to the restrictive nature of the Blood-Brain Barrier (BBB) and the aggressive, infiltrative growth of the tumour. However, nanotechnology offers a transformative solution by providing a Trojan Horse approach protecting therapeutic agents, bypassing physiological barriers, and delivering drugs directly to the malignant cells. While issues regarding long-term toxicity and regulatory standardization persist, the progress in active targeting, stimuli-responsive release, and local delivery systems like CED and intranasal routes provides a promising roadmap. As research continues to bridge the gap between material science and clinical neurology, nanotechnology stands as the most viable path toward turning GBM from a terminal diagnosis into a manageable condition.

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