Asian Journal of Pharmaceutical Sciences 20 (2025) 101034

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Perspective

Implantable devices for resected glioblastoma therapy

Xiaoyu Chang[a,b], *Hui Guo*[b], *Yunqian Li*[a,*], *Jianxun Ding*[b,c,**]

[a] *Department of Neurosurgery, the First Hospital of Jilin University, Changchun 130061, China*
[b] *Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China*
[c] *School of Applied Chemistry and Engineering, University of Science and Technology of China, Hefei 230026, China*

ARTICLE INFO

Article history:
Received 13 June 2024
Revised 30 November 2024
Accepted 26 December 2024
Available online 8 February 2025

Keywords:
Biomaterial
Implantable device
Inhibition of recurrence
Prolongation of survival
Resected glioblastoma therapy

ABSTRACT

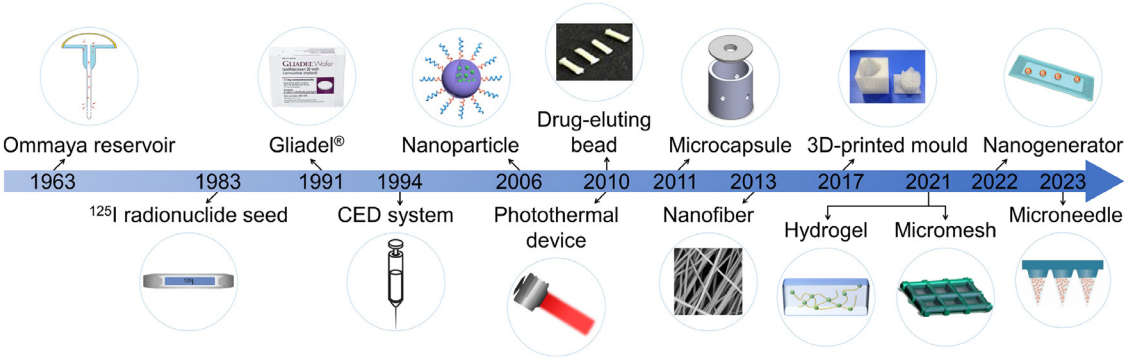
Glioblastoma (GBM) is a highly infiltrative brain tumor. The treatment of GBM is challenging due to the existence of blood brain barrier, its highly invasive nature, and its heterogeneity. Given the limitations of conventional therapies, this Perspective explores the development trajectory of implantable devices, highlighting the advantages of current models. With the progression in research, these implantable devices certainly hold promising potential for GBM therapy.

© 2025 Shenyang Pharmaceutical University. Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

Glioblastoma (GBM) is a highly diffuse and infiltrative brain tumor. The annual incidence of primary malignant brain tumors is approximately 7 per 100,000 individuals, with GBM accounting for about 49% of these cases [1]. The highly invasive nature of GBM leads to a high rate of postoperative recurrence, resulting in an overall survival rate of only two years. The standard clinical treatment for GBM is the surgical resection combined with the synergistic chemoradiotherapy. However, the efficacy of GBM treatment is challenged by the following four issues: (1) the intricate anatomical location of tumor limits the precision of neurosurgical excision; (2) the invasiveness into the healthy brain tissue and high heterogeneity lead to the resistance against traditional therapies; (3) the pathologically abnormal tumor microenvironments reduce the efficacy of various innovative treatments; and (4) the blood–brain barrier (BBB) hinders the intratumoral accumulation of bioactive agents [2]. Implantable devices have been developed as a more clinically applicable solution by enabling the local long-term delivery of active agents directly within the tumor resection

* Corresponding author.
** Corresponding author at: Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China.
E-mail addresses: yunqian@jlu.edu.cn (Y. Li), jxding@ciac.ac.cn (J. Ding).
Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2025.101034
1818-0876/© 2025 Shenyang Pharmaceutical University. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)



Scheme 1 – Historical development timeline of implantable devices for resected GBM therapy.

cavity, thereby bypassing the challenges posed by the specific pathological features of GBM [3]. Advances in materials and technology have progressively enhanced the variety and efficacy of implantable devices for GBM therapy (Scheme 1 and Supplementary Tables S1 and S2).

Gliadel®, initially reported in 1991 as a carmustine implant, was approved for market in 1996 as a chemotherapeutic formulation with an excipient of 1,3-bis(p-carboxyphenoxy) propane–sebacic acid poly(anhydride) copolymer for the treatment of brain tumors, particularly GBM. Gliadel® is a biodegradable wafer implanted directly into the GBM resection cavity, designed to release carmustine over 3 weeks continuously. During surgery, up to eight wafers can be placed within the resection cavity to bypass the BBB and maintain a high local drug concentration [4]. Patients treated with Gliadel® experienced lower systemic toxicity and more prolonged overall survival than those receiving placebo wafers. However, due to its rigid composition, Gliadel® does not conform well to the postoperative anatomical cavity, potentially leading to severe complications, such as cerebral edema, meningitis, cerebrospinal fluid leakage, intracranial hypertension, and epileptic seizures. The displacement of Gliadel® wafers also causes brain scarring and inflammation. If the wafers obstruct the ventricular system, obstructive hydrocephalus may occur. Moreover, a small resection cavity limits the quantity of Gliadel®, preventing the accumulation of an effective drug concentration. As a result, the use of Gliadel® has been progressively abandoned in clinical practice. Similarly, other products entering clinical trials, such as OncoGel™ and CuboSphere™, were terminated due to a lack of improvement in overall survival or insufficient recruitment of volunteers.

To overcome the drawbacks of Gliadel® and other implantable products, the next generation of implantable devices has focused on applying advanced biomaterials and microfabrication techniques. These biomaterials offer an excellent capacity for sustained drug release and superior biocompatibility, biodegradability, and mechanical stability. In GBM therapy, implantable biomaterials can be designed to encapsulate various therapeutic agents, particularly those that face challenges in crossing the BBB, including chemotherapy drugs, proteins, peptides, nucleic acids, immunotherapy agents, and so forth, based on distinct treatment requirements, as listed in Supplementary Table S1. The smart biomaterials-based implantable devices achieve stimuli-responsiveness and targeting capabilities by incorporating various components. The microfabrication techniques enable the direct production of various micron-sized implantable devices with superior precision, excellent controllability, and on-demand configuration capabilities, making them an ideal choice for orthotopic GBM therapy. For example, implantable pumps sustain real-time drug delivery within the postoperative cavity through convection-enhanced delivery.

The implantable device facilitates the delivery of drugs with shorter half-lives, such as proteins, peptides, and nucleic acids, significantly broadening the range of available treatment options. Microchips utilize an array of reservoirs to load various drugs and employ a pump to modulate the release curve of distinct medications. Those equipped with penetrating microelectrode arrays ascertain drug release conditions by recording neural signals in the brain. Microcapsules encapsulate drugs directly and regulate their release rates by adjusting the dimensions of release orifices. Additionally, the binding mode—whether physical or chemical—between the microcapsules and drugs further affects the release rate and control of drug delivery. Furthermore, various combinations of microcapsules adjust the release of distinct drugs at different stages of disease progression, reducing dosing frequency. Microneedles adhere closely to the postoperative glioma cavity, preventing the rebound effect of implants on the brain tissue and substantially enhancing drug concentration near the wound, facilitating the elimination of residual glioma cells. The comparison of advantages and limitations of various implantable devices are discussed in Supplementary materials and shown in Supplementary Table S2.

The advanced biomaterials-based implantable devices for postoperative GBM therapy offer unique advantages but pose challenges in the clinical applications. These challenges may stem from a lack of comprehensive consideration of the physical, chemical, and biological properties of the implants during their design. (1) The stiffness of implantable biomaterials influences the behaviors of glioma cells. Recent studies have indicated that when

the implantable devices are stiffer than normal brain tissue, this enhances the proliferative and migratory capabilities of glioma cells [5]. Conversely, softer devices failed to provide sufficient adhesiveness, resulting in a lack of tumor-targeted drug accumulation. (2) Non-injection and non-deformable biomaterials may induce inflammation and brain scarring due to the physical damage incurred during the implantable operation and device dislodgement. Insufficient adhesive properties also result in drugs being unable to penetrate to the expected depth, as glioma cells tend to infiltrate into normal brain tissue up to 2–3 cm. (3) The long-term presence or non-degradability of materials also leads to neuronal death and loss of brain function. For biodegradable biomaterials, the accurate characterizations of the behavior of various biomaterials *in vivo* are crucial for controlling degradation rates, ensuring therapeutic efficacy, and minimizing inflammatory responses during the breakdown process. (4) Most materials cannot regulate the immune microenvironments in GBM. Within glioma masses, 70% comprise non-functional macrophages and microglial cells, severely impeding the effectiveness of drugs. Hence, activating the dynamic balance of immune microenvironments may be crucial in preventing recurrence. Subsequent designs of implantable devices for glioma must consider the abovementioned parameters to enhance the therapeutic efficacy.

Innovative implantable devices have been explored for the treatment of GBM. For example, a self-powered and wirelessly controlled gas therapy device was developed to deliver nitric oxide and inhibit GBM growth and recurrence. In addition, a near-infrared activatable up-conversion nanoparticle implant enhanced the efficacy of photodynamic therapy. The role of implantable devices extended beyond direct therapeutic purposes in GBM. Using implantable ultrasound devices to control the opening of BBB represents a unique drug delivery strategy [6]. In brain capillaries, microbubbles oscillate in response to ultrasound stimulation, generating mechanical stress on the endothelial wall that facilitates BBB opening. Furthermore, implantable devices encapsulating contrast agents and chemotherapeutic drugs enabled real-time monitoring of therapeutic effectiveness. Guided by these principles, implantable devices are expected to emerge as promising weapons in treating GBM.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (U23A20591 and 52273158). The figures and tables with “S” before the serial number are included in the Supplementary material.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2025.101034.

References

[1] Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain malignancies in adults: A review. JAMA 2023;329(7):574–87.
[2] Bastiancich C, Malfanti A, Préat V, Rahman R. Rationally designed drug delivery systems for the local treatment of resected glioblastoma. Adv Drug Deliv Rev 2021;177:113951.
[3] Padmakumar S, Amiji MM. Long-acting therapeutic delivery systems for the treatment of gliomas. Adv Drug Deliv Rev 2023;197:114853.
[4] Lillehei KO, Kalkanis SN, Liau LM, Mydland DE, Olson J, Paleologos NA, et al. Rationale and design of the 500-patient, 3-year, and prospective Vigilant ObservatIon of GlIadeL WAfer ImplaNT registry. CNS Oncol 2018;7(2):CNS08.
[5] Miroshnikova YA, Mouw JK, Barnes JM, Pickup MW, Lakins Johnathan N, Kim Y, et al. Tissue mechanics promote IDH1-dependent HIF1α–tenascin C feedback to regulate glioblastoma aggression. Nat Cell Biol 2016;18(12):1336–45.
[6] Sonabend AM, Gould A, Amidei C, Ward R, Schmidt KA, Zhang DY, et al. Repeated blood-brain barrier opening with an implantable ultrasound device for delivery of albumin-bound paclitaxel in patients with recurrent glioblastoma: A phase 1 trial. Lancet Oncol 2023;24(5):509–22.