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Review

Lipidic and Inorganic Nanoparticles for Targeted Glioblastoma Multiforme Therapy: Advances and Strategies

Ewelina Musielak * and Violetta Krajka-Kuźniak

Department of Pharmaceutical Biochemistry, Poznan University of Medical Sciences, Rokietnicka 3, 60-806 Poznan, Poland; vkrajka@ump.edu.pl

* Correspondence: emusielak@ump.edu.pl; Tel.: +48-61-641-84-74

Abstract: Due to their biocompatibility, nontoxicity, and surface conjugation properties, nanomaterials are effective nanocarriers capable of encapsulating chemotherapeutic drugs and facilitating targeted delivery across the blood–brain barrier (BBB). Although research on nanoparticles for brain cancer treatment is still in its early stages, these systems hold great potential to revolutionize drug delivery. Glioblastoma multiforme (GBM) is one of the most common and lethal brain tumors, and its heterogeneous and aggressive nature complicates current treatments, which primarily rely on surgery. One of the significant obstacles to effective treatment is the poor penetration of drugs across the BBB. Moreover, GBM is often referred to as a "cold" tumor, characterized by an immunosuppressive tumor microenvironment (TME) and minimal immune cell infiltration, which limits the effectiveness of immunotherapies. Therefore, developing novel, more effective treatments is critical to improving the survival rate of GBM patients. Current strategies for enhancing treatment outcomes focus on the controlled, targeted delivery of chemotherapeutic agents to GBM cells across the BBB using nanoparticles. These therapies must be designed to engage specialized transport systems, allowing for efficient BBB penetration, improved therapeutic efficacy, and reduced systemic toxicity and drug degradation. Lipid and inorganic nanoparticles can enhance brain delivery while minimizing side effects. These formulations may include epitopes—small antigen fragments that bind directly to free antibodies, B cell receptors, or T cell receptors—that interact with transport systems and enable BBB crossing, thereby boosting therapeutic efficacy. Lipid-based nanoparticles (LNPs), such as liposomes, niosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), are among the most promising delivery systems due to their unique properties, including their size, surface modification capabilities, and proven biosafety. Additionally, inorganic nanoparticles such as gold nanoparticles, mesoporous silica, superparamagnetic iron oxide nanoparticles, and dendrimers offer promising alternatives. Inorganic nanoparticles (INPs) can be easily engineered, and their surfaces can be modified with various elements or biological ligands to enhance BBB penetration, targeted delivery, and biocompatibility. Strategies such as surface engineering and functionalization have been employed to ensure biocompatibility and reduce cytotoxicity, making these nanoparticles safer for clinical applications. The use of INPs in GBM treatment has shown promise in improving the efficacy of traditional therapies like chemotherapy, radiotherapy, and gene therapy, as well as advancing newer treatment strategies, including immunotherapy, photothermal and photodynamic therapies, and magnetic hyperthermia. This article reviews the latest research on lipid and inorganic nanoparticles in treating GBM, focusing on active and passive targeting approaches.

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1. Introduction

Glioblastoma multiforme (GBM) is the most aggressive and lethal primary brain tumor, characterized by profound heterogeneity at both cellular and molecular levels. The hallmark features of GBM include rapid proliferation, diffuse infiltration into healthy brain tissue, high angiogenesis, and resistance to conventional therapies. These characteristics are driven by genetic and epigenetic alterations in key signaling pathways such as the PI3K/AKT/mTOR, MAPK, and WNT pathways. GBM is also known for its hypoxic microenvironment, which promotes tumor progression, angiogenesis, and therapy resistance by upregulating hypoxia-inducible factors [1]. Standard treatment for GBM in adults typically includes postoperative radiotherapy combined with Temozolomide (TMZ) chemotherapy. However, TMZ's response rate remains below 50%, and the invasive nature of GBM significantly limits therapeutic outcomes. Consequently, the median survival for patients is only 12 to 15 months, with a five-year survival rate of about 5% [2,3]. Additionally, cranial irradiation, a cornerstone of GBM management, often results in cognitive impairments due to damage to neurons and endothelial cells. Glioblastoma multiforme (GBM) poses significant treatment challenges, particularly in its 'cold' phenotype, which is defined by the absence or scarcity of cytotoxic T lymphocytes (CTLs) within the tumor microenvironment (TME). This immune-desert state results from dense extracellular matrix barriers, immune checkpoint overexpression, and the secretion of immunosuppressive cytokines. These features limit immune cell infiltration and suppress antitumor immune responses, rendering immunotherapies less effective. Consequently, cold GBM is associated with poor prognoses and limited therapeutic options. These challenges underscore the urgent need for more effective and less harmful treatment options. Recent research efforts aim to overcome the limitations of traditional therapies by developing innovative strategies to deliver chemotherapeutic agents across the blood–brain barrier (BBB) with minimal adverse effects [4].

Nanotechnology has introduced various nanomaterials as potential drug carriers, leveraging their size, stability, high drug-loading capacity, and biocompatibility to target brain tumors effectively. Lipid-based carriers, specifically designed to cross the BBB, are a growing study area with promising applications in GBM treatment. Notably, carmustine-loaded nanoparticles (Gliadel®) have been developed to deliver localized, sustained-release chemotherapy in the postoperative period, maintaining therapeutic levels for up to 120 h. Systemically administered chemotherapy options, including Temozolomide and nitrosoureas like carmustine, are used to treat recurrent GBM, though nitrosoureas have notable side effects, such as bone marrow suppression, hepatotoxicity, nephrotoxicity, and interstitial lung disease, which limit their applicability [5,6]. Recent advances in nanotechnology offer promising approaches to overcome these challenges. Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, can be engineered to deliver immunostimulatory agents (e.g., immune checkpoint inhibitors or cytokines) directly to the tumor site. Similarly, inorganic nanoparticles, such as gold nanoparticles and mesoporous silica, can modulate the TME by enhancing antigen presentation, disrupting immunosuppressive networks, and promoting CTL recruitment. These strategies hold the potential to transform cold GBM into a more immunologically active state, enhancing the efficacy of existing therapies. The interplay between GBM's aggressive pathophysiology and its immunosuppressive nature creates significant barriers to treatment. Current therapies,

including surgical resection, radiation, and Temozolomide chemotherapy, have limited efficacy, with a median survival of 12–15 months. The blood–brain barrier (BBB) further complicates treatment by restricting the delivery of therapeutic agents to the tumor site. Addressing the dual challenges of therapy resistance and immune evasion requires innovative approaches, such as nanotechnology-based platforms, to enhance drug delivery and reprogram the TME [7].

Overall, while nanotechnology offers a promising avenue to improve GBM therapy by enhancing targeted drug delivery and minimizing toxicity, ongoing research is essential to overcome the BBB's constraints and to refine these carriers for practical clinical use [8].

2. Brain Tumors—Glioblastoma Multiforme

The brain is the most important and most complex organ in the human body. It is responsible for many functions, including control over all internal organs and physiological processes, regulation of memory, and sensitive motor functions. It comprises the cerebrum, cerebellum, brain stem, and four lobes: frontal, parietal, occipital, and temporal (Figure 1) [9].

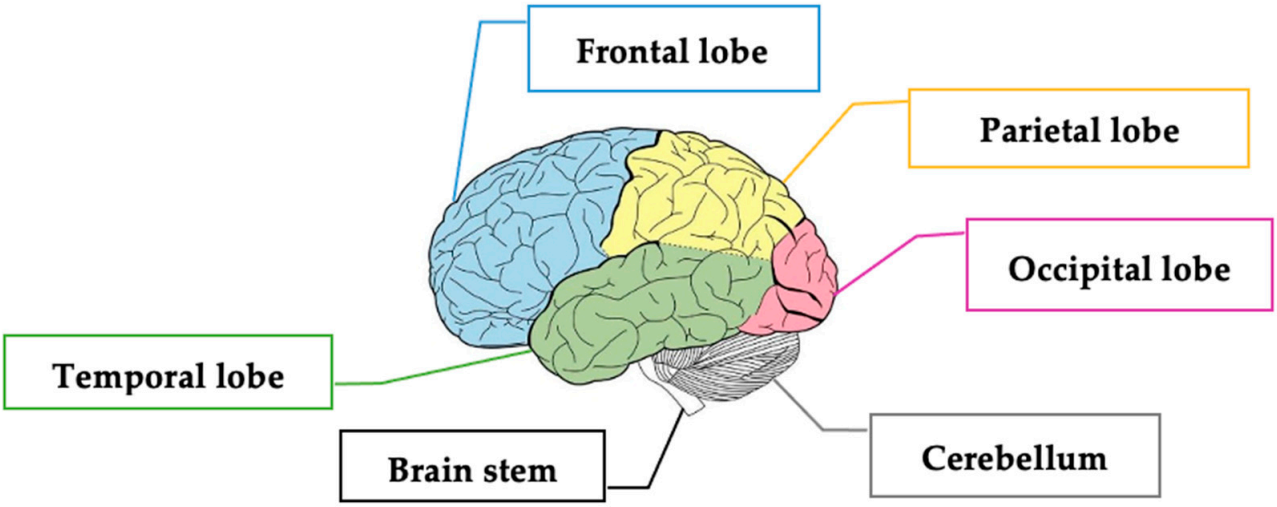


Figure 1. Diagram of the structure of the human brain [9].

The cerebellum is the largest part of the brain. It accompanies the right and left hemispheres and performs essential motor, sensory, and movement control functions. The cerebellum and cerebrum are connected to the spinal cord via the brain stem, located in the lower part of the brain. In addition, the four lobes of the brain are associated with properly propagating behavioral functions. Any abnormalities in the brain's anatomical structure and abnormal cell growth in an uncontrolled way lead to disruption of its proper functioning [10].

Brain tumors are divided into two groups: the so-called primary tumors, which arise and are located in the brain, and secondary (metastatic) tumors, which originate from a primary tumor outside the central nervous system and spread to the brain. According to research, metastatic tumors are more common in adults, while primary tumors are the most common solid tumors in childhood. The most common brain tumors are tumors derived from glial cells, so-called gliomas, which represent a broad group of tumors, from slow-growing tumors to very aggressive tumors. The WHO has classified gliomas into four grades [11]:

- grade I—pilocytic astrocytoma;
- grade II—diffuse astrocytoma;

- grade III—anaplastic astrocytoma;
- grade IV—glioblastoma multiforme.

Grades III and IV are considered gliomas with a high degree of malignancy and are associated with an inferior prognosis. The 5-year survival rate for glioblastoma multiforme, which accounts for half of primary brain tumors, is less than 10% [11]. Brain metastases are the most common intracranial tumors in adults and develop in 8–10% of patients, although the incidence of metastases varies considerably depending on the type of primary tumor. It is estimated that nearly 70% of brain metastases result from lung, breast, colon, or melanoma cancers [12]. The most common, very high-grade brain tumors are glioblastoma multiforme. They are considered to be highly lethal due to their high invasiveness and resistance to surgery, chemo- and radiotherapy.

Treatment of brain tumors is complicated, mainly due to their intracranial location [13]. Intracranial tumors are effectively protected from the effects of most systemically administered cytostatic agents. The brain parenchyma and most intracranial tumors are protected by the blood–brain barrier (BBB). The BBB is responsible for maintaining the brain microenvironment and serves as a physical and metabolic barrier regulating the access of molecules to the brain. The physical barrier is formed by tight connections between neighboring endothelial cells, with no capillary fenestration and deficient pinocytotic activity. The metabolic barrier is formed by degradative enzymes, specialized transport receptors, and endothelial cell efflux pumps [14].

Glioblastoma multiforme is a type of cancer that begins with cell growth in the brain or spinal cord. It proliferates and can invade healthy tissue. The most characteristic symptoms of glioblastoma are severe headaches, nausea and vomiting, blurred or double vision, and seizures. Currently, there is no effective treatment for glioblastoma multiforme, and the therapies used can only slow down the progression and relieve the symptoms of the cancer [15]. There are currently several known methods of treating glioblastoma, but usually, several techniques are used simultaneously to enhance the therapeutic effects. The most important methods of treating glioblastoma are listed in Table 1 [16].

Table 1. Treatment options for glioblastoma multiforme [16].

Type of Treatment	Method Description
Surgery	Glioma often grows into healthy tissue, so removing all cancer cells can be difficult. Many patients who have had the tumor removed also use other methods of treatment.
Radiotherapy	During radiotherapy, a device directs radiation to specific points in the brain. Radiotherapy is usually recommended after surgery, and chemotherapy is often used in addition.
Chemotherapy	Chemotherapy is often used after surgery and during and after radiotherapy. Intravenous chemotherapy drugs are most often used to treat recurrent GBM.
Alternating Electric Field Treatment (TTF)	TTF uses an alternating electric field to disrupt the growth of cancer cells. The technique involves applying sticky pads to the scalp. The pads are connected to a portable device that generates an electric field. TTF is used in conjunction with chemotherapy.
Targeted therapy	Targeted therapy uses appropriate drugs that act on a specific diseased site. By using targeted therapies, it has become possible to inhibit cancer development.

Central nervous system tumors continue to pose a significant challenge for both clinical oncology and research. According to statistics, mortality among patients with CNS

tumors is one of the highest among all known tumors [17]. Currently, combined therapies of surgery with Temozolomide (a drug used in cancer chemotherapy, a derivative of dacarbazine) and radiotherapy are used worldwide. In order to increase positive treatment outcomes, alternative treatment options are being studied, such as therapies based on antibody and drug conjugates and immunotherapies, as well as treatment options based on nanotechnologies [18].

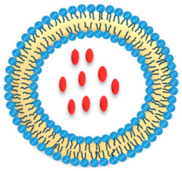
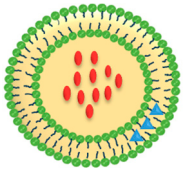
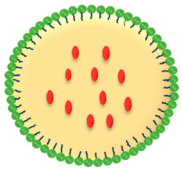
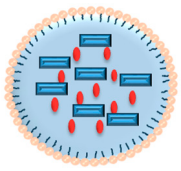
3. Nanotechnology and Drug Delivery in GBM Treatment

To enhance therapeutic outcomes in glioblastoma multiforme (GBM), innovative strategies have been developed to optimize drug delivery across the blood–brain barrier (BBB) while minimizing adverse effects. Nanotechnology has been instrumental in these advancements, enabling the creation of nanomaterials as drug carriers with key advantages such as nanoscale size, high drug-loading capacity, stability, and biocompatibility. Among these, lipid-based and inorganic nanoparticles have emerged as promising tools for crossing the BBB, paving the way for targeted and efficient GBM treatment. These nanoparticles facilitate passive and active drug transport to brain tumors, including glioblastoma multiforme [19]. Passive drug delivery leverages the enhanced penetration and retention (EPR) effect, which involves the movement of molecules of specific sizes across the BBB in tumor regions [20]. However, active transport systems are essential for effective drug delivery in areas where the BBB remains intact. This approach involves designing nanoparticles with surface ligands that target glial tissue or BBB-specific receptors, enabling receptor-mediated or adsorptive endocytosis [19]. The zeta potential of nanoparticles plays a critical role in their interaction with the BBB and distribution within the brain. A moderately positive charge enhances electrostatic interactions with negatively charged endothelial cells, facilitating BBB penetration. However, excessive positive charges can increase aggregation risk and immune activation. On the other hand, neutral or slightly anionic nanoparticles minimize non-specific interactions, extend circulation time, and improve their ability to cross the BBB effectively.

3.1. Lipid-Based Drug Carriers

Lipid-based formulations are widely favored for their exceptional properties and versatile drug delivery capabilities. Their unique structures address the challenges of biodistribution and bioavailability often associated with conventional drug delivery methods. These formulations facilitate targeted drug delivery to specific cells, enhancing drug stability and prolonging therapeutic effects. Lipid-based nanoparticles can be employed for various administration routes, including topical, oral, intravenous, and intrapulmonary delivery. Among the many lipid-based carriers explored for the treatment of glioblastoma multiforme (GBM), particular attention has been given to liposomes, niosomes, and lipid matrix nanoparticles such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) (Table 2) [21]. While the lipid nanoparticles in Table 2 are described within a broad size range (10/50–1000 nm), this does not imply that all particles within this spectrum are equally effective for GBM therapy. Nanoparticles between 50 and 200 nm are optimal for crossing the BBB and achieving effective drug delivery. Larger particles (>200 nm) may face challenges with biodistribution and clearance, whereas particles smaller than 50 nm may have reduced drug-loading capacity and stability.

Table 2. Comparison of lipid-based carriers.

Characteristic	Liposomes	Niosomes	SLN	NLC
Structure				
Composition	Phospholipids and cholesterol	Phospholipids, cholesterol, and non-ionic surfactants	Solid lipids, emulsifying agents	Solid lipids, liquid lipids (oils), emulsifying agents
Size	10–1000 nm	10–1000 nm	50–1000 nm	40–1000 nm
Routes of administration	Oral, parenteral, topical, brain pulmonary, transdermal, ophthalmic, nasal	Oral, parenteral, topical, pulmonary, transdermal, brain	Oral, parenteral, topical, transdermal, brain	Oral, transdermal, brain
References	[22]	[23]	[24]	[25]

Liposomes are small, spherical lipid vesicles that are capable of encapsulating hydrophilic and lipophilic drugs. Liposomes offer many advantages as drug carriers because they are biodegradable, non-toxic, and can encapsulate water-soluble and lipophilic substances [22]. However, traditional liposomes have limited ability to cross the BBB. Niosomes have been developed to address these limitations. The most significant difference between liposomes and niosomes is their robustness in the physiological environment. Niosomes are more robust and can be used in a continuous drug delivery system [23]. Compared to liposomes, lipid nanoparticles provide a larger surface area and have the potential to increase solubility, improve bioavailability, improve controlled release, and allow for more precise targeting of the encapsulated material. Solid lipid nanoparticles are colloidal carriers synthesized as an alternative to systems based on liposomes, emulsions, and polymeric micro- and nanoparticles [24]. On the other hand, nanostructured lipid carriers constitute the second generation of solid lipid nanoparticles. They were designed to eliminate the limitations of SLNs related to the necessity of using only solid lipids for their preparation [25].

When selecting the appropriate carrier, the size of the nanoparticles is of great importance. According to the literature, an extensive range of lipid vesicle sizes is reported, even from 50 to 1000 nm, but the most desirable sizes of lipid-based nanoparticles are 100–250 nm. Lakkadawala et al. [26] proposed the synthesis of two liposomes containing cell-penetrating peptide (TAT or QLPVM peptides) and transferrin (Tf) for the delivery of doxorubicin and erlotinib for the treatment of GBM. Both liposomes were prepared using the thin-film hydration method and had an average size of 174.90 $\pm$ 4.45 nm. Anilkumar et al. [27] developed a formulation combining photothermal (PTT) and photodynamic (PDT) therapies in functionalized liposomes with hyaluronic acid for the treatment of GBM. After sonication and extrusion, magnetic liposomes with a particle size of 221.9 $\pm$ 16.9 nm were obtained.

The chemical composition of lipids significantly influences the in vitro and in vivo efficacy, pharmacokinetics, nanoparticle stability, and cellular uptake (Table 3). Phospholipids,

such as HSPC, provide structural integrity and biocompatibility, enhancing nanoparticle stability. Cholesterol improves membrane rigidity, which can prolong circulation time in vivo. PEGylated lipids, such as DSPE-PEG2000, increase hydrophilicity and reduce opsonization, enhancing pharmacokinetics. For instance, incorporating PEGylated lipids in liposomes improves cellular uptake by reducing aggregation and promoting receptor-mediated endocytosis in glioblastoma cells. Furthermore, the ratio of lipids in the formulation can modulate zeta potential, affecting nanoparticle interactions with cellular membranes [28].

Table 3. Influence of lipid chemistry on in vitro and in vivo efficacy, pharmacokinetics, nanoparticle stability, and cellular uptake.

Lipid Type	Key Properties	Effect on Stability	Effect on Cellular Uptake	Impact on Pharmacokinetics	Ref.
Phospholipids (e.g., HSPC)	Structural integrity, biocompatibility	Enhances stability of lipid bilayers	Moderate uptake via endocytosis	Stable circulation with a moderate half-life	[29]
Cholesterol	Membrane rigidity	Improves bilayer integrity	Reduces premature release	Prolongs systemic circulation	[30]
PEGylated lipids (e.g., DSPE-PEG2000)	Hydrophilicity, stealth properties	Prevents aggregation	Facilitates receptor-mediated uptake	Reduces clearance, increases bioavailability	[31]

Zeta potential, which represents the charge strength on the particle surface, is used to assess the quality of the obtained lipid carriers, and a high absolute value (usually above 30 mV) is usually required to stabilize the nanocrystal system, where electrostatic repulsion is the only stable mechanism [32].

3.1.1. Advantages and Disadvantages of Lipid-Based Drug Carriers

All lipid carriers have unique features that make them valuable in treating glioblastoma multiforme, but they have certain limitations (Table 4). Ongoing research to improve the properties of lipid carriers focuses on improving their stability, efficiency, and shelf life through novel synthesis mechanisms and surface modifications.

Table 4. Advantages and disadvantages of lipid-based drug carriers for the treatment of GBM.

LNP Type	Advantages	Disadvantages	Ref.
Liposomes	• Biocompatibility and biodegradability, • Ability to encapsulate hydrophilic and hydrophobic drugs, • Surface modification (e.g., PEGylation) improves BBB crossing, • High encapsulation capacity for hydrophilic and lipophilic substances; serum stability confirmed in U87 cell lines.	• Limited BBB penetration without active targeting, • Susceptible to oxidation and low stability, • Short systemic circulation time.	[33]

Table 4. *Cont.*

LNP Type	Advantages	Disadvantages	Ref.
Niosomes	• Improved stability compared to liposomes, • Cost-effective synthesis, • Can encapsulate a variety of drugs, • Controlled release, • Targeted distribution of niosomes, • High in vitro activity.	• Moderate BBB penetration, • Tendency for aggregation and leakage.	[34]
Solid Lipid Nanoparticles (SLNs)	• Stable and scalable production, • High encapsulation efficiency for hydrophobic drugs, • Prolonged systemic circulation with active targeting, • Enhanced BBB penetration and tumor mass reduction in GL261 mouse models.	• Low drug payload for hydrophilic drugs, • Challenges with BBB penetration for larger particles (>200 nm), • Concerns about cytotoxicity due to the nature and concentration of matrix lipids, • Limited drug-loading capacity, • Difficulty in tailoring drug release profile, • Possible aggregation or fusion of particles during storage.	[35,36]
Nanostructured Lipid Carriers (NLCs)	• Enhanced stability and drug release profile, • Reduced water content improves BBB transport, • Suitable for dual-drug delivery and functionalization, • NLCs combine solid and liquid lipids, enabling the co-encapsulation of hydrophilic and hydrophobic drugs. Their surface can be modified with targeting ligands for enhanced delivery to specific sites.	• High production costs, • Risk of aggregation during long-term storage.	[35]

Liposomes are characterized by biocompatibility, the ability to encapsulate various compounds, and the potential for surface modification, which make them versatile carriers. However, limitations such as poor flexibility, susceptibility to oxidation, and relatively short circulation time in the bloodstream may hinder their effectiveness in long-term applications [37]. On the other hand, niosomes show better delivery capabilities to the body than liposomes, which allow for better penetration through the BBB. Niosomes also show high biocompatibility and more excellent stability compared to liposomes. However, niosomes face several significant challenges, such as aggregation, variable drug distribution, and low flexibility, which may limit their application [38]. Lipid nanoparticles offer much better benefits in treating glioblastoma multiforme due to significantly reduced side effects. Solid lipid nanoparticles can be easily scaled up from the laboratory to the industrial scale. They are characterized by high thermal stability and have very low toxicity. NLCs, on the other hand, contain much less water in their structure than SLNs and vesicular carriers. They are biocompatible and biodegradable, as well as stable [39,40].

The effectiveness of lipid-based nanoparticles (LNPs) for brain drug delivery is significantly influenced by their physicochemical properties, including particle size and surface

charge. Smaller nanoparticles (50–200 nm) are more efficient at crossing the BBB due to their ability to navigate tight endothelial junctions. Larger particles (>200 nm) are often excluded from entering the brain or are rapidly cleared by the mononuclear phagocyte system. Surface charge also plays a pivotal role: neutral or slightly positive particles (zeta potential: 0 to +15 mV) exhibit better BBB penetration due to reduced opsonization and favorable electrostatic interactions with the negatively charged endothelial cells. However, highly positive charges (>30 mV) may cause aggregation and toxicity. LNPs such as SLNs and NLCs demonstrate high encapsulation efficiency for hydrophobic drugs, making them particularly suitable for anti-GBM agents like Temozolomide and paclitaxel. NLCs, with their mixed solid–liquid lipid matrix, improve drug stability and release profiles compared to SLNs. However, the aqueous dispersion phase of SLNs can reduce long-term stability, leading to aggregation and reduced efficacy [41]. Nanostructured lipid carriers (NLCs) provide a dual-drug delivery advantage by encapsulating hydrophilic drugs within the aqueous phase and hydrophobic drugs within the lipid matrix. The mixed lipid composition (solid and liquid lipids) enhances drug-loading capacity and stability. Additionally, NLCs are highly adaptable for functionalization, allowing for the integration of ligands (e.g., peptides or antibodies) that enable targeted delivery and improved pharmacokinetics. The type and content of lipids are important parameters for obtaining lipid carriers, effective loading, and controlled drug release in the treatment of glioblastoma multiforme. Studies conducted by Amini et al. [42] suggest that appropriate lipids are of great importance in the design of lipid carriers, especially in terms of their size. They obtained hybrid polymer–lipid NPs (PLNs) made of myristic acid, allowing them to obtain much smaller carriers. This procedure allows for deeper penetration of tumor tissue and increased cellular uptake. In addition, Zwain et al. [43] used two polyunsaturated fatty acids, γ-linolenic acid (GLA) and α-linolenic acid (ALA), functionalized to obtain NLCs, which significantly improved the penetration through the BBB and selective uptake by GBM cells.

Another important factor in the design of lipid carriers is surface chemistry, a key physicochemical property that significantly affects the behavior of LNPs in the physiological environment. Electrostatic interactions and the polar surface of nanocarriers have been confirmed to correlate with BBB permeability [44]. The positive charge may contribute to BBB penetration via adsorption-mediated transcytosis. This property may be more significant for gene drugs, as different lipids may contribute differently to nucleic acid encapsulation and delivery efficiency [45].

Functionalization with ligands such as transferrin, lactoferrin, and peptides targeting integrins (e.g., RGD peptide) enhances the specificity of LNPs to glioblastoma cells. For example, NLCs functionalized with cyclic RGD peptides have shown improved targeting efficiency and tumor penetration in GBM mouse models. Additionally, surface modification with polyethylene glycol (PEG) enhances systemic circulation and minimizes immune clearance. Compared to polymeric nanoparticles and inorganic systems, LNPs provide superior biocompatibility, safety, and BBB-crossing potential. Polymeric nanoparticles, while versatile, often face challenges with biodegradability and immune clearance. Inorganic nanoparticles, such as gold or mesoporous silica, excel in imaging and theranostic applications but may exhibit cytotoxicity at higher concentrations. LNPs combine biocompatibility with flexibility for functionalization, making them ideal for targeted and sustained drug delivery in GBM therapy [46].

3.1.2. Lipid Carriers in the Treatment of Glioblastoma Multiforme

Research on glioblastoma multiforme (GBM) has increasingly focused on lipid-based carriers due to their potential to enhance drug delivery across the blood–brain barrier (BBB) and improve therapeutic outcomes. Lipid nanoparticles (LNPs), such as liposomes,

niosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), offer distinct advantages, including efficient drug delivery, enhanced efficacy, and reduced systemic toxicity. Spherical or near-spherical nanoparticles are favored for drug delivery due to their enhanced cellular uptake and stability. The spherical shape minimizes hydrodynamic drag and ensures uniform contact with the cell membrane, facilitating receptor-mediated endocytosis or other uptake pathways. This mechanism is particularly effective in glioblastoma cells exhibiting high endocytic activity. Additionally, the lower surface energy of spherical nanoparticles compared to elongated or irregular shapes reduces the aggregation risk, thereby enhancing colloidal stability in biological environments.

The effectiveness of lipid-based carriers in GBM therapy is closely linked to their physicochemical properties. Particle size plays a crucial role, with optimal sizes between 50 and 200 nm facilitating BBB penetration and tumor retention through the enhanced permeability and retention (EPR) effect. For instance, in preclinical models, RGD-functionalized liposomes (~150 nm) have demonstrated superior BBB penetration and glioma cell targeting. Morphology is another important factor in lipid nanoparticle (LNP) design. Lactoferrin-functionalized spherical LNPs encapsulating Temozolomide showed improved drug retention and antitumor activity. The surface charge also impacts performance, with a slightly positive zeta potential (0 to +15 mV) promoting efficient interaction with negatively charged cell membranes while maintaining stability in circulation. For example, cationic LNPs delivering siRNA achieved a twofold increase in cellular uptake compared to their neutral counterparts [41]. Lipid carriers are often functionalized with targeting moieties to enhance specificity and efficacy. Ligand functionalization, such as conjugation with transferrin, lactoferrin, or cyclic RGD peptides, enables receptor-mediated transcytosis across the BBB. Angiopep-2-modified liposomes, for instance, demonstrated a threefold increase in glioma cell uptake compared to non-targeted liposomes [47]. Additionally, pH-sensitive systems, including nanostructured lipid carriers (NLCs) functionalized with folic acid or cyclic peptides, exploit the acidic tumor microenvironment for targeted drug release, significantly enhancing therapeutic efficacy [48].

LNP-based systems have demonstrated substantial preclinical success in enhancing glioma therapy. Their physicochemical properties and active targeting strategies enable efficient drug delivery and improved therapeutic outcomes. Several formulations, such as RGD-functionalized liposomes and siRNA-loaded SLNs, have progressed to clinical trials, highlighting their translational potential. However, challenges such as large-scale production, regulatory approval, and overcoming the heterogeneity of glioblastoma remain. Future research should focus on integrating personalized medicine approaches and optimizing these systems for clinical applicability.

Zhang et al. [49] developed cell-permeable NF-κB inhibitor (CB5005) liposomes loaded with doxorubicin (DOX) for targeted glioblastoma therapy in U87 glioma cells and mouse xenograft models. The obtained liposome complex gave a particle size of 111.7 ± 0.23 nm, a PDI of 0.150 ± 0.034, and a zeta potential of -4.94 ± 0.99 mV. Mechanistically, the CB5005 peptide inhibited NF-κB, overexpressed in U87 cells, facilitating targeted delivery. In vitro studies confirmed nuclear localization of DOX and CB5005 liposomes in U87 cells, demonstrating enhanced uptake. In vivo biodistribution studies using DiR-loaded (1,1′-dioctadecyl- 3,3,3′,3′-tetramethyl indotricarbocyanine iodide) CB5005 liposomes showed significantly enhanced tumor targeting in mice xenografts compared to non-peptide liposomes ($p < 0.05$). In intracranial glioblastoma-bearing mice, complex liposomes prolonged survival time (33.5 days) compared to DOX liposomes (LS/DOX) (28.5 days), free DOX (27.5 days), and saline (25 days; $p < 0.001$). These findings suggest that the liposome's size, negative charge, and peptide functionalization synergistically contributed to improved tumor targeting and anti-GBM efficacy. Similarly, Zhu et al. [50] reported a liposomal

formulation containing ginsenoside Rg3 (Rg3-LP) and paclitaxel for C6 glioma cells. Compared with cholesterol liposomes (C-LP), Rg3-LPs significantly improved cellular uptake and penetration into glioma in vitro and significantly increased the active targeting of glioma and intratumoral diffusion capacity in vivo. Paclitaxel-loaded Rg3-LPs showed more antiproliferative effects on C6 glioma cells than paclitaxel-loaded C-LPs. The obtained complex significantly prolonged the median survival time of mice/rats with intracranial C6. This was achieved by activating the immune microenvironment in glioma, facilitating T cell immune responses with the expansion of the CD8+ T cell population. The macrophage M1/M2 ratio was increased, while the number of regulatory and suppressor T cells was decreased. The obtained results showed that ginsenoside Rg3 is a good alternative to cholesterol in liposomes for drug delivery and has synergistic effects with loaded anticancer drugs. Hu et al. [51] further advanced liposomal research by formulating liposomes for intranasal delivery of small interfering RNA (siRNA) against c-Myc coupled with a penetrating-derived peptide, 89WP. This approach, tested in an orthotopic mouse model of glioma, successfully prolonged survival through apoptosis induction. Zheng et al. [52] also used liposomes to co-deliver honokiol and disulfiram/copper complex. The antitumor activity of honokiol is attributed to its inhibition of the phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway, a key regulator of GBM cell growth. In the described study, peptide-defunctionalized liposomes targeted $\alpha 7$ nicotinic acetylcholine receptor (nAChR) DCDX in glioma cells. A brain-targeted liposomal delivery system of encoded honokiol and disulfiram/copper (CDX-LIPO) was developed for combination therapy by regulating the mTOR (mammalian target of rapamycin) pathway to remodel tumor metabolism and the TIME (tumor immune microenvironment). Honokiol may act synergistically with disulfiram/copper in the treatment of GBM. CDX-LIPO has been shown to trigger autophagy of tumor cells and induce immunogenic cell death. In addition, the CDX–LIPO complex promotes M1 macrophage polarization and facilitates mTOR-mediated glucose metabolism reprogramming in glioma. The studies were conducted on two cell lines in orthotopic glioma mice, U87 and C6. The C6 glioma, a commonly used animal model of brain tumors, and its immunological properties were similar to human mesenchymal GBM. The median survival time of the orthotopic C6 mice in the CDX–LIPO group was 27 days, which was significantly longer than that of mice treated with PBS (9 days, $p < 0.0001$), free drug injections (17 days, $p < 0.0001$), and free drug combination (21 days, $p < 0.01$). This study developed a potential combination therapy strategy by regulating glioma-targeted drugs' timing and delivery system.

Research on niosomes for GBM is limited but promising. De et al. [53] generated niosomes loaded with Temozolomide (TMZ) and modified with chlorotoxin (CTX), a peptide derived from scorpion venom that targets glioma cells. Active targeting using nanosized particles facilitated a 3.04-fold increase in drug accumulation in the brain. These niosomes increased the permeability of TMZ and could cross the BBB due to their small size and lipid composition. Temozolomide-loaded niosomes were prepared using a conventional thin-film hydration method. Chlorotoxin-coated niosomes were prepared with a size of 220 $\pm$ 1.45 nm, with an entrapment efficiency of 79.09 $\pm$ 1.56%. Quantitative tissue distribution studies indicate increased drug penetration into the brain due to surface modification with less deposition in highly perfused organs.

Solid lipid nanoparticles (SLNs) have also shown efficacy in the treatment of GBM. Ak et al. [36] prepared SLNs formed from cetyl palmitate with monocarboxylate transporter-1 (MCT-1)-targeting molecules: β-hydroxybutyric acid and anticancer agents: carmustine (BCNU) and Temozolomide (TMZ) to enhance antiproliferation against GBM. SLNs loaded with BCNU and TMZ had a zeta potential of -25 mV $\pm$ 4 and a hydrodynamic size of 227 nm $\pm$ 46. The obtained results showed a rapid release of the drug at the beginning,

followed by a gradual and continuous release. SLNs loaded with BCNU and TMZ showed a significant increase in antitumor activity compared to free drugs and induced apoptosis in U87MG cells. This study demonstrated that BCNU- and TMZ-loaded SLNs could act as a proper antitumor system for targeted therapy of GBM.

Kadari et al. [54] incorporated docetaxel into SLNs with surface-modified angiopep-2. The peptide-modified nanoparticles (A-SLN) showed increased cytotoxicity, cellular internalization, and marked apoptosis compared to unconjugated nanoparticles against human U87MG glioma cells and mouse GL261 glioma cells. The complex's significant dual-targeting effect ($p < 0.0001$) was confirmed in vivo by real-time fluorescence imaging studies in a glioma-induced C57BL/6 mouse model. Pharmacokinetic and tissue distribution studies showed selective targeting with a higher accumulation of A-SLN in the brain compared to Taxtotere, a commercially available formulation of docetaxel. After treatment with A-SLN, the median survival time of the animals was significantly increased from 24 days to 39 days. In conclusion, this study demonstrated that solid lipid nanoparticles containing angiopep-2 could be an excellent option as a targeted drug delivery system for GBM therapy.

Recently, Wang et al. [55] investigated a novel oral prodrug, catalase 3 (CAT3), which showed potent activity against Temozolomide-resistant GBM. In this study, a novel conjugate of oleic acid and CAT3 (OA-CAT3) was synthesized for the first time to enhance the lipid solubility of CAT3. OA-CAT3-loaded solid lipid nanoparticles (OA-CAT3-SLN) were constructed using ultrasonic to enhance the bioavailability and Cmax of PF403 in plasma. CAT3 was amorphous in the lipid core of OA-CAT3-SLN, and the in vitro release was controlled. Moreover, the zeta potential was -26.7 ± 0.46 mV, and the encapsulation efficiency was $80.65 \pm 6.79\%$. In vitro cell viability of OA-CAT3-SLN in C6 glioma cells decreased to $29.77\% \pm 2.13\%$ after 48 h and $10.75\% \pm 3.12\%$ after 72 h. Compared with CAT3 suspension, in vivo, pharmacokinetics in rats indicated that the plasma bioavailability and Cmax of PF403 delivered by OA-CAT3-SLN increased by 1.7- and 5.5-fold, respectively. The results indicate that OA-CAT3-SLN may be an effective treatment system for glioma.

Lipid nanoparticles are versatile carriers that can encapsulate immune-stimulating molecules, such as cytokines (e.g., interleukin-2) or RNA-based therapies, to activate immune pathways. For instance, liposomes functionalized with immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies, have shown promise in overcoming the immunosuppressive barriers characteristic of cold GBM. Solid lipid nanoparticles have also been developed to co-deliver chemotherapeutic agents and immunomodulators, synergistically reducing tumor burden and stimulating CTL infiltration [56].

Nanostructured lipid carriers (NLCs) have gained popularity in GBM therapy due to their advanced targeting capabilities. Song et al. [57] developed TMZ-loaded NLCs functionalized with arginine–glycine–aspartic acid peptide (RGD). They obtained RGD-conjugated polyethylene glycol-b-distearoylphosphatidylethanolamine (PEG-DSPE). An in vitro cytotoxicity study of TMZ/NLC was performed on malignant glioma U87MG cells. RGD-TMZ/NLC effectively inhibited U87MG cells in vitro. RGD-TMZ/NLC also showed the highest antitumor efficacy in vivo compared to all other formulations used for comparison. These RGD-modified vectors may provide a better drug delivery nanosystem and achieve therapeutic efficacy, and these studies may prove to be a promising new strategy for treating malignant glioma. Later studies by Zhang et al. [58] also showed that NLCs containing TMZ and vincristine, functionalized with RGD peptide and lactoferricin, reduced mouse tumor size. In this study, dual-ligand lipid carriers (L/RT/V-NLCs) of lactoferrin and arginine–glycine–aspartic acid (RGD), Temozolomide, and vincristine were introduced and loaded simultaneously. L/RT/V-NLCs showed sustained release behavior, high cellular uptake, high cytotoxicity and synergy effects, enhanced drug ac-

cumulation in tumor tissue, and tumor inhibition efficiency with low systemic toxicity. L/R-T/V-NLCs may be a promising drug delivery system for glioblastoma multiforme chemotherapy. Recently, Basso et al. [59] encapsulated atorvastatin and curcumin in NLCs modified with folic acid, cyclic pentapeptide cRGDfK, and pH-modified peptide H7K(R2)2 to target the acidic microenvironment of GBM cells. Using magnetic resonance imaging and spectroscopy, they assessed the nanocarriers' biodistribution, tolerability, and efficacy. Hierarchical modification of usNLCs promotes preferential brain-targeting behavior while sparing other organs. Furthermore, ultra-small nanostructured lipid carriers (usNLCs) were found to be well tolerated by mice and could impair tumor growth in an orthotopic xenograft model, whereas in mice treated with unencapsulated therapeutic compounds, tumor growth exceeded 181%. Finally, relevant biomarkers extracted using metabolic spectroscopy were identified as potential tumor signatures.

Nicoleti et al. [60] developed a kaempferol–NLC (K-NLC) complex that showed high drug loading efficiency, a stable release profile, and enhanced cytotoxicity in U87MG cells in vitro. The complex was characterized by an average size of 120 nm, a zeta potential of −21 mV, and a polydispersity index of about 0.099. K-NLC showed a high kaempferol encapsulation efficiency of about 93%, a drug loading of 3.58%, and a stable release profile of kaempferol, even up to 48 h. Encapsulation in NLC promoted cellular uptake by 75%, confirming the observed enhanced cytotoxicity in U-87MG cells. The results confirm the promising anticancer properties of kaempferol and the key role of NLC as a platform enabling efficient delivery of lipophilic drugs to cancer cells, improving their uptake and therapeutic efficacy in glioblastoma multiforme cells.

These studies illustrate the growing potential of lipid-based carriers in overcoming the challenges of BBB permeability, improving targeted drug delivery, and enhancing the efficacy of GBM treatments.

3.1.3. Emerging Role of LNP-Based Vaccines in GBM

Glioblastoma multiforme (GBM) is an immunologically "cold" tumor due to its limited cytotoxic T lymphocyte (CTL) infiltration and the presence of an immunosuppressive tumor microenvironment (TME). These factors significantly reduce the efficacy of conventional immunotherapies. Lipid nanoparticles (LNPs) have emerged as a versatile platform for vaccine delivery in GBM therapy (Table 5). By encapsulating mRNA, peptides, or tumor antigens alongside immune adjuvants, LNPs aim to overcome immune resistance and stimulate robust antitumor immune responses [61]. LNP-based vaccines function by delivering their cargo to antigen-presenting cells (APCs), such as dendritic cells. Once internalized, these APCs process and present tumor-associated antigens to cytotoxic T lymphocytes (CTLs), initiating a cascade of immune activation targeting glioblastoma cells. mRNA vaccines play a central role by encoding tumor antigens, such as *EGFRvIII* or *IDH1* mutations, to drive specific immune responses. Neoantigen vaccines, on the other hand, are personalized to target patient-specific tumor mutations, thereby enhancing immune specificity. To further boost their effectiveness, adjuvants are often co-delivered, including molecules like toll-like receptor (TLR) agonists, which enhance dendritic cell activation and CTL response. Lipid nanoparticles (LNPs) present several advantages over alternative delivery systems, including viral vectors and polymeric nanoparticles. They are highly safe and biocompatible, as they are non-immunogenic and suitable for repeated administration without triggering adverse immune responses. Their lipid composition enables efficient delivery, facilitating targeted transport to antigen-presenting cells (APCs) and overcoming biological barriers such as the blood–brain barrier (BBB). LNPs are also highly customizable, with ligands that can be functionalized to enhance specificity and improve targeting of glioblastoma cells. Furthermore, they provide exceptional stability,

protecting delicate mRNA and peptide-based cargo from enzymatic degradation. Finally, LNPs formulations are scalable and cost-effective, making them ideal for the production of personalized therapies on a larger clinical scale [62].

Table 5. Examples of LNP-based vaccines in preclinical and clinical studies.

Vaccine Type	Key Findings	Ref
mRNA-loaded LNPs	Efficacy in murine GBM models, encoding antigens like EGFRvIII, significantly prolonging survival.	[63]
Peptide vaccines	Combined with checkpoint inhibitors (e.g., anti-PD-1), these formulations reduce tumor size in preclinical models.	[64]
Neoantigen vaccines	Personalized LNP-based neoantigens elicit enhanced immunogenicity, improving immune responses in clinical trials.	[65]

Despite their potential, LNP-based vaccines face several challenges, including developing more efficient delivery systems for brain tumors and strategies to overcome the immunosuppressive tumor microenvironment (TME). Current research is exploring innovative approaches to address these issues. One promising direction involves the co-delivery of checkpoint inhibitors or cytokines to counteract immune suppression and enhance the overall therapeutic response. Another focus is the development of stimuli-responsive LNPs designed to release their payload specifically within the TME, improving precision and minimizing off-target effects. Ongoing efforts aim to optimize vaccine formulations to enhance stability, targeting accuracy, and bioavailability. These advancements position LNP-based vaccines as a transformative tool in glioblastoma therapy, potentially converting GBM from an immunologically cold tumor into a disease amenable to targeted and synergistic treatment strategies [49–51].

Despite their promise, LNP-based vaccines face challenges, including efficient delivery to brain tumors and overcoming the immunosuppressive TME. Future strategies aim to enhance vaccine efficacy by co-delivering checkpoint inhibitors or cytokines to reverse immune suppression and using stimuli-responsive LNPs to achieve localized release in the TME. Advancements are needed in formulation techniques to improve stability and targeting.

3.2. Inorganic Drug Carriers

Inorganic nanoparticles (INPs) represent a versatile class of nanocarriers with unique physicochemical properties that can be tailored to enhance drug delivery. These particles, including gold nanoparticles (AuNPs), mesoporous silica nanoparticles (MSNs), superparamagnetic iron oxide nanoparticles (SPIONs), and dendrimers, possess structural stability, high surface area, and ease of functionalization [66,67].

Additionally, carriers utilizing core-shell nanostructures have gained attention for their ability to deliver therapeutic agents effectively to GBM. These nanocarriers are designed to improve drug stability, targeting efficacy, and penetration into the brain's tumor microenvironment. Lipid–polymer hybrid nanoparticles (LPNs) combine the biocompatibility of lipids with the stability and tunability of polymeric cores, successfully encapsulating drugs like paclitaxel and doxorubicin to enhance therapeutic outcomes [68]. Magnetic nanoparticles (MNPs), incorporating iron oxide cores with biocompatible shells such as chitosan or polyethylene glycol (PEG), enable drug delivery under the influence of an

external magnetic field, improving BBB penetration and targeting specificity [69]. Polymeric nanoparticles, including core-shell systems like poly(lactic-co-glycolic acid) (PLGA) combined with PEG, have demonstrated improved stability and targeted delivery of drugs such as Temozolomide to GBM tissues [70].

The therapeutic efficacy of these systems has been demonstrated in preclinical studies, showing significant promise in enhancing the pharmacokinetics and biodistribution of GBM therapies.

AuNPs offer several advantages, including low toxicity, ease of synthesis, and potential for surface modification. Their unique surface plasmon resonance property enables the conversion of light energy into heat, which is particularly valuable in hyperthermic and photodynamic cancer therapies. Functionalization with polyethylene glycol (PEG) and biomolecules enhances their efficiency in targeted drug delivery [71].

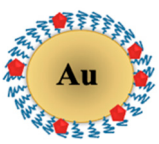
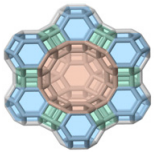
MSNs have been employed for decades in drug delivery due to their structural stability, high surface area, and modifiability with magnetic materials or organic groups for targeted therapy. Their high density of silanol groups provides ample binding sites for drug molecules, though concerns about drug leakage and cytotoxicity persist [72].

SPIONs are particularly advantageous for brain tumor imaging as MRI contrast agents. Their magnetic properties allow for precise targeting using external magnetic fields. Coating SPIONs with polymers improves biocompatibility and prevents particle aggregation [73].

Dendrimers, characterized by a unique branched structure, provide monodispersity and surface polyvalence, making them effective for drug encapsulation. Their architecture, which includes a central core, a branched interior, and a functionalized outer shell, allows for the attachment of multiple therapeutic molecules [74].

The distinct characteristics of these inorganic carriers, including their structure, size, shape, and routes of administration, are summarized in Table 6.

Table 6. Comparison of inorganic compound carriers.

Characteristic	Gold Nanoparticles	Mesoporous Silicas	Superparamagnetic Iron Oxide Nanoparticles	Dendrimers
Structure				
Composition	Gold particles in oil-in-water emulsion	Silica sources, e.g., TEOS, surfactants	Maghemite (γ-Fe_2O_3) and/or magnetite (Fe_3O_4) particles	Central core, branching units, terminal groups
Shape	Spheres, rods, stars, cubes, triangles	Porous honeycomb-like structure	Spherical, hexagonal, rods, cubes	Spherical due to highly branched structure
Size	5–400 nm	2–50 nm	10–100 nm	1–15 nm
Route of administration	Oral, parenteral, topical, pulmonary, transdermal, ophthalmic, brain	Intravenous, subcutaneous, intramuscular, ophthalmic, pulmonary, nasal, dermal, oral routes, brain	Oral, parenteral, topical, transdermal, brain	Intravenous, intraperitoneal, ocular, transdermal, oral, intranasal, pulmonary
References	[75]	[76]	[77]	[78]

TEOS—tetraethylorthosilicate.

This diversity of properties and innovative approaches, including core-shell nanostructures, highlights the potential of inorganic carriers to overcome challenges in GBM treatment, such as drug delivery across the BBB, tumor specificity, and reduction of systemic toxicity.

3.2.1. Advantages and Disadvantages of Inorganic Carriers

Each type of inorganic carrier has distinct advantages and limitations. For instance, AuNPs are easy to modify but may have high production costs, while MSNs offer high stability and surface area yet pose risks of cytotoxicity. SPIONs are effective for imaging and targeted delivery but may aggregate, and dendrimers provide high control over size and shape but suffer from low water solubility [79].

The most important advantages and disadvantages of carriers based on inorganic compounds are given in Table 7.

Table 7. Advantages and disadvantages of lipid colloidal systems for the treatment of glioblastoma multiforme.

Type of System	Advantages	Disadvantages	Ref.
Gold nanoparticles	Ease of synthesis and surface modification, minimal side effects	Toxic, complicated synthesis, high production costs, difficulties in introducing to the market	[80]
Mesoporous silicas	Stable structure, open pores and large surface area, controlled pore size, biocompatibility and biodegradability	The surface density of silanol groups, drug leakage, melanoma development, and hemolysis	[81]
Superparamagnetic iron oxide nanoparticles	Biocompatible, biodegradable, and low toxicity	Occurrence of side effects, tendency to aggregate	[82]
Dendrimers	Monodispersity with complete control over shape, size, and number of ligands	Low hydrosolubility and high nonspecific toxicity	[83]

To mitigate potential cytotoxicity and improve biocompatibility, several strategies have been employed. Coating inorganic nanoparticles with biopolymers such as chitosan or polyethylene glycol (PEG) enhances their biocompatibility while reducing immune recognition. Functionalization with ligands, including peptides and antibodies, enables targeted delivery to glioblastoma cells, improving therapeutic specificity and reducing off-target effects. These surface modifications also minimize aggregation and enhance colloidal stability in biological environments, making INPs more effective in clinical settings. These inorganic carriers hold substantial potential for GBM therapy. Ongoing research focuses on optimizing their stability, bioavailability, and delivery efficiency to enhance their clinical application in glioblastoma treatment.

3.2.2. Inorganic Drug Carriers in the Treatment of Glioblastoma Multiforme

Inorganic carriers have revolutionized biomedical research due to their unique properties. Inorganic nanocarriers, such as gold and iron oxide nanoparticles, can reprogram the tumor microenvironment through various mechanisms. Gold nanoparticles functionalized with immune-activating ligands have demonstrated the ability to enhance dendritic cell activation and antigen presentation, critical steps in recruiting CTLs to the tumor site. Furthermore, when loaded with adjuvants like cyclic dinucleotides, mesoporous silica nanoparticles have shown efficacy in stimulating the Stimulator of Interferon Genes

(STING) pathway, leading to robust innate immune activation and subsequent CTL recruitment in GBM models [84].

Currently, no gold nanoparticle-based drugs have been clinically approved, and the potential use of GNPs as drug carriers in the treatment of glioma is still being investigated [85]. In their study, Allena et al. [86] combined a cancer-specific antisense oligonucleotide antinucleolin aptamer AS1411 and polyethylene glycol (PEG) with AuNPs and then tested the antiproliferative effects on the GBM U87MG cell line. Kumthekar et al. [87] published the results of a Phase 0 clinical trial to treat recurrent glioblastoma multiforme in humans who underwent tumor resection with RNAi-based GNPs. Importantly, no toxicity was observed, and the pharmacokinetics of GNPs indicated accumulation in tissues and tumor-associated cells. In another study, Coluccia et al. [88] obtained gold nanoparticles conjugated with cisplatin to treat GBM. They conducted studies on glioma cell lines U251 and U87.

Recently, Bielecki et al. [89] developed MSNs loaded with cyclic diguanylate monophosphate (cdGMP), which is a stimulator of interferon gene agonist (STING), with reversal of GB-induced immunosuppression in the tumor microenvironment (TME). This study was conducted in female C57BL/6 albino mice. A study by Zhu et al. [90] showed that treating paclitaxel-loaded MSNs with angiopep-2 could prolong the survival in vitro and in vivo of rats implanted with C6 glioma cells.

Empty SPIONs can be used for intratumoral delivery of hydrophobic drugs. Zhu et al. [91] described SPIONs containing doxorubicin (DOX@SPION) and applied the obtained systems to U87 glioma cells.

Advances in research on new carriers have primarily focused on developing less cytotoxic and cell-specific targeting dendrimer designs. For example, Perez et al. [92] experimented with a larger dendrimer complex that carried siRNA to T98G and J774 glial cells. Dendrimers of this size are rarely used because more recent studies have shown that smaller dendrimers are more efficient at crossing the BBB. Yan et al. [93] developed cancer cell-specific dendrimers for drug delivery by developing a G5 PAMAM dendrimer coupled to cyclic peptides targeting tumor blood vessels and the BBB-permeable peptide angiopep-2. These studies were conducted on U87MG cells.

One of the future directions of dendrimer synthesis is the formation of hybrid dendrimers consisting of several different single dendrimers. Singh et al. [94] mixed PAMAM-(NH_2) dendrimers with PAMAM-(COOH) dendrimers and combined them with the chemotherapeutic drug Docetaxel (DTX) to form a complex. The solubility profile of the docetaxel amine–dendrimer complex (A-DTX), docetaxel–sodium carboxylate complexes (C-DTX), and hybrid docetaxel–amine–carboxylate complexes of AC-DTX dendrimers were studied. The AC-DTX complex showed the highest solubility among the four complexes. Experiments were performed on glioblastoma multiforme U87MG (human primary glioblastoma multiforme) and GL261 (mouse glioblastoma multiforme) cells.

Most studies focus on improving the stability and bioavailability of dendrimers, but another major obstacle to overcome in the treatment of glioma is achieving high specificity for cancer cells while minimizing cytotoxicity. Bae et al. [95] designed a poly(amidoamine) (PAMAM) dendrimer with surface modifications in phenylalanine, histidine, and arginine. The complexes formed delivered a cancer cell-specific gene, apoptin. These studies were conducted on human primary glioma lines (GBL-14) and human dermal fibroblasts in vitro.

4. Products Introduced to the Market Based on Lipid and Inorganic Carriers

Currently, many preclinical studies are using lipid-based and inorganic carriers for treating glioblastoma multiforme, but only a few have been commercialized. Table 8

summarizes the most essential lipid-based and inorganic nanoparticle-based products for treating GBM.

Table 8. Nanoparticle-based drug delivery systems that have entered clinical trials for the treatment of GBM.

Name	Carrier	Drug/Mechanism of Action	Coating	Administration Route	Ref.
Onyvide®	Liposome	Irinotecan +/− TMZ	PEG	Intravenous injection/convection-enhanced delivery	[96]
SGT-53	Liposome	Wildtype p53 sequence	Anti-TfR	Intravenous injection	[97]
Caelyx®	Liposome	Doxorubicin	PEG	Intravenous injection	[98]
2B3-101	Liposome	Doxorubicin + glutathione	PEG	Intravenous injection	[99]
NanoTherm®	SPION	Thermal ablation via alternating magnetic field	Aminosilane	Intratumor injection	[100]
NU-0129	Gold nanoparticles	Apoptosis inducer via Bcl2L12 targeting	Spherical nucleic acid	Intravenous injection	[87]

The examples in Table 6 demonstrate the diversity of nanoparticle-based drug delivery systems explored for glioblastoma multiforme (GBM) treatment. These systems include lipid-based carriers (e.g., liposomes) and inorganic carriers (e.g., superparamagnetic iron oxide nanoparticles (SPIONs), gold nanoparticles).

Onyvide® is a liposome-based carrier formulation that combines irinotecan with Temozolomide, utilizing PEGylated liposomes for targeted delivery. This formulation enhances drug solubility and stability while reducing systemic toxicity, making it a promising candidate for GBM therapy. Preliminary clinical trials have shown favorable pharmacokinetic profiles and tumor localization, though additional studies are needed to confirm its efficacy [96].

NanoTherm® is a SPION-based system designed for thermal ablation therapy. Administered intratumorally, the nanoparticles generate localized heat under an alternating magnetic field, selectively destroying cancer cells while minimizing damage to surrounding healthy tissue. This approach complements standard chemotherapy or radiotherapy, offering a promising adjunct treatment [100].

NU-0129, a gold nanoparticle-based therapy, uses functionalized gold nanoparticles with spherical nucleic acids to target apoptosis pathways in GBM cells. A Phase 0 clinical trial demonstrated effective tumor penetration without significant toxicity, highlighting its potential for clinical application [87].

These examples underscore the strides made in integrating nanotechnology with GBM treatment. However, overcoming the blood–brain barrier (BBB), ensuring biocompatibility, and mitigating long-term toxicity remain critical hurdles for widespread clinical adoption.

5. Summary

Nanotechnology-based drug delivery systems are gaining significant attention for their potential to advance cancer treatments. With ongoing advancements in biomedical technology, these systems are emerging as a promising therapeutic strategy, particularly

for glioblastoma multiforme (GBM)—a disease that remains incurable and shows limited response to conventional therapies. However, most nanoparticle (NP)-based approaches targeting GBM have not progressed beyond animal models, primarily due to insufficient evidence regarding drug safety, long-term toxicity, immunogenicity, and pharmacokinetic and pharmacodynamic profiles. Various types of nanoparticles have been developed and tested in vitro and in vivo using GBM models, demonstrating remarkable versatility owing to differences in size, shape, surface charge, and composition. These properties influence their ability to cross the blood–brain barrier (BBB), serum half-life, and capacity to encapsulate specific drugs. Among lipid-based carriers, NLCs stand out due to their ability to simultaneously encapsulate multiple types of drugs and their versatility in functionalization for targeted therapies.

Inorganic nanoparticles, such as gold nanoparticles (GNPs) and superparamagnetic iron oxide nanoparticles (SPIONs), offer significant potential in advancing glioblastoma therapy due to their unique properties and functionalization capabilities. However, safety evaluations remain critical to their clinical translation. Future research should prioritize systematic studies on biocompatibility, pharmacokinetics, and long-term effects to ensure these nanocarriers' safe and effective application in clinical settings.

In addition to serving as drug delivery vehicles, they act as radiosensitizers to enhance radiotherapy efficacy, assist in lesion characterization via MRI, and induce hyperthermia for therapeutic purposes, functioning as nanotheranostics. As research progresses and these technologies continue to show encouraging results, increased investment in nanoparticle production will be essential to transition from preclinical studies to clinical trials. This progress is vital for moving these innovative therapies from Phase I to Phase III clinical applications. Although glioblastoma multiforme remains a challenging disease, mainly due to its cold phenotype, the emergence of lipid-based and inorganic nanocarriers presents a promising solution. These technologies can improve immune cell infiltration, reprogram the tumor microenvironment, and enhance the delivery of therapeutic agents, potentially offering significant improvements in outcomes for patients with cold GBM.

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