

# Localized Drug Delivery Systems in High-Grade Glioma Therapy—From Construction to Application

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High-grade gliomas are the most common and most malignant primary brain tumors. Current therapy approaches only reach unsatisfactory results, still not providing a long-lasting time to relapse or a curative treatment. A novel approach to overcome the present challenges of medical attendance, as drug resistance, systemic side effects, and limited drug availability due to the blood-brain barrier, are localized drug delivery systems (DDSs), which are already used in clinical trials. Further development of this therapy regime may clearly improve patient's outcomes. In order to design compact, biocompatible, robust, and highly flexible systems which permit a prolonged drug release, a broad knowledge of the technical and medical field is required. Thus, this interdisciplinary article reviews different designs, testing, and validation models, and finally, clinical applications of localized DDSs, to utilize this available experience as a basis for the desperately needed reform of glioma treatment.

considered incurable due to the high invasiveness of the tumor cells and considerably drug resistance. Enhancements of therapy approaches are thus imperative. Currently, surgical resection precedes systemic therapy using temozolomide (TMZ), an alkylating chemotherapeutic agent, and local radiation. Nevertheless, the median survival of patients can only be extended from 9 months without any treatment attempts to 15 months.<sup>[1]</sup> Desired high local doses of the chemotherapeutic agents are afflicted with systemic side effects, which often necessitate to pause or even terminate the administration. Furthermore, resistance against currently applied chemotherapeutic agents, which seems to be associated with the, for example, so-called tumor stem cells, contributes to the failure of the treatment.<sup>[2]</sup> The application

## 1. Introduction

Highly malignant gliomas are the most frequently occurring primary brain tumors linked to a massive limited expectation of life. The most malignant glioma, the so-called glioblastoma (GBM), is characterized by a distinct intra- and intertumoral heterogeneity, which makes treatment especially difficult. Despite increasing knowledge at a molecular level, which allowed a subclassification of the heterogeneous GBM into different subtypes (classical, mesenchymal, and proneural), the disease is still

of novel auspicious drugs to overcome drug resistance is restricted by the blood-brain barrier (BBB). One possibility to overcome the poor bioavailability of drugs in the brain due to the inability of the drug to cross the BBB can be achieved by novel nanoparticle-based drug delivery approaches. These approaches take advantage of different physiological mechanisms underlying the BBB, for example, provoking a transient permeability of the BBB or increasing the interaction of nanoparticles with the endocytosis mechanisms by, for example, surface modifications.<sup>[3]</sup> Another promising approach to cope with the previously mentioned challenges is localized drug delivery systems (DDSs), which allow for a prolonged and continuous release of the drug. Additionally, the BBB can be bypassed by local implantation of the DDS into the brain.

The development of advanced fabrication techniques has led to different designs of DDSs such as microspheres and fibers as well as their assembly into 3D wafers, discs, and meshes.<sup>[4–6]</sup> Technical progress allows the development of increasingly smaller systems, adjusted to the particular anatomy, and consisting of different biocompatible materials. In addition, technical advances might permit a smart drug release of the systems, for example, leading to an automatically prompt liberation of the drug in case of the development of a tumor recurrence. The therapy could be hence applied in an early stage of the disease.

Due to the heterogeneity of GBM and its complex pathomechanisms and underlying physiology, valid in vitro and in vivo testing models are required not only to evaluate the general

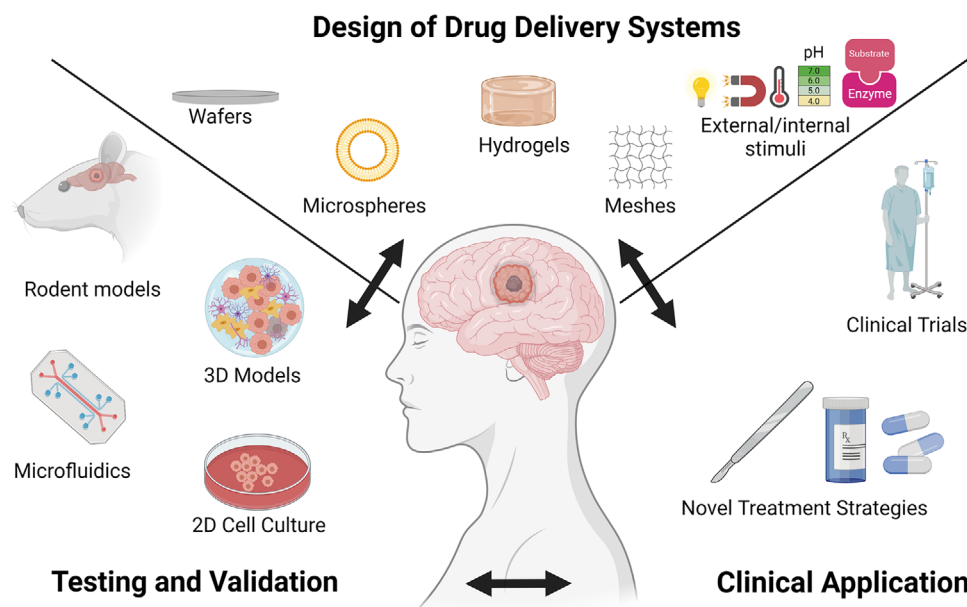
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**Figure 1.** Schematic illustration of the three main areas involved in the interdisciplinary development of localized DDSs for high-grade glioma therapy.

efficacy of local DDSs but to investigate important key elements like the therapeutic window of a locally applied drug and subsequent tailoring of the release kinetics of the DDSs. There is a wide range of in vitro models available ranging from 2D monolayer cell cultures to complex multicellular co-cultures grown in 3D or even the design of patient-specific models, which differ in complexity and functionality. Each of these models has its own advantages and disadvantages and the choice of model is thus largely depending on the field of application. Despite recent advancements in the development of more complex in vitro models, in vivo models are still an important tool to evaluate the efficacy of local DDSs, bridging the gap between in vitro testing and clinical trials. The main difference of the numerous rodent models available is given by the use of an immune-competent or immune-compromised model resulting in xenograft or allograft model as well as the growth of orthotopic or subcutaneous tumors. Thus, the use of in vivo models enables more specified testing and evaluation of local DDSs and allows for more accurate tailoring of, for example, release kinetics to in vivo conditions.

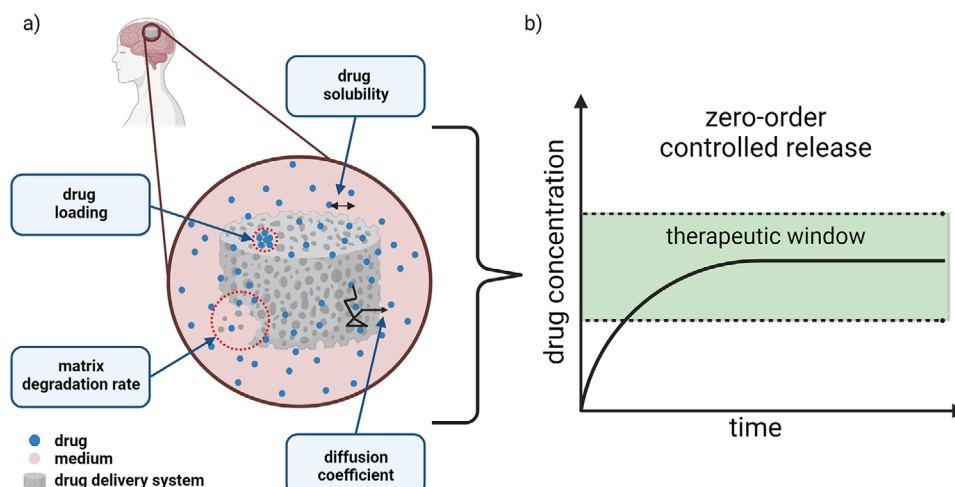
Nevertheless, so far only some of the developed and preclinical tested local DDSs have been already applied in clinical trials as the polymerically delivered carmustine (BCNU) wafers.<sup>[7]</sup>

This review article aims to provide a status quo of localized DDSs in glioma therapy including the present unique technical and biological system requirements. Through an interdisciplinary contemplation from a materials science, biochemical and medical point of view, we review different designs, testing, and validation models, and finally, clinical applications of localized DDSs (Figure 1). This provided interdisciplinary experience of previous studies shall yield a basis for the advancement of existing localized DDSs as a new product development. The evolution of such compact, biocompatible, robust, and highly flexible systems which permit a prolonged drug release might depict a breakthrough in glioma treatment.

## 2. Requirements for Implantable DDSs in High-Grade Glioma Therapy

High-grade gliomas are a highly complex type of brain tumor that pose extensive requirements for the development of appropriate implantable DDSs. First of all, the aim is to provide suitable drug release kinetics in combination with an effective drug to achieve a successful tumor treatment. Thus, applied systems should ideally exhibit a zero-order controlled release to maintain a constant drug concentration within the therapeutic window at the tumor site for an extended period of time.<sup>[8]</sup> Here, the drug release kinetics depend on various factors including drug loading and solubility, diffusion coefficient of the drug, and degradation rates of the matrix for biodegradable systems (Figure 2).<sup>[9]</sup> Further, the DDS should be biocompatible and not cause any damage to the brain tissue. This includes suitable mechanical properties to match the stiffness of the brain tissue and by this preventing a foreign body response.<sup>[10]</sup> Most commonly used polymers such as poly (lactide acid) (PLA), poly ( $\epsilon$ -carpolactone) (PCL), Alginate, and poly (lactic-co-glycolic acid) (PLGA) are FDA-approved and well known for their biocompatibility, non-toxic properties, and biodegradability.<sup>[11]</sup> However, implants may trigger a foreign body response, a protective mechanism aiming to isolate the unrecognized object from the surrounding tissues. This body reaction develops as a chronic inflammation and is characterized by three main stages, as extensively reviewed by Fayzullin et al.<sup>[12]</sup> The immunogenicity of especially long-lasting implantable and injectable materials represents a recognized problem that may have a significant impact on, that is, the drug release kinetics of the DDS or the interaction between the implant and the surrounding tissue and therefore influences treatment efficiency, safety, and clinical outcome.<sup>[12,13]</sup>

Since the treatment strategy involves the implantation of the DDS into the tumor cavity, it is advantageous if the DDS



**Figure 2.** a) Schematic illustration of the most important factors influencing the drug release kinetics. b) Ideal zero-order controlled release profile.

conformally adheres to the surface of the cavity, facilitating drug penetration into the brain tissue. In addition, biodegradable systems are favorable because further surgery to remove the DDS is avoided.

### 3. General Design of DDSs

In the last decades, multiple DDSs of various designs and shapes have been developed for the local therapy of gliomas. This includes system designs such as microspheres, nanoparticles, gels, fibers, meshes, and wafers.<sup>[5,14–18]</sup> In general, applied materials for DDSs are mostly biocompatible polymers and hydrogels,<sup>[9,19–21]</sup> whereby soft hydrogels offer an advantage over rigid polymer implants which usually reveal a mechanical mismatch with the brain tissue.<sup>[22]</sup> Depending on the material properties the drug release is either controlled by biodegradation of the matrix material or by diffusion if the material is non-biodegrading.<sup>[9,19]</sup> In the following paragraphs, we shortly explain different designs of implantable DDSs and highlight promising advances in the development of DDSs suitable for the treatment of GBM. **Table 1** summarizes the main types of DDS including the common materials, their fabrication methods, the typical advantages, limitations and challenges, and advances to overcome the latter.

#### 3.1. Wafers, Microspheres, (Nano-)Fibers, and Meshes

So far, the only US Food and Drug Administration (FDA)-approved and probably most prominent device for localized GBM therapy is the carmustine (bis-chloroethyl-nitrosourea (BCNU))-loaded polyanhydride wafer Gliadel which has been extensively researched and reviewed.<sup>[18,23,34–36]</sup> The FDA itself is responsible for protecting public health by ensuring the safety, efficacy, and security of for example human drugs and biological products. These wafers are prepared by compression molding of spray-dried microspheres consisting of a biodegradable polycarboxyphenoxyp propane and sebacic acid (PPCA-SA) copolymer and BCNU.<sup>[6]</sup> The drug is released upon biodegradation

of the polymer and in vivo most of the BCNU is released within less than one week.<sup>[23]</sup>

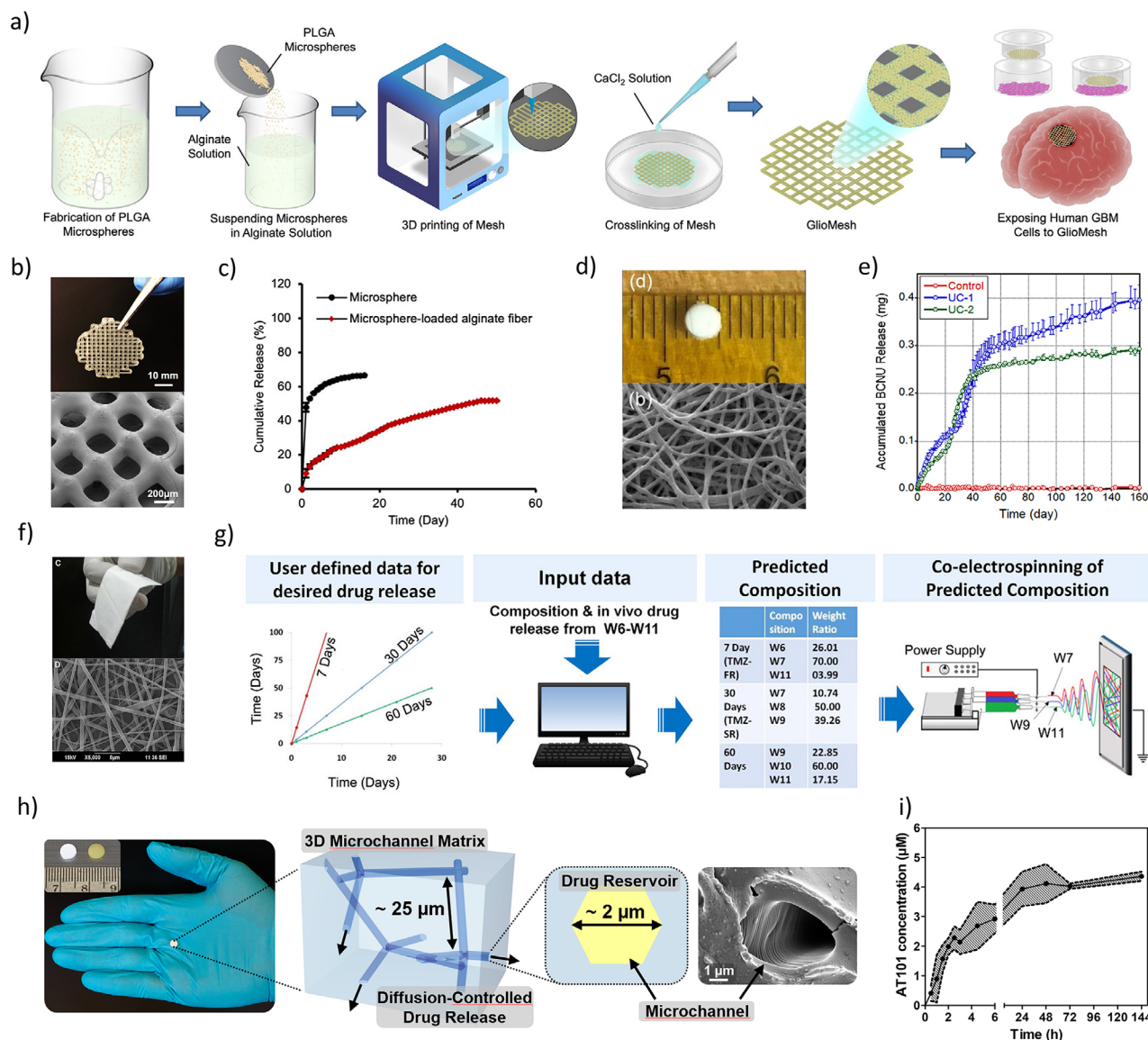
In order to increase the drug release time, different approaches have been researched. As for the Gliadel wafer, this also includes the further development of drug-encapsulated microspheres, which have been reviewed broadly.<sup>[14,21]</sup> Such microspheres often consist of biodegradable polymers such as polyesters, poly (ortho esters), polyanhydrides, polyphosphazenes, and polysaccharides.<sup>[21]</sup> Preparation techniques for microspheres include single and double emulsion methods, phase separation, spray drying, and in situ polymerization.<sup>[14,20,21]</sup> The drug release kinetics are controllable by adjusting the biodegradation kinetics of the matrix, physicochemical properties of the polymers and drugs, and the particle size.<sup>[20,21]</sup> This can be done by adapting the formulations and parameters during preparation,<sup>[14]</sup> and offers the possibility to adapt to the patient's needs. But enhancements are still necessary, for example, the fabrication techniques need to be improved to offer a sufficient control over the microsphere size distribution which is required for precise control over release rates.<sup>[20]</sup> Another challenge is to reach a reasonable drug loading efficacy during preparation usually limited by the drug properties, for example, the encapsulation of TMZ into poly(lactic-co-glycolic acid) (PLGA) nanoparticles is difficult by common oil-in-water (O/W) or water-in-oil-in-water (W/O/W) emulsion methods as TMZ is amphipathic.<sup>[37]</sup> This challenge has been, for example, addressed by Hosseinzadeh et al.<sup>[5]</sup> They developed a hydrogel-based 3D-printed mesh, called GlioMesh, containing TMZ-releasing PLGA microparticles: The researchers were able to increase the drug loading efficacy in the microparticles from <7% to about 61% by employing a novel approach of oil-in-oil (O/O) emulsion solvent evaporation. The prepared microparticles were suspended into an alginate solution which was finally printed into a mesh and crosslinked (**Figure 3a,b**). By embedding the PLGA microparticles into alginate fibers the initial burst effect was reduced and a sustained TMZ release over 7 weeks was achieved (**Figure 3c**).<sup>[5]</sup>

Besides microspheres also nanofibers have emerged as a versatile platform for advanced DDSs.<sup>[4,17,26,38,39]</sup> Chen et al. broadly review the applications of electrospun nanofibers in different areas

**Table 1.** Main types of implantable DDSs for high-grade glioma therapy.

DDS type	Materials	Fabrication method	Typical advantages	Typical limitations and challenges	Advances to overcome limitations and challenges	Ref.
Wafer (e.g., Gliadel™)	PPCA-SA	Compression molding of spray-dried microspheres	Only (FDA)-approved DDS for GBM treatment, biodegradable	Limited drug release times, burst release	Oil-in-oil emulsion solvent evaporation method for improved drug loading	[6, 23]
Microspheres	Mostly biodegradable polymers such as polyesters, poly(ortho esters), polyanhydrides, poly-phosphazenes, polysaccharides	Single and double emulsion methods, phase separation, spray drying, in situ polymerization	Biodegradable, release kinetics controllable by fabrication parameters, incorporation into other structures possible (e.g., wafers, meshes)	Limited drug loading efficacy, burst release, limited control over size distribution, and drug release rates	Improved drug loading efficacy and reduction of burst effect by embedment into alginate fibers	[5, 14, 20, 21, 24, 25]
(Nano-)fibers	Mostly biodegradable polymers such as polyesters and polyanhydrides	Electrospinning (depending on polymer and drug properties either blend, emulsion, or coaxial)	Biodegradable, release kinetics tailorable by fabrication parameters and resulting microstructures, assembly into other structures possible (e.g., meshes, discs)	Burst release and by this limited drug release times	Core-sheath fiber structure by coaxial electrospinning for reduced burst effect and prolonged drug release, combination of fibers with different release rates for improved control over drug release kinetics	[4, 17, 26]
Hydrogels	Natural or synthetic polymers crosslinked to form water-absorbing networks	Gelation by physical or chemical cross-linking	Stiffness matching brain tissue, conformality to tumor cavity, injectable	Limited loading of hydrophobic drugs	Nanoparticle-loaded hydrogels for delivery of lipophilic drugs	[19, 27]
Mesher, membranes, mats	Polymers, hydrogels	By assembly of building blocks, for example, microspheres and (nano-)fibers	Combination of different building blocks for improved drug release kinetics, stiffness matching brain tissue, conformality to tumor cavity	Depending on the individual building blocks	Improvement of the individual building blocks and their combinations	[4, 5, 17]
Stimuli-responsive DDS	Stimuli-responsive polymers, hydrogels, combination with nanomaterials (e.g., gold nanoparticles, graphene)	Strongly depending on design and materials	On-demand drug release, for example, in case of a tumor recurrence, possibility for cyclic drug release	Challenge to incorporate external or internal triggers	Wireless mild-thermic actuation by alternating radio frequency magnetic field, acid-sensitive drug release from Ace-DEX scaffolds	[28–33]





**Figure 3.** DDSs for the localized treatment of glioblastoma (GBM). a) Preparation of GlioMesh, containing TMZ releasing PLGA microparticles. b) Photograph and SEM image of GlioMesh. c) TMZ release from microsphere and microsphere-loaded alginate fiber. a–c) Adapted with permission.<sup>[5]</sup> Copyright 2019, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. d) Photograph and SEM image of NanoMesh consisting of multi-layered core-sheath fiber membranes releasing BCNU. Adapted under terms of the CC-BY 4.0 Creative Commons Attribution License.<sup>[4]</sup> Copyright 2019, The Authors, published by Springer Nature. The images are an excerpt of the original figure and have been recompiled. e) BCNU release from NanoMesh with 18 (UC-2) and 36 (UC-1) nanofiber membrane layers. Reproduced under terms of the CC-BY 4.0 Creative Commons Attribution License.<sup>[4]</sup> Copyright 2019, The Authors, published by Springer Nature. f) Photograph and SEM image of TMZ-releasing nanofiber implant. Adapted under terms of the CC-BY 4.0 Creative Commons Attribution License.<sup>[26]</sup> Copyright 2017, The Authors, published by Springer Nature. The images are an excerpt of the original figure and have been recompiled. g) Application scheme of nanofiber library for the preparation of nanofiber implants with suitable and individualized release kinetics. Adapted under terms of the CC-BY 4.0 Creative Commons Attribution License.<sup>[26]</sup> Copyright 2017, The Authors, published by Springer Nature. This section is an excerpt of the original figure. h) Structure of 3D macroscopic PDMS microchannel matrix. Reproduced with permission.<sup>[47]</sup> Copyright 2020, American Chemical Society. i) In vitro release of AT101 from PDMS microchannel matrix. Adapted with permission.<sup>[47]</sup> Copyright 2020, American Chemical Society.

of cancer research including drug delivery.<sup>[17]</sup> The drug-releasing nanofibers are prepared by electrospinning and assembled into mats, membranes, meshes, or 3D scaffolds. Electrospinning offers the possibility to tailor the release kinetics by adapting the polymer composition, fiber diameter, porosity, and morphology. Depending on the hydrophilicity or hydrophobicity of the

respective polymer and drug either blend, emulsion, or coaxial electrospinning are applied to incorporate the drug. Furthermore, the different techniques lead to distinct microstructures of the fibers which have a strong impact on the release kinetics—for example, blend electrospinning results in a homogeneous distribution of the drug and an initial burst effect, whereas coaxial

x electrospinning creates core-sheath structured fibers exhibiting a reduced burst effect.<sup>[17]</sup> The advantage of a core-sheath fiber structure has been demonstrated by Han et al., who developed an implantable disc (NanoMesh) consisting of multi-layered core-sheath fiber membranes (Figure 3d).<sup>[4]</sup> The BCNU-containing nanofibers were prepared by coaxial electrospinning. By this, fibers composed of a BCNU-incorporated polyanhydride poly(1,3-bis-(p-carboxyphenoxy) propane)-co-(sebacic acid) (pCPP-SA) core encapsulated by a hydrophobic poly( $\epsilon$ -caprolactone) (PCL) sheath were obtained. Han et al. showed that the hydrophobic sheath prevents a burst release, and a prolonged drug release of 160 days was achieved (Figure 3e).<sup>[4]</sup> The challenge of achieving suitable release kinetics has also been addressed by Ramachandran et al., who generated a nanofiber library that catalogs fibers from different PLGA-poly(lactic acid) (PLA)-PCL blends and their respective in vitro and in vivo release times of TMZ.<sup>[26]</sup> Based on this library, suitable blends with different release times were selected numerically to create one nano-implant exhibiting a constant release rate ranging from days to months (Figure 3f,g). By combining fibers with different release rates and enabling fiber-by-fiber switching it is possible to overcome abrupt degradation of bulk eroding polymers. Additionally, this procedure opens up the possibility of providing individualized drug release kinetics. Implants with a constant drug release for 7 or 30 days were fabricated by co-electrospinning of suitable polymer-drug blends and finally tested in vivo in an orthotopic C6 rat glioma model. Ramachandran et al. achieved a survival of more than three months for >85% of the TMZ-wafer implanted animals.<sup>[26]</sup>

### 3.2. Alternative Fabrication Techniques for DDSs

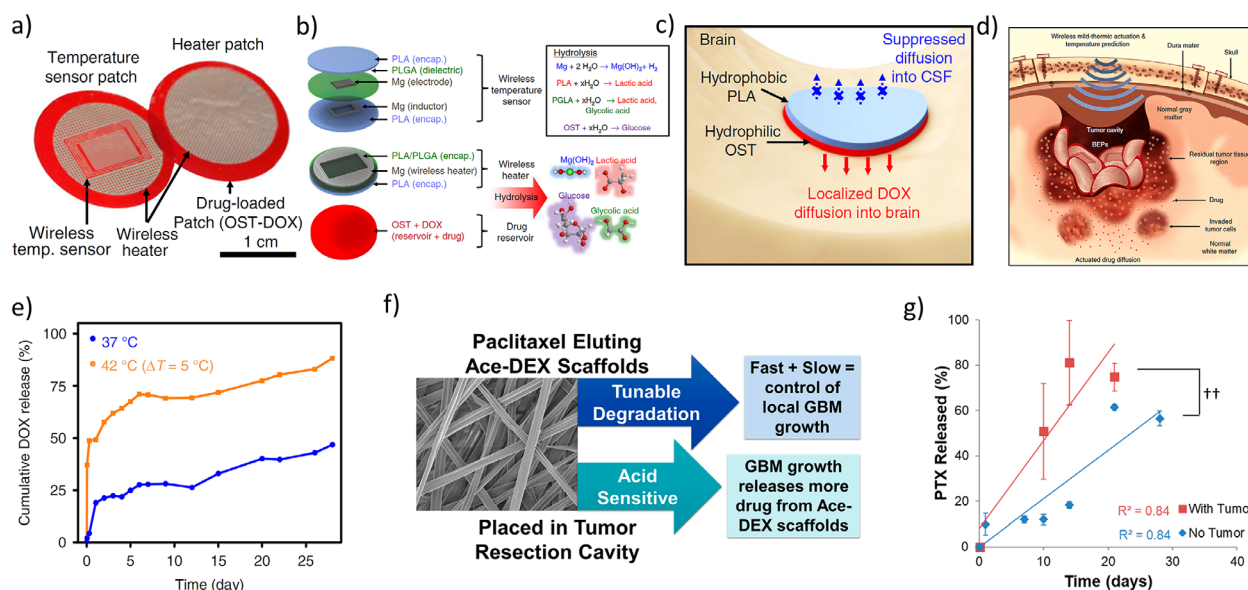
Nevertheless, the challenge of providing very defined release kinetics to ensure a constant drug concentration within the therapeutic window at the tumor site still remains. We are convinced that alternative fabrication techniques, for example, additive manufacturing, may offer the possibility to prepare implants with precisely controllable release kinetics. Especially 3D-printing appears promising to us as it facilitates a very accurate and reproducible preparation of complex designs.<sup>[40]</sup> Furthermore, this manufacturing process also makes it possible to create patient-specific implants with a shape matching the individual resection cavity of each patient.<sup>[41–43]</sup> For example, Yang et al. used MRI data to manufacture patient-specific DNA-nanocomplex-releasing implants suitable for localized GBM treatment.<sup>[42]</sup> So far, 3D printing has been established particularly for applications in the fields of dentistry and tissue engineering.<sup>[43–45]</sup> Nevertheless, there has also been research on 3D-printed DDSs such as tablets, transdermal microneedles, and implants.<sup>[41,46]</sup> However, there are still advancements needed as especially the speed of fabrication needs to be increased and the printability of suitable polymers needs to be ensured.<sup>[46]</sup> Approaches may include the opportunity to print devices with release-determining structures,<sup>[40]</sup> or to use the technique to incorporate other drug-releasing systems, such as micro- or nanoparticles, into a matrix and print the desired shape as demonstrated by Yang et al.<sup>[42]</sup> and Hosseinzadeh et al.<sup>[5]</sup> The first option has been shown by Son et al., who 3D-printed a needle-sized cylinder (Biocage) consisting of a drug

reservoir which is surrounded by a perforated shell surface with pores of 5  $\mu$ m diameter for drug release.<sup>[40]</sup> The Biocage was processed by using a two-photon polymerization 3D printer which is able to print structures on a millimeter-scale with micron-level precision. The materials used for the preparation of the Biocage are the photoresists IP-Dip and IP-S but Son et al. point out that the 3D-printing method may be adapted to other biocompatible and biodegrading materials.<sup>[40]</sup> Another alternative fabrication method was recently presented in our previous work, in which Rasch et al. prepared a 3D polydimethylsiloxane (PDMS) matrix containing a microchannel network for the treatment of GBM with the drug AT101 (Figure 3h).<sup>[47]</sup> A sacrificial t-ZnO template, consisting of interconnected ZnO tetrapods, was used to transfer the t-ZnO network structure to a PDMS matrix in the sense of a bottom-up fabrication method. The release kinetics of the prepared DDS are controllable by modifying its macroscopic size, the microchannel density, the fraction of drug-releasing microchannels, and the concentration of the inserted drug. The implants showed an in vitro release of AT101 for 10 days (Figure 3i).<sup>[47]</sup>

### 3.3. Stimuli-Responsive DDSs

Besides the advances of DDSs providing a constant release rate, there has been effort towards stimuli-responsive systems. These systems go one step further and offer the possibility of a triggerable drug release either by an external or internal stimulus. A DDS responding to an external stimulus makes it possible to control the drug release from outside, for example, by ultrasound irradiation, magnetic fields, or light. In contrast, internal stimuli are mostly based on changes in the microenvironment associated with a tumor recurrence. The resulting changes in, for example, the redox-potential or pH trigger a drug release.<sup>[30,31]</sup>

These triggerable DDSs are often based on stimuli-responsive materials, such as polymers and hydrogels, which can either be thermo-, redox-, pH-, electro- or magnetically responsive.<sup>[30,32]</sup> However, there is also research on incorporating nanomaterials into the polymer matrices such as gold nanoparticles or graphene.<sup>[31,33]</sup> The latter has been discussed extensively as a platform for different applications in GBM treatment by Afshar et al.<sup>[48]</sup> Graphene combines a high electrical and thermal conductivity as well as high mechanical strength which has been exploited by Servant et al., who prepared an electro-responsive graphene-hydrogel composite for a pulsatile drug release.<sup>[49]</sup> Ball-milled graphene sheets were dispersed into an electro-active (poly(methacrylic acid), PMAA) hydrogel matrix. The PMAA-based hydrogel exhibits an anisotropic deformation upon application of an electrical voltage due to different underlying electromechanical processes including migration of ions to the anode so that a drug release from the graphene-hydrogel composite can be turned on and off by switching on and off an electrical voltage. The drug release was studied in vitro with radiolabelled (14C)-sucrose and with radiolabelled (14C)-doxorubicin (DOX) as well as in vivo with radiolabelled (14C)-sucrose. It was shown that the incorporation of graphene enhances the response to the stimulation at lower voltages, reduces resistive heating of the device and surrounding tissue, and improves swelling and deswelling kinetics.<sup>[49]</sup> Triggerable DDSs have also been demonstrated for



**Figure 4.** Stimuli-responsive DDSs for the localized treatment of glioblastoma (GBM). a) Image of the bioresorbable electronic patch (BEP). b) Schematic illustration of the composition of the different BEP parts. c) Schematic illustration of the hydrophobic top side and the hydrophilic bottom side of the BEP. d) Schematic illustration of the drug release from the BEP by mild-thermic actuation. e) Release of DOX from OST at 37 and 42 °C. a–e) Adapted under terms of the CC-BY 4.0 Creative Commons Attribution License.<sup>[29]</sup> Copyright 2019, The Authors, published by Springer Nature. These sections are excerpts of the original figures and have been recomplied. f) Paclitaxel (PTX) eluting Ace-DEX scaffolds. Reproduced with permission.<sup>[28]</sup> Copyright 2020, American Chemical Society. g) In vivo release of PTX from Ace-PTX scaffolds in mice with and without tumor. Adapted with permission.<sup>[28]</sup> Copyright 2020, American Chemical Society.

the specific local treatment of GBM.<sup>[28,29]</sup> Lee et al. developed a wireless electronic patch for the controlled release of DOX and TMZ.<sup>[29]</sup> The completely bioresorbable and flexible patch consists of a drug-loaded oxidized starch (OST) film and magnesium-based films containing a heater and temperature sensor which make a mild-thermic actuation possible (Figure 4a,b). The hydrophilic and sticky bottom OST film ensures a conformal adhesion to the brain tissue when implanted into the tumor cavity. In contrast, the top side of the patch is coated with a hydrophobic PLA film preventing drug leakage to the cerebrospinal fluid (CSF) (Figure 4c). The actuation takes place wirelessly by an alternating radio frequency magnetic field which triggers the drug release as well as improves the intercellular drug diffusion and drug penetration depth (Figure 4d). The elevated temperature leads to an increased drug release (Figure 4e). In vivo studies demonstrated an improved survival rate for the treatment with the bioelectronic patch.<sup>[29]</sup> Graham-Gurysh et al. demonstrated an acid-sensitive drug release of paclitaxel from acetylated dextran (Ace-DEX) scaffolds for the treatment of GBM (Figure 4f).<sup>[28]</sup> They explored the effect of the drug release rate on the efficacy of the treatment and additionally, showed by in vitro and in vivo studies that the Ace-DEX scaffolds are responsive to the pH decrease associated with a GBM growth opening up possibilities for an on-demand drug release (Figure 4g).<sup>[28]</sup>

## 4. Models for Testing and Validation of DDSs

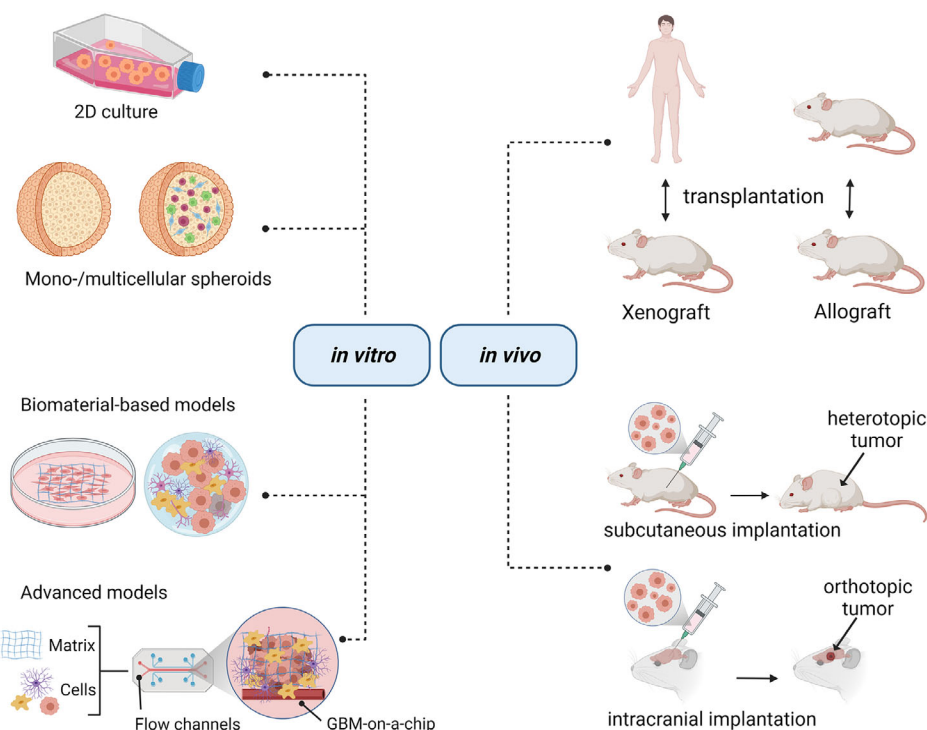
### 4.1. In Vitro Models

Until now, the major challenge in the development of new therapeutic strategies for high-grade glioma is to replicate the complex

structural organization of the brain in an in vitro setup. Different elements have been shown to play a major role in the study of DDSs: I) the type of tumor cells; II) the tumor microenvironment (e.g., tumor supporting cells, crosstalk); III) liquor flow, and IV) scaling. Therefore, in vitro models have been developed with the goal of I) using multiple cell types in a co-culture; II) switching from 2D models to 3D models; III) building patient-specific models (Figure 5). Cellular models play a significant role in all phases of drug development as well as to analyze DDSs and are the major tool used in target validation studies and high-throughput screenings in order to evaluate drug transport, metabolism, and toxicity. Over the last decades, advancement in tumor cell biology, 3D cell culture, tissue engineering, and biomaterials have enabled the rapid development of a wide range of in vitro tumor models.<sup>[50]</sup> The choice of model is usually dependent on the field of application due to differences in complexity and functionality. The next paragraphs will focus on the evaluation of existing and most popular in vitro tumor models regarding their suitability as testing platforms for DDSs, reviewing their advantages and disadvantages.

Cancer cell lines are the go-to model in the initial phase of studying the efficacy of a certain therapy strategy, since they are easy to grow and maintain, allow the direct comparison of experimental results, and are widely used to study molecular mechanisms of tumor cell biology.<sup>[51]</sup> Following the development of a certain DDS and the optimization of material-based properties, the first step comprises in vitro cytotoxicity or cell viability assays, which are mostly performed using 2D monolayer cell culture.<sup>[52]</sup> Various cytotoxicity studies analyzing drug delivery by, for example, microspheres or nanofibers showed that the drug released from such a delivery system induced enhanced cytotoxic effects





**Figure 5.** Schematic illustration of different in vitro and in vivo GBM models used for testing and validation of DDSs.

on cells compared to administration of the pure drug. Zhang et al. investigated the effects of TMZ/ PLGA/nano-hydroxyapatite microspheres on the behavior of C6 glioma cells.<sup>[53]</sup> It appeared that the cytotoxicity of TMZ to C6 glioma cell line was enhanced when TMZ was delivered from a PLGA carrier. Another approach analyzed paclitaxel-delivering PLGA microspheres entrapped in a gel matrix.<sup>[54]</sup> Although the PLGA-delivered drug was found to pose similar cytotoxicity as the systemically administered pure drug, cells treated with the loaded microspheres showed a low cellular recovery rate due to near-constant drug release. In contrast, the pure drug, which was cleared off after one day resulted in cellular recovery and reduced apoptosis after 6 days. These increased cytotoxic effects of drugs mediated by their carrier-based delivery were also observed in studies on nanofibers.<sup>[55,56]</sup> Guo et al. analyzed the antitumor activity of the curcumin-loaded poly( $\epsilon$ -caprolactone)-poly(ethylene glycol)-poly( $\epsilon$ -caprolactone) (PCL-PEG-PCL, PCEC) nanofibers against glioma 9L cells. The cytotoxic effect of the curcumin-loaded fibers was kept over the whole experiment process, while the antitumor activity of pure curcumin disappeared within 48 h. Despite the influence of material-based properties on the drug efficiency, various studies have shown that drugs do not work as effectively in vivo as in 2D monolayer cultures due to the 3D nature of a tumor. As an example, Horning et al. developed microparticles made from PLA polymer loaded with three anticancer drugs.<sup>[52]</sup> The analysis of these microparticles revealed that the IC50 values in a 3D model were 12- to 23-fold higher compared to the 2D model. Additional analysis indicated that the difference in the IC50 values did not seem to be dependent on the drug lipophilicity alone. Furthermore, in a solid tumor, not all the cells are exposed to the same concentration of drug because of poor drug

diffusion through the extracellular matrix (ECM) of the tumor and the lack of vasculature.<sup>[57]</sup> In another study of 3D tumor models for in vitro evaluation of anticancer drugs, researchers found that the antiproliferative effect of a drug in a 3D model was significantly lower than in a 2D monolayer, which was evident from differences in their IC50-values. They further found that the collagen content of the cells grown in 3D models was twofold higher than of the cells grown in 2D, suggesting increased synthesis of ECM in the 3D model, which might act as a barrier for drug diffusion.<sup>[52]</sup> These findings indicate that, besides the comparably easy setup and rapidity, 2D cell-based assays are of little value when it comes to predicting the clinical efficacy concerning both general cytotoxicity as well as molecular target specificity.<sup>[58]</sup> Thus, in the following paragraph some 3D cell culture models, which are useful to analyze DDSs, are highlighted more comprehensively.

Spheroids are aggregates of cells grown in suspension or embedded in a 3D matrix using 3D culture methods.<sup>[59–63]</sup> Spheroids can be used to recapitulate the basic 3D structure of tumors, including a multicellular structure, central necrosis, and proliferation gradients depending on the type of tumor. Thus, unlike classical monolayer-based models, spheroids mirror therapeutically relevant pathophysiological gradients of in vivo tumors.<sup>[61]</sup> Especially conditions like necrosis and regions of hypoxia present in many cancers have been identified as one cause of drug resistance and modeling those within spheroids allows for accurate testing of drug efficacy.<sup>[64]</sup> Furthermore, spheroids reflect cell-cell interactions comparable to those present in in vivo tissue. Although more expensive and time-consuming in comparison to 2D cell culture, cancer spheroids are widely used to study tumor response and sensitivity to chemotherapeutics, combinational



therapies (e.g., chemotherapy and small-molecule inhibitors), and DDSs.<sup>[65,66]</sup> It was found in various studies, that chemosensitivity differed between 2D monolayer cultures and the same cell line grown as multicellular spheroids.<sup>[65,67,68]</sup> Sarisozen et al. for example used cancer cell spheroids and in vivo tumor models to evaluate the co-delivery of paclitaxel and curcumin, which were co-loaded into the PEG-phosphatidyl ethanolamine (PE) based polymeric micelles.<sup>[66]</sup> The analyses in the in vivo model showed a good correlation with the 3D cell culture experiments, which suggests the spheroid model can be used as an intermediate model for the evaluation of the delivery of anticancer compounds. There are various types of spheroid-based glioma models known in literature like glioma spheroids, glioma tumoroids, or brain organoids, which can be cultured both free or matrix-supported.<sup>[69]</sup>

In addition, recent advantages on the fabrication of engineered, biomaterial-based models providing an ex vivo experimental platform have been made. The focus is thereby set on the creation of materials that promote cellular attachment, proliferation, migration, differentiation, long-term viability, and proper cell functioning, ideally in a controllable manner.<sup>[70]</sup> These materials can be constructed either 2D, that is, as surfaces with seeded cells on top, or as a 3D scaffold with controlled ingrowth and maturation of cells.<sup>[70]</sup> Thus, highly controllable microenvironments more accurately mimicking the in vivo 3D nature of tumors and physiological functions could be obtained, such as 3D cell cultures in hydrogel biomaterials,<sup>[71]</sup> and attached cultures on porous scaffolds,<sup>[72]</sup> which will in turn increase target validation and subsequent clinical efficacy of drugs in patients. An example of such a 3D-scaffold-based ex vivo model for GBM is the bioprinted, reconstituted GBM consisting of patient-derived tumor cells, vascular endothelial cells, and decellularized ECM from brain tissue in a compartmentalized cancer–stroma concentric structure developed by Yi et al.<sup>[73]</sup> It was shown that the GBM-on-a-chip model recapitulated the structural, biochemical, and biophysical properties of the native tumors and that it reproduced clinically observed patient-specific resistances to treatment with concurrent radiochemotherapy. Another study developed 3D-bioprinted mini-brains consisting of GBM cells and macrophages as a tool to test therapeutics that target the interaction between these two cell types.<sup>[74]</sup> Treatment of these mini-brains with carmustin showed a higher IC<sub>50</sub>-value in 3D cultures compared to 2D cultures, which might be related to the poor diffusion due to high cell-to-cell interactions. On the contrary, tumor cells isolated from co-cultured mini-brains showed significantly higher growth rates compared to the ones isolated from the monocultured mini-brains.

Furthermore, there have been various studies combining different culture methods to create a more complex in vivo mimicking in vitro system. Ma et al. for example integrated a multicellular spheroid matrix system into a microfluidic device to mirror culture parameters including a 3D solid tumor architecture, compounds of the ECM (collagen), and fluid shear conditions.<sup>[75]</sup> Fan et al. developed a 3D brain cancer chip composed of hydrogel for drug screening and utilized this chip for high-throughput GBM cancer spheroid formation, multiple simultaneous drug administration, and parallel testing of cellular drug response.<sup>[76]</sup> More complex in vitro models are additionally a powerful tool when studying the underlying mechanism of action of a certain

drug. As an example, Zhang et al. evaluated the effects of TMZ/PLGA/nano-hydroxyapatite microspheres on the behavior of U87 glioma cells focusing on the invasive behavior of glioma cells using a transwell assay.<sup>[77]</sup> Schmitt et al. established an in vitro GBM co-culture model mimicking the complete and incomplete GBM resection as a model for drug testing.<sup>[78]</sup> Here, different proportions of residual GBM cells and healthy brain cells (microglia and astrocytes) were used to define the microenvironment of the tumor cavity after GBM resection (complete or incomplete). The model was used to evaluate the efficiency of a two-drug treatment strategy applying TMZ in combination with AT101, which was found to induce strong cytotoxic effects in GBM primary cultures. Interestingly, Schmitt et al. found that the co-culture conditions protectively influenced the cell death and growth rates of primary GBM cells after the treatment in comparison to GBM cells cultured as mono-cultures.

In summary, there are various cultural methods available, each with individual advantages and disadvantages that every researcher needs to evaluate concerning the scientific problem. Not only the distinct culture approaches itself are continuously developed to bridge the gap between in vitro and in vivo conditions, but also the combination of various approaches could lead to powerful tools, especially when it comes to drug testing or the development of DDSs, with future application for patient-specific drug screening and individualized therapy. **Table 2** summarizes the advantages and limitations of the discussed in vitro models for testing and validation of DDSs.

#### 4.2. In Vivo Models of GBM—Preclinical Models

Rodent models offer an opportunity to develop and utilize a reproducible, spontaneously manipulated, and more accurate pre-clinical model of human cancers, enabling a more specified system to test promising therapies. Various murine models of GBM are known, but the extent to which they recapitulate the characteristics of human GBMs remains controversial. Genetically engineered, xenograft, allograft, viral-mediated, and chemically induced rodent models of GBM were extensively reviewed by Miyai et al.<sup>[79]</sup>

The preclinical work on the development of a local DDS comprises in vitro and in vivo analysis. Subsequently to the assessment of general cytotoxicity and pharmacokinetics using cell culture-based models, the DDSs are tested in an in vivo animal model. Thereby, subcutaneous xenografting (heterotopic) of human glioma cells in immunocompromised mice is a frequently used approach to obtain preclinical proof of concept for the efficacy of targeted drugs, although in recent years orthotopic (intracranial) xenograft models are increasingly used (Figure 5).<sup>[80]</sup> For both heterotopic and orthotopic studies, xenograft and allograft tumors are usually established from permanent human GBM lines.<sup>[79]</sup> Smith et al. for example investigated the in vivo efficiency of a drug-releasing PLGA/PEG paste for GBM therapy.<sup>[81]</sup> The paste was loaded with the chemotherapeutic agent etoposide and was placed into the cavity of a partially resected tumor in a flank murine GBM xenograft model. The results indicate efficient antitumor effects of the paste with no toxicity and the study will be continued in orthotopic GBM models. The advantage of xenografts or allografts grown

**Table 2.** In vitro models for testing and validation of DDSs.

Model		Advantages	Challenges and limitations	Ref.
2D culture	Cell lines	Easy to grow and maintain Low costs Reproducibility Suitable for high-throughput screening Commonly used for preliminary screening of drugs	Due to prolonged tissue cultures, the genetic and morphological characteristics do not accurately reflect those typically found in primary tumors Little value in predicting clinical efficacy Poorly mimic the solid tumor microenvironment	[51–54, 58]
	Primary cultures/ patient-derived tumorgrafts	Capture heterogeneity of cells in a tumor Potentially reflect tumor histomorphology and global gene expression profile	Time-consuming Tumor cell monolayers poorly mimic the solid tumor microenvironment	[50]
3D culture (free)	Spheroids	Reflect the basic 3D structure of the tumor (multicellular structure, central necrosis, and proliferation gradients) Mimic therapeutically relevant pathophysiological gradients Reflect cell–cell interactions Long-term culture	More expensive and time-consuming Not suitable for high-throughput screening Challenging to form and maintain spheroids of uniform size, with small number of cells, or making tissue-like multi-cellular spheroids	[50, 57, 58, 61, 64, 65, 67–69]
	3D culture (matrix-based)	Mimics the extracellular matrix (ECM) Materials can promote cellular attachment, proliferation, migration, differentiation, and long-term viability, ideally in controllable manner Can be tailored regarding material properties and microenvironmental parameters on GBM physiology	More expensive and time-consuming Not suitable for high-throughput screening	[50, 52, 62, 70–73]
Microfluidic systems		Construction of well-defined 3D tumor microenvironments, for example, solid tumor architecture, ECM components, and fluid shear conditions Multiple-simultaneous drug administration When using patient biopsy material: patient-specific drug screening and individualized therapy	Costly and time-consuming Experimental throughput is too low for simultaneous multi-parameter analysis	[50, 70, 73–76]

subcutaneously comprises the ability to follow the tumor development visually in terms of tumor size, which in turn allows for rapid testing of treatment efficacy. When testing a drug that is targeting the tumor-microenvironment interaction, it needs to be considered that the heterotopic xenografts in comparison to orthotopic xenografts are lacking an appropriate CNS microenvironment.<sup>[82]</sup>

Various in vivo studies were performed in order to test the in vivo efficacy of drug delivery by PLGA microspheres loaded with different drugs. As an example, Menei et al. investigated the effects of stereotactic implantation of 5-fluorouracil(5-FU)-loaded PLGA microspheres in C6 glioma-bearing rats.<sup>[83]</sup> 5-FU is a hydrophilic and antimetabolic drug that does not cross the BBB efficiently. Furthermore, it is a powerful radiosensitizer. The microspheres were found to enable a long, sustained release of 5-FU over 12 to 20 days and decreased to mortality of C6 tumor-bearing rats. A subsequent study on the therapeutic effectiveness of 5-FU-loaded microspheres for local GBM therapy performed in F98 glioma-bearing rats confirmed the improvement of median survival of rats treated with 5-FU-loaded microspheres in comparison to animals treated with 5-FU solution, suggesting the efficacy of a sustained drug release for local GBM therapy.<sup>[84]</sup>

In a different study, the in vivo fate and therapeutic efficiency of PLGA microspheres loaded with the anti-angiogenic C-terminal fragment of platelet factor 4 (PF-4/CTF) were evaluated in an orthotopic human GBM model in nude mice.<sup>[85]</sup> Previously to the intracranial injection of the microspheres, the group demonstrated that the growth of subcutaneous tumors was reduced by the local administration of anti-angiogenic agents. Following up on these promising results, the efficacy of this system and the therapeutic effects needed to be demonstrated in an in vivo orthotopic tumor model before the approach can be investigated in clinical trials, prospectively. After intracranial administration the microspheres were found to be located throughout the tumor bed and showed a continuous release of PF-4/CTF over 14 days, leading to a reduction of the tumor volume, decrease in angiogenesis, and an increase in apoptosis observed in treated animals. Zhang et al. used a C6 rat glioma model to study the efficacy of TMZ-loaded PLGA microparticles implanted directly into the tumor cavity after resection.<sup>[86]</sup> It was found, that the tumor volume of the microparticle-treated group reduced by 45.94% when compared with that of rats treated with the pure drug, indicating that TMZ-loaded PLGA-microparticles could inhibit tumor growth more effectively, which might be due to

a continuous release and subsequent gradual biodegradation of TMZ. In case of a nanofiber-mediated drug delivery, Tseng et al. implanted biodegradable 1,3-bis[2-chloroethyl]-1-nitroso-urea-, irinotecan-, and cisplatin-eluting poly[(d,l)-lactide-co-glycolide] (BIC/PLGA) on the brain surface of C6 glioma-bearing rats, which led to the reduced malignancy of C6 glioma.<sup>[87]</sup>

Another DDS that yielded promising results in both in vitro and in vivo studies are biodegradable BCNU-embedded wafers. Tamargo et al. performed the first in vivo study on BCNU-wafers for which rats were implanted with 9L gliosarcoma.<sup>[88]</sup> BCNU was incorporated into polymers adjacent to the 9L gliosarcoma. The controlled release and drug efficacy were assessed both in subcutaneous and intracranial models. Strikingly, the animals treated with local wafers showed a longer survival compared to those treated with systemic chemotherapy or distantly, that is, subcutaneously, implanted wafers. Zu et al. proposed a different approach of local delivery of BCNU.<sup>[89]</sup> In this study, BCNU-loaded PLGA microspheres were implanted into tumor-bearing C57BL/6 mice. It was shown that the implantation of the microspheres improved the survival of the mice and inhibited tumor proliferation, induced more cell apoptosis, and did not increase therapy resistance.

#### 4.3. From Preclinical Work to Clinical Trial

An evaluation of local DDSs makes it inevitable to contemplate the incorporated chemotherapeutic agents since the medication significantly determines the effects and side effects of the utilized system. Furthermore, it has to be considered that the clinical benefits and safety profile of local DDSs could differ in the primary versus the recurrent surgery setting since gliosis could prevent the diffusion of drugs into the brain parenchyma. Furthermore, the effects of prior therapy need to be evaluated in a relapse setting.

To date, only a few local drug-delivery systems have found their way into clinical trials. In general, clinical trials are classified into five phases, which have to be passed through in the process of therapy development to application. Phase 0 trials are only optional and the first-in-human trial performed in order to examine pharmacodynamics and pharmacokinetics in humans. In this phase, a small number of probands receive a single subtherapeutic dose of the drug studied. Obligatory phase I trials serve as a screening for treatment safety and include a small group of probands. Here, among others, safe dose ranges and side effects are determined. To establish the preliminary efficacy of a newly developed therapy in a "treatment group," usually against a placebo control group, the proximate phase II trial is performed. Subsequently, a phase III trial finally confirms the safety and efficiency of a new treatment in large groups of probands. The last phase IV trial takes place during the whole active medical use of the treatment and gathers data of safety and benefits.

The only DDS, which has passed the phase III trial so far, the 1 mm × 14 mm measuring biodegradable polymer releasing the chemotherapeutic agent carmustine, was developed in 1990 at the Johns Hopkins University School of Medicine. The chemotherapeutic agent carmustine, a highly lipid-soluble, non-ionized nitrosourea with good BBB penetration, was chosen since it was considered to be the most effective chemotherapy

against high-grade glioma at the time the first polymeric delivery system was developed.<sup>[7]</sup> To date, no other chemotherapeutic agent released from a polymer wafer has been examined in human clinical trials. However, other DDSs as microspheres, pellets, or polymeric depots have been investigated in clinical trials and will be discussed in the following paragraphs.

## 5. Clinical Trials

### 5.1. BCNU-Wafer

Depending on the size of the resection cavity up to 8 of the polyanhydride wafers are inserted after tumor resection or debulking. This DDS was initially designed to release carmustine for 2–3 weeks. Nevertheless, preclinical in vivo studies showed approximately 50% of the BCNU in the wafers to be released in 3 d, and over 95% after 6 d.<sup>[7]</sup> Besides avoidance of systemic toxicity, local chemotherapy can cover the critical time gap between surgical resection and initiation of cranial radiation.

The FDA approved BCNU-wafer for the treatment of recurrent high-grade glioma (WHO grade IV) in 1997 and of newly diagnosed high-grade glioma (WHO grade III, IV) in 2003. This approval is based on several studies in human high-grade gliomas.<sup>[6,35,90–94]</sup>

The first clinical phase I-II trial demonstrating the safety and efficacy of BCNU wafers was performed by Brem et al., who treated 21 patients suffering from recurrent malignant glioma with the wafers. No adverse reactions or systemic effects to the BCNU wafer treatment itself were observed.<sup>[6]</sup> The following trial combining the wafer implantation with postoperative standard radiation therapy in 22 patients with newly diagnosed malignant glioma did also not reveal an increase in neurotoxicity, systemic toxicity, or wound infections due to the wafer implantation. Nevertheless, an altogether higher rate of severe adverse events compared with earlier trials was found, which included seizures, intracranial hypertension, and neurologic decline in the postoperative period.<sup>[90]</sup> Furthermore, in both mentioned studies, efficacy was suggested in some patients.<sup>[6,90]</sup> Based on these encouraging results, a randomized, placebo-controlled (implantation of polymer wafers with versus without carmustine), prospective phase III study to evaluate the effectiveness of BCNU wafers to treat recurrent malignant gliomas in 222 patients was carried out. The median survival was shown to be significantly increased in patients receiving the drug-loaded wafer. Likewise, no clinically important adverse reactions related to the carmustine polymer, either in the brain or systemically were noted.<sup>[91]</sup> Another significant phase III study evaluating the effect of the locally applied BCNU wafer in 32 patients with newly diagnosed malignant gliomas in a prospective, randomized double-blind design of an active treatment group versus a placebo group was performed by Valtonen et al., which also found a favorable effect on the life span due to the localized therapy.<sup>[92]</sup> Since Valtonen et al. only recruited a small number of patients, a larger phase III trial with 240 patients with newly diagnosed high-grade glioma was carried out. In this double-blind, randomized, and prospective study BCNU wafer implantation was also compared with placebo wafers implantation, both followed by external radiotherapy. Despite benefits concerning the median survival, increased adverse effects like CSF leak and intracranial hypertension were observed

in the treatment group.<sup>[35]</sup> A long-term follow-up of the patients demonstrated a survival advantage even after 2 and 3 years compared with placebo.<sup>[93]</sup>

To further evaluate adverse effects of BCNU wafers Attenello et al. published a 10-year (1996–2006) institutional experience with implantation of BCNU wafer at Johns Hopkins University School of Medicine. Including 1013 patients, the use of BCNU wafer was not associated with an increase in perioperative morbidity.<sup>[95]</sup> Nevertheless, clinical case reports described profound complications as cerebral edema,<sup>[96]</sup> a higher incidence of infection,<sup>[97]</sup> and the development of a severe hydrocephalus leading to death after the lateral ventricles had been opened and fibrin glue-secured BCNU wafer were implanted.<sup>[98]</sup> In addition, a retrospective cohort study of 260 patients who underwent fluorescent supported resection of high-grade glioma did not show a significant survival benefit of insertion of BCNU wafers over resection alone and also revealed a trend to a higher incidence of wound infection in those who received the wafers.<sup>[99]</sup>

Although BCNU wafer remains a safer and more effective strategy than intravenous administration of carmustine, local side effects, drug resistance, poor drug penetration in brain tissue, rapid drug release, implant dislodgement, and the invasive nature of the procedure label this system as non-ideal for GBM therapy.<sup>[100]</sup>

## 5.2. 5-Fluorouracil-Releasing Microspheres

Another local biodegradable polymeric technology that has been used in clinical trials is PLGA microspheres. Their mean size of 45  $\mu\text{m}$  even allows a less invasive stereotaxic administration. Among different drugs encapsulated, 5-FU revealed the most promising results in preclinical studies of the implant, hence, it was used in further clinical trials. Based on preclinical results, a Phase I pilot study including 8 patients with newly diagnosed GBMs was carried out. After resection, microspheres were implanted all around the walls of the surgical resection cavity, inheriting increasing doses of 5-FU. Since dose-escalation led to brain swelling this scheme was stopped. Besides this, no abnormal wound healing, infection, or systemic side effects were observed. Sustained concentrations of 5-FU were found in the CSF and were still present 1 month after microsphere implantation.<sup>[24]</sup> Stereotactic implantation of the 5-FU releasing microspheres was furthermore performed in the setting of newly diagnosed, inoperable, malignant gliomas in 10 patients (phase I trial), where it was well tolerated.<sup>[25]</sup> In the largest phase II trial of Menei et al., 77 participants with newly diagnosed high-grade glioma were randomized to perioperative stereotaxic injections of 5-FU-releasing microspheres into the walls of the resection cavity followed by early radiotherapy. Altogether there was no significant difference in median overall survival between the treatment arms, although the trend favored PLGA microspheres.<sup>[101]</sup> To date, the concept of 5-FU-releasing microspheres in glioma therapy has since not been pursued in clinical studies.

Another clinical phase I trial (NCT02433392) using biodegradable hydrogel microspheres as a DDS for the chemotherapeutic agent irinotecan hydrochloride in recurrent GBM was terminated due to recruitment problems. The results are not publicly available.

## 5.3. Bucladesine-Loaded Pellets

In a randomized prospective study by Dalbasti et al. including 40 patients, bucladesine-loaded biodegradable polymeric sustained release (bcl-SR) pellets were placed in the tumor resection cavity at the time of recurrence of GBM. The used polymer, poly-dl-lactide-co-glycolide, which has a molecular weight of 80000, showed a drug release of approximately 4–5 months. A statistically significant delay of recurrence was observed due to the localized therapy approach. Furthermore, no bone marrow suppression nor bucladesine-loaded polymer-associated wound infections occurred. Altogether, the best treatment results were obtained from the local bcl-SR administration in combination with systemic fotemustine, a cytostatic drug.<sup>[102]</sup> Certainly also due to these results, subsequent studies rather focused on systemic fotemustine—continuative studies using bucladesine-loaded pellets have not been performed yet.<sup>[103,104]</sup>

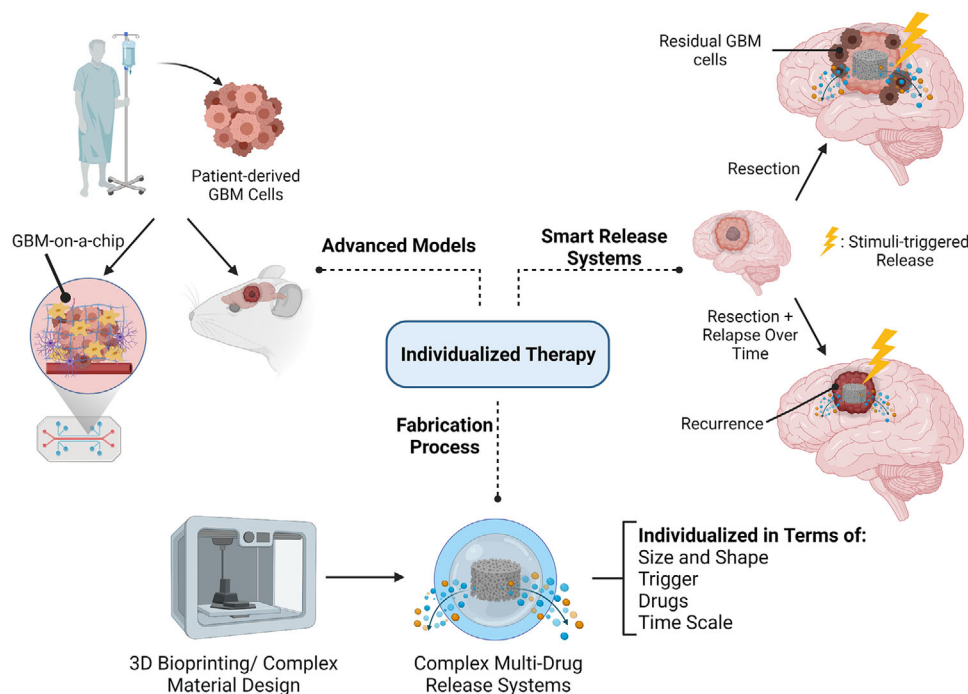
## 5.4. Cisplatin-Incorporated 6-Carboxycellulose Polymer Depots

In a study by Sheleg et al. the administration of local chemotherapy with biodegradable 6-carboxycellulose polymer incorporating cisplatin was examined. After subtotal removal of the tumor, 20 1.5  $\times$  1.5 cm polymer plates were implanted into the tumor bed of 17 patients with newly diagnosed GBM. The control group (21 patients), only receiving subtotal tumor ablation, and the treatment group underwent cranial irradiation at 2 or 3 weeks after resection. A statistically increased median survival for patients of the treatment group was observed.<sup>[105]</sup> Furthermore, no side effects of the surgery like brain edema or seizures, or systemic toxic effects were observed. Despite the encouraging results, no more clinical studies using 6-carboxycellulose polymer depots in glioma therapy took place to date.

## 6. Conclusion

Localized DDSs depict a promising therapy strategy, preventing systemic side effects and generating high local doses of chemotherapeutic agents. These biocompatible and flexible DDSs providing suitable release kinetics facilitate the effective therapy of gliomas. Simultaneously, recent advances in the development of a variety of in vitro and in vivo GBM models have made a valuable contribution to detailed testing and validation of newly developed DDSs. On this basis, the future research towards an individualized therapy could significantly contribute to a successful treatment. This includes the design of smart drug release systems and the further development of advanced testing models and fabrication methods (Figure 6). Especially, the control of the drug release by external or internal stimuli will offer an optimized therapy. In this context, a tumor recurrence itself could trigger the local release of the chemotherapeutic agent even before clinical symptoms or conspicuous features in the imaging techniques occur. Hence, smart DDSs might also contribute to an early diagnosis of relapse and detection of local complications at the earliest possible. For this purpose, advanced fabrication processes are indispensable. In particular, 3D bioprinting approaches offer the possibility to produce highly individualized





**Figure 6.** Future directions in high-grade glioma therapy towards an individualized therapy.

DDSs in terms of shape, flexibility, and release kinetics. This also includes the rapid creation of complex multi-gel and multi-drug constructs facilitating the design of patient-specific implants. In order to develop highly efficient and individualized local DDSs, it has become abundantly clear that interdisciplinarity is the key to success.

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## Conflict of Interest

The authors declare no conflict of interest.

## Author Contributions

J.H.F., F.S., R.A., and M.S.Y. conceived and designed the review. M.H., D.H., and C.K. wrote the paper, and all authors revised the manuscript.

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