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PII: S1226-086X(19)30336-3
DOI: https://doi.org/10.1016/j.jiec.2019.06.050
Reference: JIEC 4636

To appear in:

Received date: 4 May 2019
Revised date: 20 June 2019
Accepted date: 29 June 2019

Please cite this article as: Duwa R, Emami F, Lee S, Jeong J-Heon, Yook S, Polymeric and Lipid-based Drug Delivery Systems for Treatment of Glioblastoma Multiforme, *Journal of Industrial and Engineering Chemistry* (2019), https://doi.org/10.1016/j.jiec.2019.06.050

Polymeric and Lipid-based Drug Delivery Systems for Treatment of Glioblastoma Multiforme

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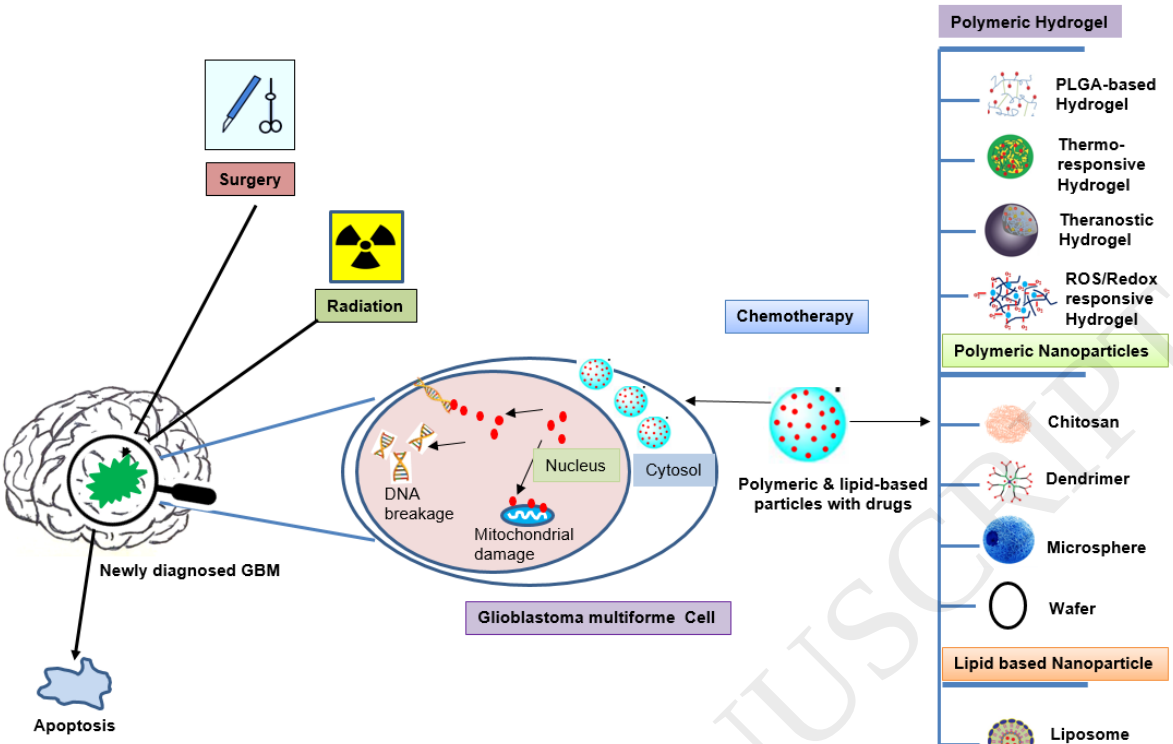
Graphical abstract



Application of lipid based and polymeric drug delivery systems for treatment of glioblastoma multiforme.

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ABSTRACT

Glioblastoma multiforme (GBM) is the most aggressive, malignant brain tumor found in adults, and has a short median survival time (MST). GBM is a heterogeneous group of brain tumors, is highly prone to develop resistance and likely to recur. In the context of GBM, the delivery of anti-cancer drugs is challenging because the blood brain barrier (BBB) restricts the passage of small molecules. Currently, nanomedicines based on liposomes, micelles, polymeric

nanoparticles, and microparticles have attracted much attention, because they can cross the BBB and deliver anti-cancer drugs specifically to brain tumors. In this context, hydrogel-based systems incorporating nanoparticles, implantable carmustine wafers, microspheres, and lipid-based nanoparticles now appear to offer more effective, safer treatment strategies than conventional chemotherapeutic regimens. This review describes different polymeric hydrogel, chitosan, dendrimers, wafers, microspheres, and lipid-based nanoparticles like liposomes and solid-lipid nanoparticles that offers prominent strategies for the treatment and diagnosis of GBM.

Abbreviations

AL= angiopep-2 modified liposome
BBB= blood brain barrier
BCNU= bis-chloroethyl nitrosourea
BMP= bone morphogenetic protein
CBP= carboplatin
CBTRUS=central brain tumor registry of the United States
CCK-8 = cell cytotoxicity kits – 8
CDDS= control drug delivery system
CED= convection enhanced delivery
Ch/β-GP = chitosan/β-glycerophosphate (Ch/β-GP)
CI= confidence interval
CNS= central nervous system

CPT/PLGA/TGP =CPT loaded PLGA microsphere with TGP

CPT= camptothecin

CTLA-4 =cytotoxic T-lymphocytes associated protein-4

Dch/β-GP = dialyzed chitosan solution gel

DDSs=drug delivery systems

DOX=doxorubicin

DTT = dithiothreitol

DTX-P80-PPI = DTX loaded PPI with P80

DTX-PPI = DTX loaded PPI

DTX =docetaxel

EA = ellagic acid

EPR= enhanced permeability and retention effect

FDA= food and drug administration

Gal-1= Galectin-1

GBM=glioblastoma multiforme

Gem C12-LNC =lauryl gemcitabine lipid nanocapsule

GSC=glial stem cells

GSH = glutathione

H= hazard ratio

HR = hypoxic responsive

HSPC liposome-TMZ = TMZ loaded hydrogenated soya phosphatidylcholine liposome

HSPC=hydrogenated soya phosphatidylcholine

LAG-3 =Lymphocytes activation gene-3

LGTT = liquid gel transition temperature

Liposome-DOX = DOX loaded liposome

Liposome-TMZ = TMZ loaded liposome

MEL=Melatonin

Microsphere-CBP =CBP loaded microsphere

Microsphere-DOX =DOX loaded microsphere

Microspheres-BCNU= BCNU loaded microsphere

MLTH= magnetic resonance imaging-monitored long-term therapeutic hydrogel

MRI=magnetic resonance imaging

MST= median survival time

NIPAAm= N-isopropylacrylamide

NL=normal saline

P(NIPAM-co-AAc) = poly (N-isopropylacrylamide-co-acrylic acid)

P= P-value

PAMAM= polyamidoamine

PCNA = proliferating cell nuclear antigen

PD-1 =programmed death-1

PD-L1= programmed death-ligand 1

PEG-PLA= poly (ethylene glycol)-poly (lactic acid)

PEG= poly (ethylene glycol)

PLA= poly (lactic acid)

PLG = poly(lactide-co-glycolide)

PLGA microsphere -CBP = CBP loaded PLGA microsphere

PLGA microspheres-BCNU = BCNU loaded PLGA microspheres

PLGA= poly (lactic-co-glycolic acid)

PMAA= poly (methacrylic acid)

PPI= poly (propyleneimine)

pSTAT3 =phospho- signal transducer activator of transcription 3

PTX= paclitaxel

RCTs= randomized controlled treatment

ROS= reactive oxygen species

siRNA= small interfering RNA

SLNs-DOX= DOX loaded solid-lipid nanoparticles

SLNs= solid-lipid nanoparticles

SPIO = superparamagnetic iron oxide

TCF-4 =transcription factor-4

TGP-DOX= DOX loaded TGP

TGP+liposome-DOX = TGP with liposome-DOX

TGP+microsphere-DOX = TGP with microsphere-DOX

TGP= thermos-reversible gelation polymer

TIM-3 =T-cell immunoglobulin mucin-3

TMZ= temozolomide

VCR/PLGA= VCR loaded PLGA

VCR=vincristine

WHO=world health organization

XRT= X-ray telescope radiotherapy

Keywords: Glioblastoma multiforme, Polymeric nanoparticles, Nanomedicine, Polymeric hydrogel, Lipid-based nanoparticles

Introduction

Glioblastoma multiforme

Glioblastoma multiforme (GBM) is a heterogeneous primary malignant brain tumor [1, 2]. GBM emerges from astrocytes and its cells rapidly reproduce due to the presence of a large network of blood vessels [3]. Uncontrolled cellular proliferation, resistance to radio and chemotherapy, growth of glial stem cells, invasion and infiltration of tumor cells, and apoptosis are characteristic of GBM [4]. GBM is also called the "octopus tumor" because it can extend tendrils to normal neighboring parenchymal cells [4, 5].

The World Health Organization (WHO) has classified astrocytoma into four grades (I, II, III and IV), and in grade IV, GBM has an incidence of 45-50%, although it may develop from low grade astrocytoma [6, 7]. The global incidence of GBM is 10 per 100,000 people [8]. According a report issued by the Central Brain Tumor Registry of the United States (CBTRUS, 2013), 12,760 new cases of GBM were predicted in 2018 [9]. In this report, relations between GBM incidence and age, gender were studied. Accordingly, due to expected increases in the size and mean age of the US population, the number of cases is expected to increase. Others have reported the incidence of GBM is highest in 75 to 84 year olds (at 15%) [8-10], and that it is greater for men than women [8, 11].

In the majority of cases, GBM is idiopathic, but some factors such as age, gender, family history, exposure to infections or strong electromagnetic fields, race, ethnicity, and a history of head injury or exposure to N-nitroso compounds are considered causes of GBM [12-14]. The clinical manifestations of GBM include edema, hemorrhage, and an altered mental status [15].

Current treatments of GBM

GBM is a highly aggressive neoplasm with an MST of 3 months if left untreated [16], though this can be improved by surgery plus radiotherapy or surgery plus chemotherapy or surgery plus radiotherapy and chemotherapy [17-19]. In 2004, the European Organization for Research and Treatment of Cancer stated GBM patients treated with radiotherapy plus temozolomide (TMZ) had an MST of 13-14 months, and radiotherapy alone had an MST of 11-13 months [8, 19]. GBM is aggressive, tends to recur, and is difficult to treat completely [20]. For newly diagnosed or recurrent GBM, the gold standard treatment is surgical resection followed by radiotherapy or chemotherapy with concomitant adjuvant TMZ chemotherapy [5] [**Fig. 1**]. Systemic treatments based on cytotoxic chemotherapy (e.g., TMZ [21], everolimus [22], or lomustine [23]) or hormonal therapy (e.g., using progesterone inhibitors, aromatase inhibitors, or hormone

release growth hormone inhibitors [24]) are also commonly used to treat GBM [25].

In addition, molecular targeted therapies such as bevacizumab (targets vascular endothelial growth factor), cetuximab or nimotuzumab (target epidermal growth factor receptor), and CSF-1R inhibitor PLX3397 [26] or BLZ945 [27] (target colony stimulating factor-1 receptor) are emerging treatments for GBM [28]. Moreover, immunotherapies such as adoptive T-cell [29], tumor vaccine [30], and immune checkpoint [31] therapies have become a focus of current research. Programmed death-1 (PD-1), T-cell immunoglobulin mucin-3 (TIM-3), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3), which inhibit T-cell activation, are negative regulators of the immune system in GBM [32], and these ligands are also viewed as possible targets for GBM therapy [33]. In particular, programmed death ligand 1 (PD-L1) is overexpressed in GBM and monoclonal antibodies that inhibit PD-L1 or PD-1 receptor or its interactions with ligands offer other means of addressing its treatment [34]. Although, no Food and Drug Administration (FDA)-approved immunotherapy is available for GBM, the phase III trial of Ipilimumab and Nivolumab in GBM patients at different stages of treatment was initiated in 2014 (NCT02017717) [33].

As regards anti-cancer drugs, FDA approved TMZ as a first line drug for the treatment of GBM in 1999. TMZ is an alkylating anti-cancer drug that has been shown to increase patient survival [35, 36]. TMZ is converted intracellularly into MTIC (5-(3-methyltriazen-1-yl) imidazole-4-carboxamide) and methylates DNA at the N^7 and O^6 positions of guanine residues, which disrupts the cell repair mechanism and eventually causes cell death by breaking down double-stranded DNA [19, 37] [**Fig. 2**]. Standard TMZ based treatments include the combined use of TMZ, surgery, and radiation, but treatment efficacies are limited.

Development of different injectable hydrogel system have been developed for the treatment of diseases that are difficult to control like GBM. Such injectable hydrogel system have potent capacity to encapsulate anti-cancer drugs and deliver successfully and efficiently at the site of action. The implantation of injectable hybrid hydrogel composed of protein-polymer conjugate to generate an effective platform for encapsulation and delivery of a DNA vaccine [38]. Similarly, pH- and temperature-responsive biodegradable copolymers were concomitant with human serum albumin to developed hybrid injectable hydrogels, that upgrade the stability and half-life of the biological drug [39]. Furthermore, the in situ forming injectable hydrogel [40] and stimuli- sensitive injectable polymeric hydrogels [41] can also be the promising formulation for

the delivery of therapeutic agents. These types of injectable formulation may control the anticancer drug release and subsequently eradicate the GBM**.** Anatomical locations, high tumor heterogeneity leading to uncontrolled cellular proliferation, resistance to radiotherapy and chemotherapy, glial stem cell growth, invasion and infiltration of tumor cells, and apoptosis are the main reasons why GBM treatments are limited. On the other hand, resection has the shortcomings of causing collateral damage to neurological tissue, adversely affecting cognitive function of patients, and the different physical barrier in central nervous system (CNS) can delay in delivering of the anti-cancer agent to the tumor site [5]. Accordingly, different delivery strategies using drug carriers such as gold nanoparticles [42, 43], microspheres, or dendrimers that deliver anti-cancer drugs to tumor site without affecting neighboring healthy cells are being actively investigated [44, 45].

GBM recurrence

Cancer regrowth at original or different sites is problematic [46]. The main problem for this is that tumors can recur at original sites or migrate/metastasize to other parts of the body [47]. Primary treatment destroys most GBM cells, but some remain viable and continue to grow. GBM tumor cells have “finger-like tentacles”, which enable the disease to spread throughout the brain [48-50].

Furthermore, under the favorable microenvironment in the presence of neighboring cells, the vascular lymphatic network, hypoxic condition, and growth factor infiltered glial stem cells (GSCs) may grow into new tumor cells [49, 51] [**Fig. 3**].

Hypoxia is a stimulus found in the brain tumors. Hypoxia-responsive (HR) nanoparticles may show better anti-tumor effects in tumor treatment [52-54]. However, the treatment of GBM using HR-nanoparticles has not well-developed.

GBM recurrence is due to the ability of cancer cells to resist chemotherapy and radiotherapy [55, 56]. In one study, conventional therapies were found to cause GSCs to become temporarily latent [57]. The MST of patients that experience GBM recurrence is 8-9 months [55], which is extended by non-invasive stereotactic radiosurgery to 6.5-30 months. On the other hand, the MST of patients that undergo second surgery or are treated with TMZ for recurrence are 3.5-9 and 4.5 months, respectively [8, 58]. These reports shows TMZ is a moderately effective treatment for recurrent GBM [58-60], as re-surgery and re-irradiation may adversely affect quality of life.

Drug delivery systems (DDSs) and GBM treatment

TMZ, lomustine, carmustine, and bevacizumab are FDA approved for the treatment of GBM [61], but MST have not meaningfully improved due to

recurrence [62]. These poor outcomes could be improved by the delivery of effective anti-cancer drugs through the BBB [63, 64]. Several developmental approaches have been devised based on chemical modifications of existing drugs, metallic or non-metallic nanoparticles [44], polymeric carriers [2, 65, 66], and lipid-based nanoparticles [28, 67-69]. Nanoparticle DDSs have been demonstrated to have potential for the treatment of GBM [70], and recently, modified nanoparticles systems were designed that exhibited self-assembly, *in vivo* stability, tumor specificity, effective drug encapsulation, prolonged drug release, and efficient drug delivery to target sites [71]. Polymeric carriers and lipid-based nanoparticles are widely used to treat GBM. In this review, we discuss the advantages and limitations of GBM treatments based on drug delivery by smart polymeric hydrogels, polymeric particles, liposomes, or solid-lipid nanoparticles (SLNs).

Polymeric DDSs used to treat GBM

Polymers play essential roles in modern drug delivery technology by providing a means to design the sustained release of hydrophilic and hydrophobic drugs [72]. Polymeric DDSs utilize different polymeric matrices such as hydrogels, nanoparticle, wafers, chitosan, and microspheres. These delivery systems provide the controlled release of different pharmaceutical active agents at high

localized concentrations with limited systemic toxicities [71]. Polymeric DDSs have gained in popularity because they are biodegradable, biocompatible, nontoxic, have high loading capacities, protect drugs from degradation, and enable long-term drug release [73, 74]. Chemo-resistance, drug degradation, systemic toxicity, and BBB are some of the challenges faced by developers, and polymeric carriers provide a means of overcoming these obstacles because their structures and functionalities can be altered by design [65]. Many researchers have focused on polymeric carriers such as hydrogels [2], poly (lactic-co-glycolic acid) (PLGA) nanoparticles [75, 76], poly (lactic acid) (PLA) nanoparticles [77], wafers [65], dendrimers [78], chitosan-based nanoparticles [79], and microspheres [66] to develop treatments for GBM **[Fig. 4]**.

Polymeric hydrogels

Hydrogels are composed of three-dimensional, hydrophilic, polymeric networks, which have the potential to absorb large amounts of water [70, 80]. Hydrogels provide valuable vehicles for drug delivery as they protect drug cargoes. Their physiochemical properties depend on their chemical compositions, on external variables (e.g., pH, temperature, and light), and on their water contents, mesh size, viscoelastic properties, flexibilities, biocompatibilities, and degradation characteristics [70, 80]. Due to these properties and their abilities to encapsulate hydrophilic and hydrophobic drugs,

hydrogels are good candidate carriers for sustained drug release and targeted drug delivery [71, 72] [**Fig. 5**].

Anti-cancer drugs such as TMZ [81], paclitaxel (PTX) [82], doxorubicin (DOX) [83] and lomustine [23] can be loaded into different hydrogels such as PLGA-based [84], thermo-responsive [85], theranostic [86], and reactive oxygen species (ROS)/redox-responsive hydrogels [87]. In addition, PLGA, PLA, and chitosan-based nanoparticles can be loaded with TMZ, PTX, DOX, or lomustine and then embedded in hydrogels to provide prolonged and sustained drug delivery at tumors [71]. Reports indicate GBM can be treated using anti-cancer drug loaded PLGA-based [84], thermo-responsive [85], theranostic [86], or ROS/redox-responsive hydrogels [87].

PLGA-based hydrogel

PLGA is a well-proven biodegradable polymer [5] prepared by the ring opening polymerization of biocompatible ingredients lactic and glycolic acid monomers [88]. These endogenous monomers are easily metabolized by the body and ensure PLGA is biocompatible and biodegradable [89, 90]. Over the last two decades, PLGA has been widely utilized for DDS and in the tissue engineering field due to its biocompatibility, non-toxicity and sustained drug release properties. Furthermore, the physicochemical properties of PLGA such as glass transition temperature, inherent viscosity (depending on the molecular weight of

PLGA), crystallinity, and tensile strength [91, 92] can be tailored by altering the lactic: glycolic monomer ratio. Lactide in PLGA hydrogels aids long-term drug release from for example implants, but lactic and glycolic acid release could cause localized pH reductions, irritate nearby tissues, and reduce drug stability [91]. Nevertheless, PLGA is FDA approved for biomedical applications and is used as DDSs to treat many diseases, including cancer, with minimal systemic toxicity [65].

Akbar et al. [93] designed a decomposable gel matrix comprised of PLGA and an FDA approved plasticizer (e.g., polyethylene glycol 400 (PEG-400), and triethyl citrate at a weight ratio of 2:3, and injected this gel matrix containing TMZ into resection cavities of a rat surgical resection model of intracranial C6-GFP glioma to study the *in vivo* safety and efficacy of novel DDSs [5, 93]. In addition, safety and tumor volume reduction efficacy studies were performed using a gel matrix-TMZ formulation in a subcutaneous human xenograft glioma model [93]. The administrations of gel matrix-TMZ to tumor sites in the subcutaneous glioma model and in an intracranial glioma resection model demonstrated TMZ released from gel matrix effectively reduced tumor volumes upto ~95% compared to blank control. Furthermore, TMZ release was observed to occur over a prolonged period indicating potential for the treatment of GBM [93, 94].

Tyler et al. [84] examined the use of OncoGel™ with or without TMZ as an adjuvant to radiotherapy in a 18 Fischer-344 rats model of GBM. OncoGel™ is a new thermo-responsive ReGel™ and is used to achieve the controlled release of hydrophobic drugs like PTX [95]. ReGel is thermosensitive, biodegradable and composed of PLGA and PEG, whereas OncoGel™ is a PTX-loaded ReGel that is implanted in resection cavities to extend time to GBM recurrence by up to 6 weeks [84, 96]. In an efficacy study performed in 18 Fischer-344 rats, the Tyler et al. [84] compared a non-treated control, a ReGel, a radiotherapy, an OncoGel™ only, an Oncogel™ loaded 6.3 mg/mL PTX with and without radiotherapy group and showed <18 Fischer-344 rats treated with Oncogel™ loaded with 6.3 mg/mL PTX administered by intracranial injection had a better survival rate than non-treated controls. It was also observed 18 Fischer-344 rats in the control and ReGel™ groups survived for just 17 days, but that those that treated with 6.3 mg/mL of Oncogel™ and radiotherapy on day 0 had an MST of 83 days. On the other hand, animals administered 6.3 mg/mL of Oncogel™ that received radiation on day 5 had an MST of 32 days. It was also reported combined radiotherapy and OncoGel™ improved survival time and reduced GBM recurrence [84].

Thermo-responsive hydrogel

These gels are temperature sensitive hydrogels that create a physical gel at body

temperature [97]. They are *N*-isopropylacrylamide (NIPAAm) cross-linked polymers that have high water absorption capacities and change conformations in an environmentally dependent manner [98]. Thermo-responsive hydrogels have reversible swelling properties [99] and gelling characteristics that are temperature-dependent. These materials form hydrogels instantly when gelation temperatures are reached. Most thermo-responsive hydrogels have low critical solution temperatures and form gels in a reversible manner when critical solution temperatures are reached [97, 100].

Ding et. al [85] designed polyethylene glycol-dipalmitoyl phosphatidylethanolamine (PEG-DPPE) calcium phosphate nanoparticles as an injectable thermo-responsive hydrogel for local and sustained delivery of PTX and TMZ to glial tumors. The double emulsion method was used to load TMZ and PTX into nanoparticles and their antiglioma effect of TMZ/PTX was determined to be (1:100) on C6 cells by the Chou and Talalay method [85, 101]. PTX and PTX-TMZ-nanoparticles were found to inhibit glioma cell proliferation, whereas the thermo-responsive gel inhibited glioma growth by autophagy.

Arai et al. [102] developed a thermo-reversible gel loaded with polymeric microspheres or liposomes and showed the unique thermally-dependent sol-gel properties of thermo-reversible gelation polymer (TGP), which was sol at room

temperature but gelled at body temperature, was suitable for DDS. TGP was produced from poly (N-isopropyl amide-co-n-butyl methacrylate) (poly (NIPAAm-coBMA)) and the hydrophilic polymer PEG [103]. Interestingly, below its liquid gel transition temperature (LGTT) TGP remained hydrophilic but became hydrophobic at higher temperatures due to the presence of its isopropyl group [103, 104]. LGTT of TGP occurred rapidly and reversibly [103].

DOX-loaded microspheres (microsphere-DOX) or liposomes (liposome-DOX) was developed and combined with TGP to achieve long-term drug delivery and their effects on cell viability assay were tested using glioma cell lines (U-87MG and LN229) [102]. The authors used TGP- loaded DOX (TGP-DOX), TGP combined with microsphere-DOX (TGP+microsphere-DOX), or TGP combined with liposome-DOX (TGP+liposome-DOX) for *in vitro* study in U-87MG and LN229 cells. On treatment days 1 and 10, TGP-DOX reduced cell viabilities by 91% and 29%, respectively, whereas TGP+microsphere-DOX and TGP+liposome-DOX did not significantly reduce tumor cell viability. This result demonstrated TGP alone had no toxic effect on U-87MG or LN229 cells and that DOX induced its anti-tumor effect after release from the TGP gel. Furthermore, TGP+microsphere-DOX and TGP+liposome-DOX showed prolonged DOX release (10-30 days) [102].

Ozeki et al. [105] developed a new formulation in which vincristine (VCR) was loaded into PLGA microspheres embedded in TGP which became a sol or gel at room and body temperature, respectively. When the formulation was implanted into GBM resection cavities in rat glioma models, TGP form gel around the injection site and PLGA microspheres localized at target sites that prevented VCR diffusion in brain tissue, and as a result VCR release from PLGA microspheres was achieved in a sustained manner. In addition, the authors implanted VCR loaded PLGA (VCR/PLGA) with or without TGP in a C6 rat glioma model and investigated its therapeutic effect. It was found the MST of VCR/PLGA without TGP increased by 23.5 days in compare to untreated rats (18 days), whereas VCR/PLGA with TGP was 33 days and increased with respect to untreated control group [105]. The localization of PLGA and the sustained release of VCR/PLGA microspheres by TGP also increased MST in a C6 rat glioma model [105].

Similarly, Ozeki et al. [106] designed camptothecin (CPT)-loaded PLGA microspheres with TGP (CPT/PLGA/TGP) for implantation after surgical glioma resection. PLGA microspheres were found to localize at injection sites after administering CPT/PLGA/TGP and sustained drug release was observed. The therapeutic effects of CPT/PLGA/TGP were also evaluated in a C6 rat glioma model. No change in survival was observed between the tumor-bearing

C6 control group and the surgical resection group, whereas CPT/PLGA/TGP alone and surgical resection plus CPT/PLGA/TGP prolonged survival showed almost same therapeutic effect and prolonged the survival days upto 24 days compared with the control and surgical resection group [106].

Theranostic hydrogel

Theranostic agents combine drugs and diagnostic agents [107], and thus, allow the deliver both by single administration [108]. Diagnostic imaging is desirable before initiating the treatment of diseases like cancer, and the use of theranostics enables assessments of drug biodistribution and selectivity that isn't possible when imaging and therapeutic agents was applied individually [109]. The properties required of theranostic nanoparticles are; (i) selective tumor accumulation, (ii) targeted delivery of therapeutic doses of anti-cancer drugs, (iii) early tumor detection, and (iv) biocompatibility and biodegradability [110, 111].

Kim et al. [112] developed an injectable theranostic formulation called magnetic resonance imaging (MRI)-monitored long-term therapeutic hydrogel (MLTH) containing a thermosensitive/magnetic poly(organophosphazene) hydrogel, irinotecan SN-38, and a hydrophobic $CoFe_2O_3$ magnetic core, and used it to observe the successful delivery of SN-38 to rodent U-87MG brain tumors. MRI experiments conducted at 7-Tesla allowed the differentiation of MLTH-treated

and non-treated areas of brain tumors. In addition, the hydrogel formulation inhibited tumor growth at 22 days after administration, which demonstrated its potential therapeutic and monitoring capabilities.

Temperature and pH sensitive magnetic nanogels are another type of theranostic hydrogel used for GBM. Jiang et al. [113] produced nanogels containing Cy5.5-labeled lactoferrin (Cy5.5-Lf-MPNA nanogels) as a contrast agent for MRI and fluorescence imaging that could be systemically administered and accumulated in the acidic microenvironment of rat brain tumors. In this study, superparamagnetic iron oxide (SPIO) nanoparticle loaded poly (N-isopropylacrylamide-co-acrylic acid) [P(NIPAM-co-AAc)] nanogel conjugated with Cy5.5-lactoferrin had a longer blood circulation time (due to slower clearance from the reticuloendothelial system) than Cy5.5-Lf-MPNA nanogels. As a result, the formulation was retained in glioma tissue due to the availability of lactoferrin. In addition, the pH/temperature sensitivities of nanogels improved passive targeting abilities. Cy5.5-lactoferrin SPIO-nanoparticles loaded [P(NIPAM-co-AAc)] nanogels enabled the targeting of rat C6 glioma tumors *in vivo*. The grafted Cy5.5 fluorochrome enabled fluorescence imaging and the SPIO-nanoparticles allowed MRI visualization of nanoparticle accumulation in brain tumors [113].

ROS/Redox responsive hydrogels

Redox stimuli/ROS responsive hydrogels may be suitable for the delivery of anti-cancer drugs to GBM tumors [114, 115]. ROS contain hydrogen peroxide, superoxide, hydroxyl radical (•OH), peroxynitrite, and hypochlorite, which play important roles in cell signaling pathways [116]. ROS are generated endogenously, for example, incomplete oxygen reduction and nicotinamide adenine dinucleotide phosphate in plasma membranes can generate ROS in mitochondria [117, 118]. ROS mediate cell functions in healthy and disease conditions [118]. During normal metabolic activities, ROS are continuously generated, converted, and consumed in tissue in a manner that maintains homeostasis, and support cell growth, migration, apoptosis, and help fight off foreign pathogens [119]. On the other hand, excessive ROS production disrupts homeostasis and cellular metabolic balance and causes oxidative stress that can damage cellular components such as proteins, lipids, and DNA [120]. During mitochondrial cancer progression, elevated ROS levels stimulate oncogenes, enhance metabolism, and damage [121]. Hydrogels can be used to provide localized and sustained drug delivery, and the effects of some physiologic parameters such as pH changes, high glutathione concentrations, and elevated ROS levels have been investigated in the context of triggering controlled drug release from hydrogels. Under oxidative stress, drugs will be released from ROS-responsive hydrogels along with the degradation of the polymeric matrix

[122].

Redox stimuli responsive biodegradable formulations might also aid the delivery of drugs to tumors [114]. However, *in vivo* swelling or shrinkage of hydrogels may cause long-term drug retention, and thus, incomplete drug release. To resolve this problem, various degradable crosslinkers containing ester, peptide, or other labile bonds, have been incorporated into hydrogels [123]. In particular, disulfides may provide excellent degradable crosslinkers as the disulfide bond (S–S) can be cleaved in aqueous media by reducing agents like dithiothreitol (DTT), glutathione (GSH), and ROS [123, 124]. In fact, several studies have reported the addition of a redox agent enhances drug release from disulfide crosslinked hydrogels [123].

Pan et al. [114] produced redox/pH dual stimuli-responsive poly (methacrylic acid) (PMAA)-based nanohydrogels using methacrylic acid and N, N-bis(acryloyl) cystamine as a crosslinker by distillation precipitation polymerization. In the presence of DTT and GSH, nanohydrogels were more easily degraded into short linear chains. According to the author, the nanohydrogels produced exhibited rapid drug release in response to pH and reducing environment. When they loaded a nanohydrogel with DOX it was observed that DOX release was faster in the presence of GSH than of DTT due to the synergic effects of reduction and charge exchange of GSH at low pH. A

colorimetric cell counting kit-8 (CCk-8) assay used to investigate the cytotoxicity of DOX-loaded nanohydrogels, showed the formulation was quickly taken up by human glioma (U-251MG cells) by endocytosis and that the nanohydrogel was then degraded to release DOX.

Lee et al. [115] developed a CPT nanoprodrug formulation targeting GBM. The formulation was prepared by nanoemulsifying a biodegradable, antioxidant CPT prodrug, and α-tocopherol [125]. The CPT formulation showed ROS scavenging ability, enzymatic activation, and *in vitro* anti-cancer efficacy against U-87MG glioma cells [126]. As regards therapeutic efficacy, the oxidized nanoprodrug was more effective than the non-oxidized nanoprodrug in oxidative tumor microenvironments, and the authors observed more intracellular uptake of the oxidized nanoprodrug through cell membranes than by endocytosis in U-87MG glioma cells. Furthermore, an *in vivo* study showed that the oxidized CPT nanoprodrug crossed the BBB and accumulated at the peripheries of brain tumors, where active proliferation occurs. In addition, the oxidized nanoprodrug inhibited tumor growth by more than 80% versus controls, and increased mouse MST from 40.5 to 72.5 days [115].

Polymeric particles

Polymeric particles are sub-micrometer sized and used for clinical diagnosis, photonics, and drug delivery [127]. Generally, polymeric particles can be

classified in two groups depending on whether they contain polymeric nanoparticles or microparticles, which range in size from 10 to 1000 nm and from 3 to 800 μm, respectively [128]. These small particles sizes and the physical properties of polymeric particles make them candidate materials in the pharmaceutical field [129]. The main properties of polymeric particles as DDSs are the ability to incorporate and release drugs, formulation stability, biocompatibility, biodistributability, and high drug loading capacity [130]. Polymeric nanoparticles and microparticles are also used for drug entrapment, which can enhance targeted drug delivery and reduce free drug-induced toxicity at neighboring organs. Solid tumors show enhanced permeability and retention (EPR) effect, which improve deliveries of drug-loaded polymeric nanoparticles and microparticles [131] [**Fig. 6**]. Furthermore, chimeric system which means nanoparticles vector entrapped in microparticles vectors can be designed for the delivery systems [132, 133]. Since microparticles are easy to produce on large scale and to store, while nanoparticles have high surface/volume ratio, this chimeric system can potentially improve the drug loading efficiency [132], as well as the efficacy and reliability of delivery system. Also, polymeric nanoparticles or microparticles protect their cargoes from degradation and increase drug concentrations at target sites [134].

Nanoparticles are classified by chemical type as carbon-based, metal,

polymeric, or lipid-based [130]. Chitosan, poly(cyanoacrylate), PLGA, and PLA [88] are used to prepare biodegradable polymeric nanoparticles/microparticles by solvent evaporation, spontaneous emulsification, polymerization, or ionic gelation [129].

Chitosan-based nanoparticles

Chitosan is a polysaccharide obtained by the deacetylation of chitin and can be used as a DDSs for implants and parental and transdermal systems [79, 135]. Furthermore, chitosan is widely used in the pharmaceutical field in combination with different polymers. Chitosan is composed of β-(1→4) linked 2-amino-2-deoxy-glucopyranose and 2-acetamido-2-deoxy-β-D glucopyranose residues [136] and drug release from chitosan nanoparticles can be achieved by utilizing swelling or drug-polymer interactions [79]. The main beneficial characteristics of chitosan nanoparticles are biodegradability, biocompatibility, a non-toxic nature, mucoadhesion, controlled drug release, enhanced drug efficacy, and targeting ability [137]. Chitosan also has anti-microbial and antioxidant properties and is little immunogenicity. It can be used as a diluent and filler in DDSs or in tablet or capsule form to control drug release [136, 138]. However, despite the many advantages of chitosan nanoparticles, they are disadvantaged by poor solubility and a tendency to swell and cause burst drug release. Chitosan nanoparticles penetrate cell membranes well, have high drug-loading

capacities and long circulating times, are multi-functional, and allow pH-dependent drug unloading [79]. For these reasons, chitosan nanoparticles are considered emerging delivery systems for chemotherapy and diagnosis.

Galectin-1 (Gal-1) is overexpressed in GBM and is related to tumor progression and to immune suppression in tumors, and also acts as an effective immune suppressor protein, and thus, facilitates disease progression and promotes angiogenesis [139, 140]. Woensel et al. [140] developed a therapeutic system based on the delivery of small interfering RNA (siRNA) to CNS tumors within an hour of the intranasal administration of Gal-1 siRNA-loaded chitosan nanoparticles. Interestingly, they observed this siRNA complex can target Gal-1 and chitosan nanoparticles provide protection to protect siRNA from RNAase degradation. Furthermore, they demonstrated that expression of Gal-1 was inhibited by anti-Gal-1 siRNA delivery in both murine GL261-WT and human GL261-BFP GBM cells, and also found delivering anti-Gal-1 siRNA into the CNS using chitosan nanoparticles did not adversely affect the efficiency of siRNA. In addition, the metastasis of tumor cells was reduced by the rapid delivery of siRNA into GL261-WT and GL261-BFP cells. Moreover, siRNA treatment reduced Gal-1 levels by more than 50% in GBM bearing mice. The results showed that intranasal siRNA-based therapies targeting Gal-1 offer a potential means of treating GBM [140].

Yadav et al. [141] developed chitosan/tripolyphosphate nanoparticles and loaded them with melatonin (MEL) to improve the anti-cancer efficacy of MEL. Cellular uptake, efficacy, and *in vitro* release studies were performed to investigate the anti-cancer properties of this formulation in human U-87MG cells. Furthermore, the *in vitro* viabilities of U-87MG glioma cells were studied to evaluate the cytotoxicity of MEL-chitosan and MEL alone. Both treatments caused cell death after 24 h of incubation, leaving only 22% and 42% of cells viable, respectively, versus untreated controls. In contrast, MEL-chitosan caused further reductions in cell viability at 48 and 72 h, indicating sustained MEL release. The experiment showed that encapsulation in chitosan/tripolyphosphate nanoparticles enhanced the anti-cancer effects of MEL on U-87MG cells [141].

Kim et al. [142] designed thermosensitive gel chitosan/β-glycerophosphate (Ch/β-GP) loaded with ellagic acid (EA) to deliver EA for the treatments of brain cancer. At body temperature, the Ch/β-GP solution formed a heat-induced gel. The authors have reported that *in vitro* release rate of EA from EA-loaded Ch/β-GP gel in the presence of lysozymes was increased by 2.5 times higher than in the absence of lysozymes. Furthermore, human U-87 glioblastoma and C6 rat glioma cells were used to study of anti-tumor effect of EA-loaded Ch/β-GP gel. The cell viability of U-87 and C6 rat glioma cell was decreased compared with the chitosan gel only after 3 days incubation ($p < 0.01$, and $p <$

0.001, respectively). Similarly, the authors have investigated that anti-proliferative effect of dialyzed chitosan solution gel (DCh/β-GP)-loaded with EA on human U-87 glioblastoma and rat C6 glioma cells in EA concentration dependent manner. The authors reported that the metabolic activities of both cells were decreased when the concentration of EA (5.5 to 10 mg 5.5) was increased in DCh/β-GP gels.

Dendrimers

Dendrimers are nano-sized, radially symmetrical molecules with a distinct homogeneous monodisperse structure and are typically composed of a core and an inner and outer shell [143, 144]. Dendrimers can entrap and/or conjugate high molecular weight hydrophilic or hydrophobic agents by host-guest interactions or covalent bonding, respectively [143], and offer an alternative means of designing DDSs and imaging methods. Various dendrimer platforms such as polyamidoamine (PAMAM), poly (propyleneimine) (PPI), poly-L-lysine, melamine, poly (etherhydroxylamine), poly (esteramine) and polyglycerol have been synthesized and explored as potential drug delivery vehicles [78]. High water solubility, biocompatibility, polyvalence, precise molecular weight, and high drug loading capacity are the main strengths of dendrimers and make them an attractive option for drug delivery and targeting applications [145]. Dendrimers conjugated with fluorochrome can be used for

cancer imaging and utilized for photodynamic, boron neutron capture, and gene therapy [146]. However, in GBM, dendrimer-based therapy is limited by poor GBM cell penetration and drug retention. The penetration of dendrimers in tumor tissue can be improved by decreasing the particles size which cause reduced retention effect. Therefore, small nanoparticles having high retention effect in the tumor are required for better GBM drug delivery [147].

Zhao et al. [147] designed a small nanoparticle DDS by conjugating the fibrin-binding peptide CREKA to PAMAM dendrimers. A PEGylated PAMAM dendrimer was used as a drug carrier because of its small size and ability to penetrate tumor sites. CREKA was used to target fibrin in GBM, and thus, to enhance tumor retention. *In vitro* binding tests showed CREKA improved dendrimer binding to fibrin. In addition, *in vivo* fluorescence imaging of nude mice with GBM and *ex vivo* brain imaging and frozen slice fluorescence study showed CREKA-modified PAMAM exhibited better accumulation and deeper penetration in GBM tissues than unmodified PAMAM. The results obtained confirmed that CREKA-modified PAMAM deeply penetrated GBM tissues and enhanced intra-tumor retention [147].

Gajbhiye et al. [148] developed a polysorbate 80 (P80) conjugated poly(propyleneimine) (PPI) dendrimer and investigated its ability to deliver docetaxel (DTX) to brain tumors. Cytotoxicity studies of the effects of free

DTX, DTX loaded PPI (DTX–PPI), and DTX loaded PPI with P80 (DTX–P80-PPI) on U-87MG glioma cells suggested DTX had a potent cytotoxic effect as evidenced by an IC_{50} value of 0.15 μM after incubation for 24 h, which was substantially higher ($p < 0.001$) than that of DTX–PPI (0.9 μM) or DTX–P80-PPI (3.5 μM). Furthermore, *in vivo* anti-cancer activities in glioblastoma bearing male albino rats showed DTX–P80-PPI dendrimer markedly reduced tumor volumes (≥50%; $p < 0.0001$). Also, the MST of brain tumor-bearing rats treated with DTX–P80-PPI (42 days) was substantially greater than that of DTX–PPI (23 days; $p < 0.001$) or free DTX (18 days; $p < 0.001$) treated rats [148].

Microspheres

Microspheres are spherical particles of average particle size 1 to 1000 μm [149, 150] and can encapsulate small drugs and proteins and improve the drug bioavailability, stability, and specificity [151]. Therapeutic efficacies of drugs can be improved by using controlled DDSs, and microspheres can be used for this purpose. Furthermore, particles size reduction of microspheres would enhance the solubility of poorly soluble drugs, and microspheres could protect drugs from enzymatic and photolytic cleavage, and provide long-term therapeutic effects [152]. Limitations of microspheres include manufacturing difficulties, instability, and susceptibility to temperature, pH, and fabrication effects [150, 153]. Polymeric microspheres are classified as biodegradable

polymeric microspheres and synthetic polymeric microspheres. Due to several advantages of microspheres, they are used as drug carriers to treat cancers including GBM [66] and colon cancer [154].

Chen et al. [66] developed a formulation for biodegradable PLGA microspheres-loaded with carboplatin (CBP) for intracerebral delivery. The developed formulation accomplished high concentrations of CBP at tumor sites with little evidence of side effects in the rat glioma models. The authors went on to examine reactions at GBM using CBP-loaded PLGA microsphere (PLGA microsphere-CBP) or free PLGA microspheres in a rat model. Free PLGA microspheres were found to induce edema and macrophage and microglia proliferation as side effects, whereas PLGA microsphere-CBP induced a phagocytic inflammatory reaction that lasted for 1 hr. The formulation was intracerebrally implanted in a rat glioma model and resulted in high CBP concentrations in tumors. In addition, the authors observed a marked MST increase and reduced weight loss in rats administered PLGA microsphere-CBP as compared with rats administered CBP systemically [66]. MST in untreated controls was only 15 days, which was ascribed to a neurological defect, whereas MST for animals treated with PLGA microsphere-CBP was 18 days [66]. It is difficult to treat malignant glioma using PLGA microsphere-CBP due to rapid tumor growth, but this problem can be solved by using low molecular weight

PLGA polymers. Furthermore, rapid degradation of low molecular weight polymer can increase drug release, and thus, increase CBP concentrations in brain tumors. The author concluded that locally delivered PLGA microsphere-CBP produced high CBP concentrations at tumor sites. Furthermore, their implanted formulation effectively minimized toxicities such as weight loss and increased the MST of animals with malignant glioma [66].

González-Gómez et al. [155] provided experimental evidence of glioma cell growth inhibition by intracranially administered bone morphogenetic protein-7 (BMP-7), which prevents cell proliferation and blocks self-renewable capacity of primary glioma cell lines that express the receptor BMPR1B cells by inducing canonical pathways, contained in controlled release microspheres. To provide effective release of BMP-7 from PLGA-microspheres, a nano-complex containing heparin and a tetronic was formulated. BMP7 activate canonical BMP signaling pathway in GBM8, as evidenced by both their translocation to the nucleus. In the presence of a high concentration (100 ng/mL) of BMP-7, a GBM8 cell sphere formation assay revealed sphere numbers and sizes in the BMP-7 treated group were smaller than in the control group, indicating inhibition of the proliferative activity of GBM. The authors observed that sphere numbers were lower for cells that are able to grow in BMP-7, suggesting cells had adopted a lower self-renewable capacity [155]. In this study, it was

observed that sphere formation in GBM8 cells treated with BMP-7 loaded microspheres was 14-fold lower than that of untreated control and that delay the treatment of tumor growth. Moreover, the expression of cell cycle inhibitors CDKN1A and CDKN2A increased, whereas the expressions of proliferation markers (e.g., proliferating cell nuclear antigen, PCNA) diminished [155].

Zhu et al. [156] developed bis-chloroethyl nitrosourea (BCNU) loaded PLGA microspheres (PLGA microspheres-BCNU) and investigated their effects on GL261 murine glioma cell growth, mean survival, and apoptosis. A significant MST difference was observed between untreated controls and PLGA microspheres-BCNU treated cells (25-30 and 43.5 days, respectively). Furthermore, the inhibitory effect of PLGA microspheres-BCNU on GL261 murine glioma cell was evidenced by decreases in tumor volumes. After 28 days of treatment, mean tumor volumes in their control and PLGA microspheres-BCNU groups were 2.10 and 1.40–1.75 mm, respectively. Furthermore, it was found that the expression of the anti-apoptotic protein Bcl-2 was lower in the PLGA microspheres-BCNU treated group. These results indicated PLGA microspheres-BCNU improved MST, inhibited tumor cell proliferation, and induced glioma cells apoptosis.

Shi et al. [157] co-loaded PLGA microspheres with aspirin and TMZ and examined their cytotoxicities in human glioma cell lines U-87 and LN229.

Treatment of cells with aspirin loaded microspheres produced less apoptosis and reduced the proliferations of U-87 and LN229 cells by reducing β-catenin transactivation. In addition, it was reported aspirin/TMZ loaded PLGA microspheres had greater anti-cancer activity, that is, they caused more apoptosis and suppressed the proliferations of U-87 and LN229 cells, more than TMZ-loaded PLGA microspheres. Moreover, intratumorally injection of aspirin/TMZ microspheres downregulated the expressions of β-catenin, transcription factor 4 (TCF4), pAKT, phospho- signal transducer activator of transcription 3 (pSTAT3), and PCNA. These results showed aspirin increased the anti-cancer efficacy of TMZ by reducing β-catenin transactivation. Furthermore, TMZ release from co-loaded microsphere show sustained release action to reduce the TMZ dosage that offer the potential treatment for GBM [157].

Emerich et al. [158] developed injectable poly(lactide-co-glycolide) (PLG) microspheres loaded with CBP or BCNU to improve MST in a rodent model of deep glioma. The authors implanted rat glioma-2 cells into rat striatum, grew them for 3 days, and then implanted microspheres directly into the centers of the small tumors formed. Animals with 8-day tumors were treated with either CBP loaded microspheres (microspheres-CBP) or BCNU loaded microspheres (microspheres-BCNU), which were injected directly into tumor centers or

perimeters. In addition, one group of rats was administered CBP by bolus injection**.** It was observed rat survival increased with microspheres-CBP, e.g., 100 µg of sustained CBP release or bolus injection of 100 µg CBP increased MST by 178% and 33% versus non-treated controls. Injection of microspheres-CBP into tumor perimeters also improved survival, e.g., 100 µg of sustained CBP release or bolus injection of 100 µg CBP increased MST by 191% and 44%, respectively. Furthermore, through the injection of microspheres-BCNU improved the survival by 25% and 105% in center and perimeter of tumor injection, respectively. The MST of CBP is higher in comparison with the BCNU treated group. These results showed that injection of sustained release microspheres into tumor perimeters was more effective than injection into tumor centers [158].

Wafers

Wafers are disc-shaped, synthetic or biodegradable implants containing an active pharmaceutical agent [159]. Wafers were developed to overcome the barrier effect of the BBB, and thus, enable the long-term delivery of drugs like carmustine [160], enhance bioavailabilities, reduce systemic toxic effects, and protect drugs.

Gliadel® wafers (also known as carmustine wafers) are composed of a biodegradable BCNU polymer impregnated with the alkylating agent

carmustine [159, 161]. Gliadel® wafers are FDA approved for the treatment of high-grade malignant glioma. These wafers are placed in resection cavities after surgery for up to 2-3 weeks to prevent GBM recurrence. The use of this wafer type has been reported to improve MST by 2-3 months in patients with newly diagnosed

GBM [162], and reported overall MST for the Gliadel wafer in newly diagnosed GBM and recurrent GBM were 16.4 ± 21.6 and 9.7 ± 20.9 months, respectively [163].

A protocol developed by Stupp et al. [19] has the potential to improve the survival of GBM patients. This protocol consists of radiotherapy, concomitant chemotherapy, and TMZ. According to this protocol, a Gliadel® wafer is implanted to span the 2-3 week gap between surgery and the commencement of adjuvant treatment (e.g., radiotherapy plus TMZ) to improve local tumor control [19, 164].

Xing et al. [165] compared the MST of randomized controlled treatment (RCT) and the results of cohort studies and clinical trials conducted with or without carmustine wafers and calculated hazard ratios. 513 patients were enrolled in the study and of these 290 were selected for placebo treatment and the remainder were treated with a carmustine wafer. The result obtained showed that the two RCTs did not significantly increase survival. The group treated with

a carmustine wafer had a hazard ratio (H), confidence interval (CI) and P-value (P) of H=0.63, CI=0.49–0.81, and P=0.019 versus untreated control , whereas the group treated without a carmustine wafer had corresponding values of H= 0.51, CI= 0.18–1.41 and P= 0.426 [159, 165, 166]. These results indicated that implantation of a carmustine-loaded wafer helped improve survival in newly diagnosed GBM patients.

Brem et al. [167, 168] demonstrated the safety and efficacy of Gliadel® wafer implantation in recurrent glioma, in which it is difficult to achieve response without inducing systemic toxicity. Wafers with or without 3.8% carmustine were implanted in resection cavities of patients and subsequently patients that received a wafer with carmustine were found to have an MST of 32 weeks, whereas patients implanted with a placebo wafer had an MST 23 weeks [168, 169]. In addition, the authors investigated the adverse effects of BCNU polymer in brain and concluded TMZ was released from wafers to GBMs and that the procedure appeared to be safe and effective for the treatment of recurrent GBM.

McGirt et al. [164] examined the use of Gliadel® wafers and adjuvant TMZ after GBM resection in patients that underwent primary GBM resection with or without Gliadel® wafer implantation and adjuvant X-ray telescope radiotherapy (XRT). Concomitant TMZ was given to all patients implanted with a wafer [19]. All patients treated with a wafer plus XRT and TMZ were evaluated to

determine overall survival and assess treatment-related morbidities. All of the 33 patients enrolled in the study were treated with a wafer and received TMZ plus XRT, and the MST of these patients was 20.7 months [164]. Surgical site infection, deep vein thrombus, cerebral edema, thrombocytopenic, and neutropenia are the main reasons for six-month morbidity in surgically treated GBM patients [159, 170], and it has also been reported patients that receive a Gliadel wafer post-resection can be treated with TMZ safely without increasing morbidity [164].

Lipid-based nanoparticles

Lipid-based nanoparticles are potent carriers that improve drug bioavailability in or around disease targets in brain as they can cross the BBB. Such lipid-based nanoparticles are physiochemically stable, biocompatible, solubilize drugs well, and reduce drug-associated side effects [171, 172]. Liposomes [173, 174] and solid-lipid nanoparticles (SLNs) [67] are lipid-based nanoparticles with the potential to deliver anti-cancer drugs to brain and treat GBM. Liposomes are not all equal from the delivery point of view and their composition is very important at this purpose. Their composition may affect the drug release as well as drug entrapment efficiency [175, 176].

Liposomes

Liposomes are phospholipid bilayer containing particles [173, 174], and have

the ability to entrap lipophilic and hydrophilic drugs [174]. The non-toxic nature, structural flexibility, specificity, biocompatibility, size, composition, and especially, the membrane permeability of lipid layers makes liposomes potent nanocarrier systems for controlled drug release [7]. Their main limitations as DDSs include low solubility, short half-life, phospholipid oxidation, and leakage of encapsulated molecules. Therapeutic applications of liposomes include site-specific targeting, reduced toxicity, and intracellular, and sustained drug release [174, 177]. Furthermore, the efficacies of liposomal formulations may be enhanced by prolonging drug release at target sites and by reducing toxic effects. Because liposomes are composed of phospholipids they easily cross the BBB, and thus, can deliver high doses of anti-cancer drugs to GBM tumors [177].

Nordling et al. [68] developed a liposomal formulation to improve the efficacy of convection enhanced delivery (CED) by enhancing drug localization at tumor sites. CED is a new therapeutic process designed to distribute therapeutic fluid in brain using a small catheter and pump to improve the distribution of concentrated infusates in brain beyond that possible by diffusion alone [178]. Nordling et al. designed a TMZ-loaded liposome (liposomes-TMZ) formulation to treat GBM by CED. TMZ solution or liposomes-TMZ were injected into GBM bearing rats that help to inhibit GBM tumor cell growth and result in

better survival. On comparing the results of TMZ in solution and liposomes-TMZ treatment, the authors observed less toxic effect but longer survival and greater inhibition of GBM cell growth in the liposomes-TMZ group. In addition, saline, free liposomes, free TMZ, and liposomes-TMZ were intracranially infused into GBM bearing rats, and it was observed that liposomes-TMZ resulted in longer survival (19.2 ± 3.5 days) than free TMZ (15.8 ± 1.4 days) or free liposomes (12.0 ± 1.0 days), but no significant survival difference was observed between the free TMZ and liposomes-TMZ groups [68]. The authors concluded that liposomes-TMZ increased MST and resulted in smaller tumor volumes than TMZ solution.

Patel et al. [179] designed a TMZ loaded hydrogenated soya phosphatidylcholine (HSPC) liposomes (HSPC liposomes-TMZ) formulation as a DDS for GBM that crosses the BBB and improves brain targeting. Different concentrations of TMZ were loaded into HSPC liposomes and compared with free TMZ with respect to anti-cancer activity in U-87MG glioma cells. HSPC liposomes-TMZ were found to be more cytotoxic to these cells than free TMZ, specifically, at concentration of 40 µg/mL, HSPC liposomes-TMZ and free TMZ killed 54% and 46% of cells, respectively. The reason behind the high cell inhibition via HSPC liposomes was due to the lower particle size of liposomes that can effectively cross BBB as well as permeate in tumor microenvironment

through fenestration in capillaries supplying blood to tumors. Furthermore, HSPC liposomes-TMZ had a lower IC_{50} than free TMZ (35 µg/mL vs. 40 µg/mL), respectively.

Danyu et al. [69] formulated a novel DOX-loaded angiopep-2 modified liposome (AL) as a DDS for GBM; angiopep-2 ligand binds to low-density lipoprotein receptor-related protein, which is highly expressed on glioma cells [180]. Free DOX, normal saline, or AL were injected via a tail vein into glioma bearing mice at a dosage of 2 mg/kg on days 2, 5, and 8 after tumor planting surgery**.** A TUNNEL (terminal deoxynucleotide transferase dUTP Nick End Labeling) assay was used to measure anti-cancer activity, and survival analysis and a toxicity study were performed. In the anti-cancer activity study, the AL treated group exhibited synergistic tumor cell apoptosis and was found to deliver DOX effectively and reduce GBM cell proliferation. In the toxicity study, DOX, liposomes-DOX, or AL were administered at 2, 5, and 8 days and mouse weights were monitored. During the treatment period (day 2 to 8) , mean body weights of control, DOX, liposomes-DOX, and AL treated groups increased by 13.47, 0.86, 1.75, and 6.43%, respectively indicating free DOX has certain toxicity and liposomes-DOX has less toxicity effect than DOX solution . MST of the free DOX, liposomes-DOX, and AL were 23, 26 and 29 days, respectively, which confirmed the better therapeutic effect of liposomes-DOX

and AL [69].

Bastiancich et al. [2] suggested surgical removal of GBM followed by radiotherapy or TMZ, but the survival rate was low due to recurrence around the resection sites. As a result, the authors designed a lauryl gemcitabine lipid nanocapsule (Gem C_{12}-LNC) based hydrogel for local delivery in resection cavities [2]. Because this formulation easily crossed the BBB, high concentrations of gemcitabine accumulated in resection sites. Different GBM cells (U251, T98-G, 9L-LacZ, and U-87MG glioma cells) were used to explore the cytotoxicity and internalization of Gem C_{12}-LNC. In an orthotopic xenograft model, the MST was greater for GemC_{12}-LNC treated mice than untreated controls (49 and 24 days, respectively). In addition, the administration of Gem C_{12}-LNC into resection cavities was found to extend tumor free survival. It was concluded that GemC_{12}-LNC nanomedicine-based hydrogel might be an effective formulation for the local delivery of gemcitabine to prevent GBM recurrence.

Solid-lipid nanoparticles (SLNs)

SLNs represent a new generation of lipid nanoparticles that provide an alternative to polymeric nanoparticles [67, 181]. SLNs have mean diameters between 50 and 1000 nm and have excellent physical stability, targeted drug delivery, biological biocompatibility and feasibility, drug absorption and

bioavailability characteristics [134, 172, 182, 183]. Several studies have shown anti-cancer drugs can be loaded into SLNs and this enhances their physicochemical stabilities and cytotoxic effects on tumor cells [67]. Battaglia et al. [67] developed SLNs using a fatty acid coacervation technique as a DDSs to enable DOX to cross the BBB. One study investigated the *in vitro* cytotoxicities of DOX-loaded SLNs (SLNs-DOX) on different primary human glioma cells, that is, U-87MG, CV17, and 01010627 cells [67]. SLNs-DOX reduced cell viability more than free DOX in all cell lines. hCMEC/D3 cells (primary human brain microvascular endothelial cell-line; a commonly used BBB model) were used to investigate the ability of SLNs-DOX to cross the BBB. It was observed loading DOX into SLNs preserved the cytotoxic properties of DOX, and interestingly, that SLN levels in hCMEC/D3 cells increased when they were loaded with DOX. These results suggest SLNs might offer a means of delivering drugs to GBM tumors.

Conclusion and future perspectives

Researchers have made great progress at developing novel nanoparticle-based formulations with the aim of treating GBM, and there appears to be no end to the creativity displayed by those developing new therapeutics to prolong survival in GBM. In addition, combinations of current standard care and cell-

targeting nano-carriers or polymeric or lipid-based nanoparticles have also been devised to address GBM cell resistance. Polymeric and lipid-based nanoparticles are viewed as promising carriers of therapeutic cargoes to GBM and have opened doors to new, feasible ways of treating this deadly tumor. Nano-carriers have been devised that deliver accurate amounts of drugs to GBM resection sites without adversely affecting neighboring normal cells, and polymeric nanoparticles have been reported to be potential carriers that also deliver accurate amounts of therapeutic agents to GBM tumors through the BBB. Furthermore, these approaches are particularly well-suited to the delivery of anti-cancer drugs because they limit adverse effects.

Furthermore, HR conjugates or nanocarriers, and their potential application may help in cancer imaging and therapy and also to overcome the limitation of current cancer therapy. Since, HR nanoparticles are stable in physiological and capable for selective delivery of hydrophobic drugs into hypoxic cells, it may be used as a potential drug carrier for the treatment of GBM. [52-54]

Liposomes, theranostic nanoparticles, and nanoparticles modified with receptor-targeting monoclonal antibodies are some of the promising therapeutic strategies developed for the treatment of GBM. We believe non-lipid and lipid-based nanoparticles will play important roles in the detection of GBM and in the development of personalized medicine for GBM, and substantially minimize the

adverse effects of current treatments.

However, much work remains to be done in the areas of nanoparticle surface modification, gene therapy and on the development of immuno-liposome delivery systems. In addition, more effort is required to develop nanotechnology-based theranostics for the treatment of GBM. We believe that such efforts will, in a relatively short time, result in the discovery of more effective therapies for GBM.

Acknowledgements

This study was supported by a grant from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (Grant Nos: NRF-2018R1D1A1B07040858 and NRF-2016R1A6A1A03011325).

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List of Figure

Fig.1 Schematic representation of different treatments used to treat GBM

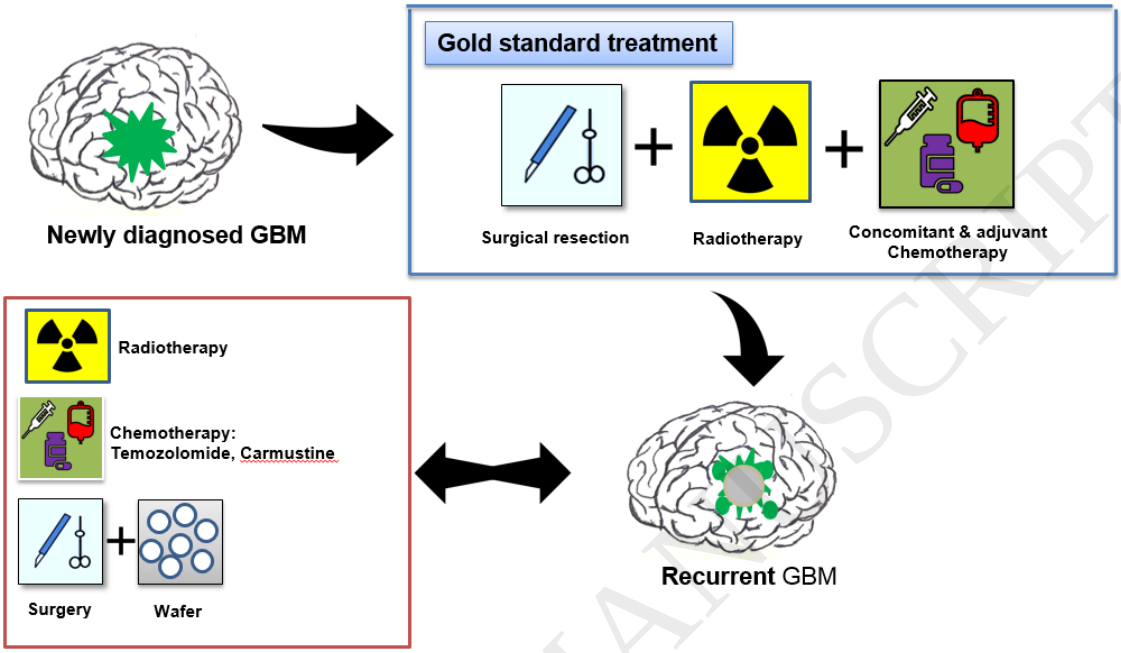

Fig. 2 Mechanism of action of temozolomide

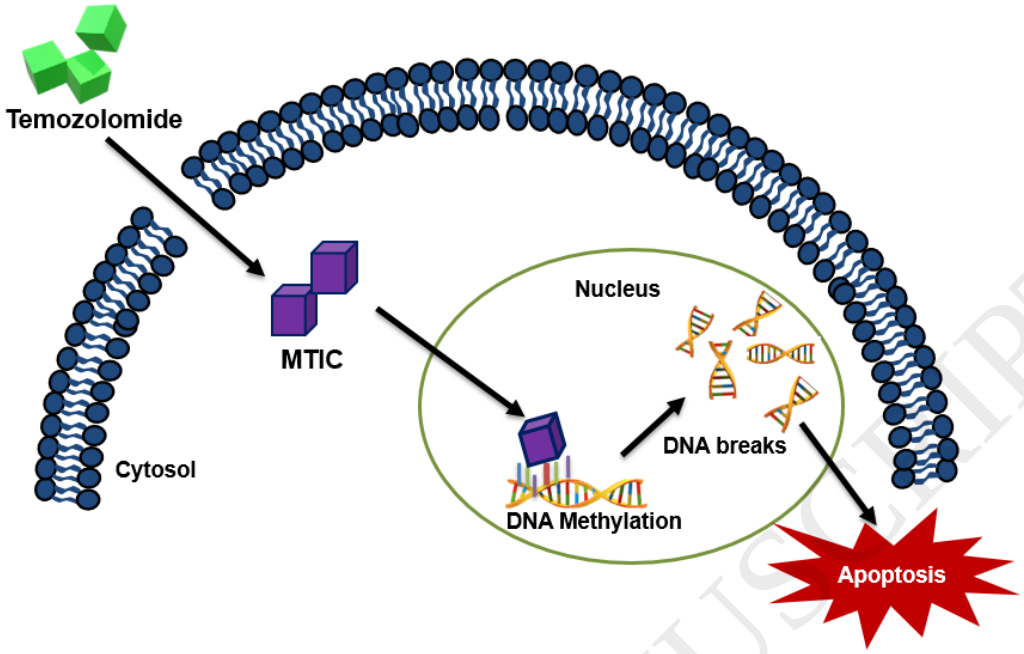

Fig. 3 Causes of GBM recurrence

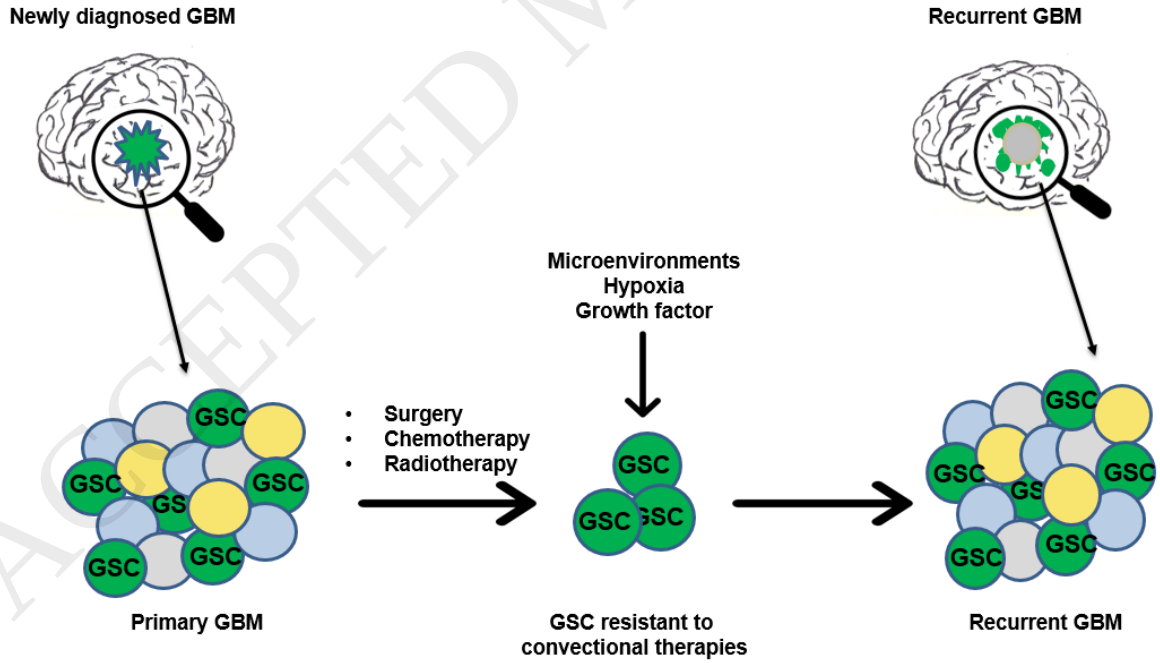

Fig. 4 Different types of nanoparticles used to treat GBM

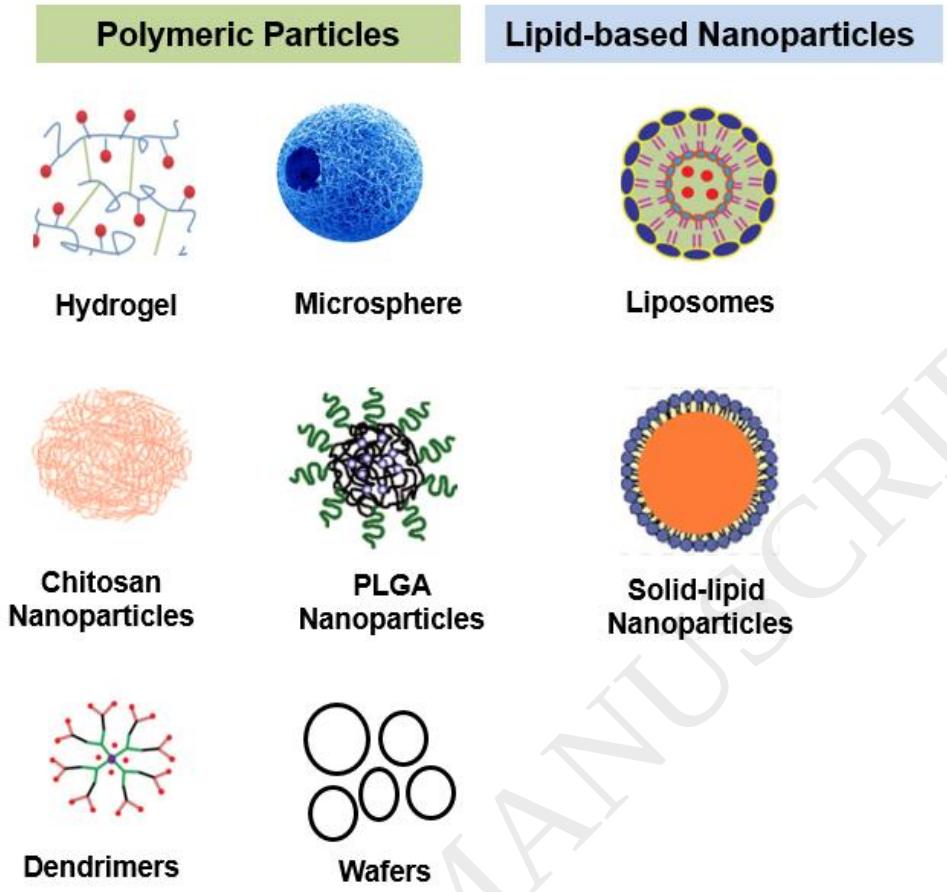

Fig. 5 Mechanism of action of hydrogel for GBM

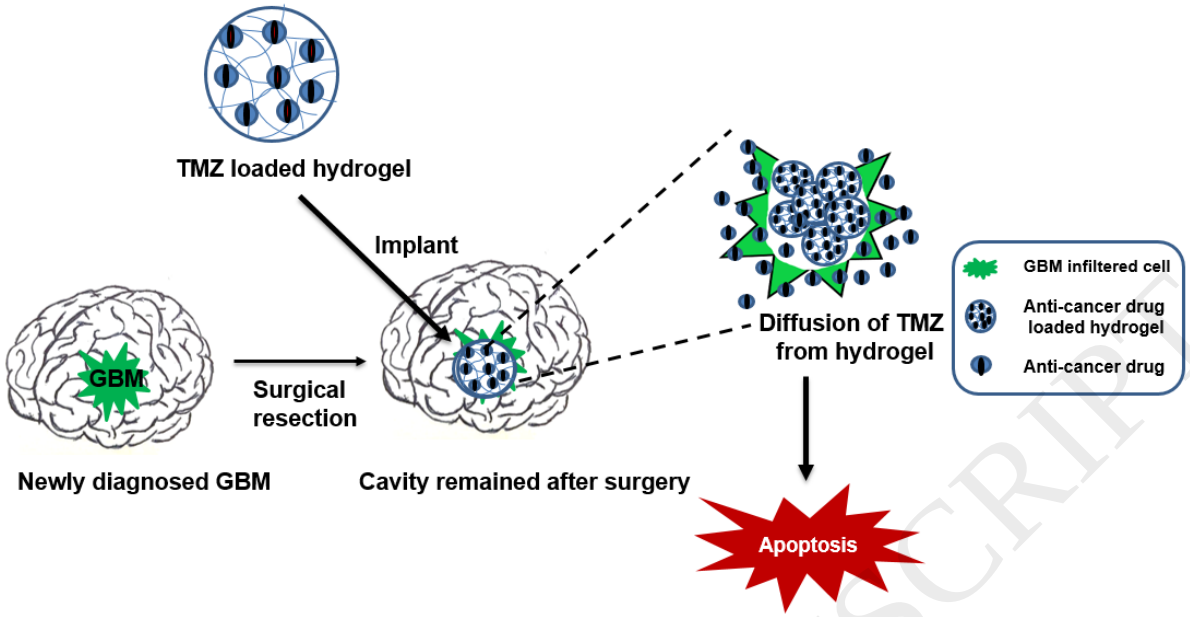

Fig. 6 Mechanism of drug penetrance and retention