Review

Advances in Hydrogels of Drug Delivery Systems for Local Treatment of Brain Tumors

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Advances in Hydrogels of Drug Delivery Systems for Local Treatment of Brain Tumors

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Abstract: The management of brain tumors presents numerous challenges, despite the employment of multimodal therapies including surgical intervention, radiotherapy, chemotherapy, and immunotherapy. Owing to the distinct location of brain tumors and the presence of the blood-brain barrier (BBB), these tumors exhibit considerable heterogeneity and invasiveness at a histological level. Recent advancements in hydrogel research for the local treatment of brain tumors have sought to overcome the primary challenge of delivering therapeutics past the BBB, thereby ensuring efficient accumulation within brain tumor tissues. This article elaborates on various hydrogel-based delivery vectors, examining their efficacy in the local treatment of brain tumors. Additionally, it reviews the fundamental principles involved in designing intelligent hydrogels that can circumvent the BBB and penetrate larger tumor areas, thereby facilitating precise, controlled drug release. Hydrogel-based drug delivery systems (DDSs) are posited to offer a groundbreaking approach in addressing the challenges and limitations inherent in traditional oncological therapies, which are significantly impeded by the unique structural and pathological characteristics of brain tumors.

Keywords: hydrogel; smart hydrogel; brain tumor; drug delivery systems; local treatment

1. Introduction

The Malignant brain tumors, including prevalent types such as glioblastoma, are histologically diverse and aggressively invasive neoplasms, leading to high morbidity rates [1]. Glioblastoma is categorized as a grade IV glioma according to World Health Organization (WHO) guidelines, with over two-thirds of primary brain tumors being aggressive in nature [2,3]. The prognosis for patients diagnosed with glioblastoma is dire, with median survival times of less than one year in half of the cases [4]. The treatment of brain tumors is particularly challenging due to their unique location and the constraints imposed by the BBB [5–7]. Recent research has identified hydrogels as promising therapeutic strategies and drug delivery systems (DDSs) for the local treatment of brain tumors [8]. As reservoirs for local drug administration, hydrogels can encapsulate therapeutic agents, facilitating sustained and targeted drug release to the tumor site [9,10].

As a reservoir for local delivery, hydrogels can be loaded with drugs or other therapeutic agents and slowly release these drugs over time to allow tumor targeting [11–13]. Hydrogels are highly biocompatible materials that will enable topical delivery of stimulus-responsive therapeutic agents with systemic effects [14–17]. Researchers are constantly exploring novel hydrogels with unique properties and exploring new applications. This paper summarizes the application of hydrogels in drug delivery systems and intelligent drug release control as shown in Figure 1. [18–21]. This article mainly summarizes the different drug delivery systems of hydrogels in the treatment of brain tumors, such as injection, spray, and implantation. At the same time, this paper also summarizes the specific applications of smart hydrogels in the treatment of brain tumors, such as temperature and pH responsive hydrogels, photoresponsive hydrogels and magnetic responsive hydrogels. Due to the

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rich water content and soft texture of brain tissue, hydrogel has good biocompatibility and more suitable for the special environment of the brain [15]. The human body is primarily composed of hydrogels and skeleton, which is an essential reason why hydrogels are widely used in biomedical fields. Therefore, the hydrogel-based drug delivery system is anticipated to provide novel therapeutic strategies to address the constraints of brain tumors with unique physiological and pathological structures [22].

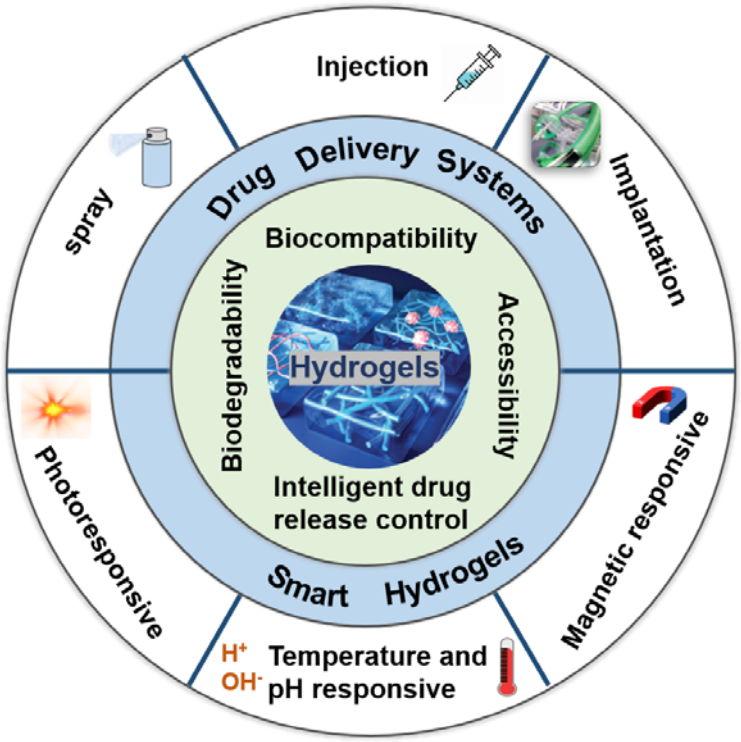

Figure 1. Hydrogels recently developed in drug delivery systems and intelligent drug release control for the treatment of brain tumors.

2. Different DDSs for Local Treatment of Brain Tumors

Researchers have made significant advancements in developing hydrogels capable of efficiently encapsulating anti-tumor drugs and releasing them in a controlled manner [23,24]. For brain tumors, hydrogels are specifically designed as precise DDSs that bypass the BBB, directly targeting the lesion and reducing systemic side effects [25–28]. The incorporation of nanoparticles within the hydrogel matrix enables targeted drug delivery. This method permits the direct injection of the hydrogel into the tumor cavity or resection site, ensuring effective delivery of therapeutic agents to tumor cells [3,29]. This paper summarizes the use of hydrogels in the treatment of brain tumors, categorizing them by delivery method, gelator material, and delivery characteristics, as detailed in Table 1. It is evident from the table that the predominant treatment methods for brain tumors involve injections, with some emerging techniques using sprays and implantations [30,31].

Table 1. Methods of hydrogels for delivery of brain tumors.

Drug delivery way	Hydrogel material	Feature	Application
Injection	Composite nanohydrogels containing drug-loaded micelles and wFIONs	Injectable heat-responsive system	Operative brain tumor therapy using injectable hydrogel nanocomposites

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	Poly (ethylene glycol)-based hydrogel crosslinked by thiol-Michael addition reaction	Chemical and physical modalities were synergistically employed for therapeutic intervention	Injectable sulfhydryl Michael addition hydrogel for glioblastoma therapy
	The gelato consists of 9-fluorenylmethoxycarbonyl Phe and Phe-Phe-dihydroxyphenylalanine	Benign biodegradability and drug release properties	Tumor-killing immunity is stimulated after surgical resection of GBM to reduce its recurrence
Spray	Pectin with nanocrystals coated with polylactic acid and polyethylene glycol (NCPPs)-loaded etoposide and olaparib	Drugs are delivered using a spray device	Bioadhesive spray hydrogels containing etoposide and olaparib polymer-coated nanoparticles
Implantation	Temozolomide+Erastin@liposome-cyclic RGD +gelatin methacrylamide	The orthotopic implantation procedure elicits ferroptosis and impedes tumor recurrence	The platform of implantable hydrogels inhibits the recurrence of GBM by inducing ferroptosis

2.1. Injectable Hydrogels

The notable research outlined in the literature demonstrates that Kang et al. developed an injectable, thermally responsive hydrogel nanocomposite for the treatment of glioblastoma multiforme Figure 2(a) [32]. Following surgical intervention, the injection of this hydrogel nanocomposite into the excised tumor site enables it to transition rapidly from a liquid to a gel state at body temperature [33]. This nanocomposite is not only responsive to thermal changes but also functions as a soft, deep intracortical reservoir for drug delivery, thereby facilitating the elimination of tumor cells post-operatively [34–36].

Moreover, the surgical excision of a tumor allows for the collection of residual GBM cells by injecting biomaterials into the resection cavity [37,38]. Khan and his colleagues developed an injectable hydrogel based on polyethylene glycol and conducted studies on hydrogels with varied physical and chemical properties by manipulating parameters such as hydration level and concentration of $NaHCO_3$ in aqueous solution Figure 2(b) [39]. This formulation exhibits minimal and slow swelling over time, potentially reducing damage to healthy neurons post-implantation into the resection cavity. It maintains stability for up to two weeks and is both biocompatible with brain tissue and biodegradable.

In addition to acting as deep drug reservoirs, hydrogels can also stimulate anti-tumor immunity post-GBM resection, reducing recurrence [40–42]. Zhang and colleagues introduced an injectable hydrogel system containing a tumor-specific immune nanomodulator, which fosters sustained T-cell infiltration Figure 2(c) [43]. When administered into the cavity of a surgically removed tumor, this hydrogel system replicates the immune ecological niche of a "hot tumor," targeting any residual tumor cells and effectively diminishing the recurrence of GBM following surgery [44].

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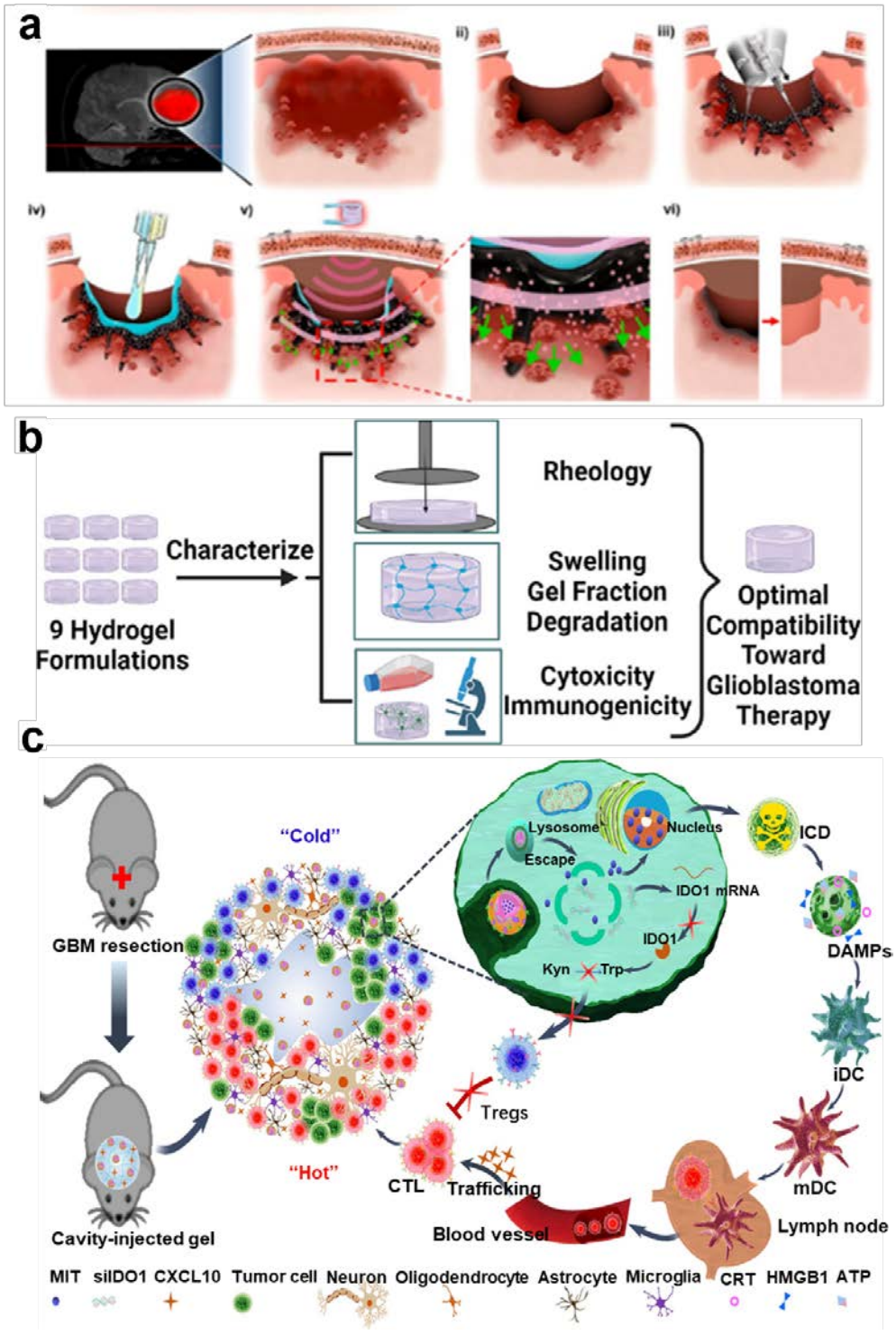

Figure 2. Schematic representation of injectable hydrogels for the treatment of brain tumors. (a) Intracortical injectable hydrogel composite nanomaterials were used to treat GBM. (b) To identify the optimal formulation for glioblastoma treatment, nine hydrogel formulations were characterized to determine the structure-property relationship between hydration/alkalinity and hydrogel properties. (c) A drug delivery system made of hydrogel that imitates a "hot tumor" immune niche locally.

2.2. Sprayable Hydrogels

The delivery of drugs via sprayable hydrogels represents a novel approach in the treatment of brain tumors. McCrorie and colleagues employed a spray device to effectively apply pectin and polymer nanocrystals (containing etoposide and olaparib) to sites of surgical resection Figure 3(a)

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[45]. This marks the first reported instance of transporting pectin to the brain and utilizing a spray device in neurosurgery for the local administration of drugs around the incision site. As an innovative DDS, sprayable hydrogel not only mitigates the adverse effects of surgery but also has the potential to extend patient survival [46].

2.3. Implantable Hydrogels

Implantable hydrogels serve not only to deliver chemotherapy drugs directly to the tumor but also to monitor the tumor's response in real time [47,48]. This could enable the adjustment of drug dosage based on the tumor's characteristics, thus optimizing treatment and minimizing side effects [20]. This approach to personalized medicine holds the potential to transform the therapy of brain tumors. Wang and his colleagues developed a novel 3D-printed hydrogel nanoplatform for intracranial implantation Figure 3(b) [49]. Hydrogels act as drug reservoirs, and through the modification of targeted peptides, an effective DDS can be established. They also incorporated temozolomide and erastin into gelatin methacrylamide (GelMA) to induce synergistic effects in tumor treatment. The intracranial implantation of this hydrogel liposome system can enhance the sensitivity of chemotherapy drugs and also modulate the tumor microenvironment, showing considerable promise for the treatment of brain tumors [50].

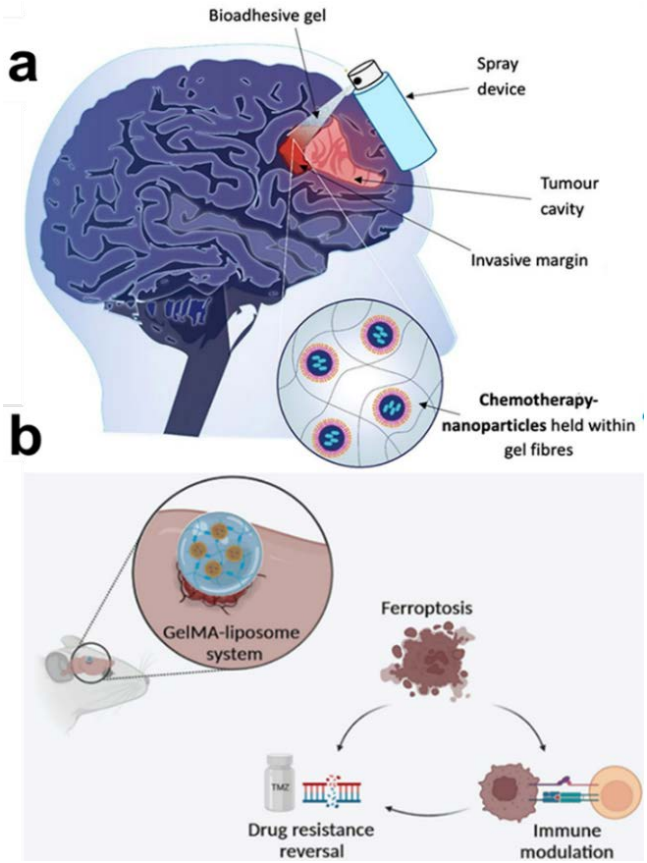

Figure 3. Schematic representation of hydrogels for different modes of brain tumor delivery. (a) Schematic illustration of a local DDS consisting of a nebulizing device, pectin and NCPPs. (b) Schematic illustration of a GelMA-liposome system that is coated with temozolomide and erastin.

3. Smart Hydrogels for Local Treatment of Brain Tumors

Smart hydrogels release encapsulated bioactive substances in response to external stimuli [51–54]. Hydrogels that are responsive to temperature, light, or magnetism fall into the category of smart hydrogels. These external stimuli induce changes in the properties of the hydrogels [55,56]. In the context of treating brain tumors, smart hydrogels efficiently control drug release through external

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stimuli, significantly reducing systemic adverse reactions due to their excellent biocompatibility [57–60].

3.1. Temperature and pH Responsive Hydrogels

Temperature-responsive hydrogels demonstrate varying behaviors in response to temperature fluctuations [61,62]. Below the critical temperature of the solution, the hydrogel remains in a fluid state, transforming into a gel state above this threshold. The swelling behaviour of pH-responsive hydrogels is acutely sensitive to the pH of the solution, rendering them suitable as DDSs for proteins and cells [63–65]. Hydrogels that respond to both temperature and pH have the potential to facilitate precise, targeted therapy of tumors under multiple stimuli, thereby proving highly effective in sustained-release applications [8]. Kang and colleagues developed a gelatin hydrogel with dual stimulus responsiveness, grafted with oligomeric sulfadiazine (OSM) and combined with paclitaxel (PTX) to inhibit GBM progression Figure 4(a) [66]. This gelatin-OSM complex transitions from a fluid to a gel state dependent on temperature and pH, maintaining its gel state for approximately ten days. The dual-responsive hydrogel thus provides sustained drug release within the tumor environment, effectively impeding GBM progression.

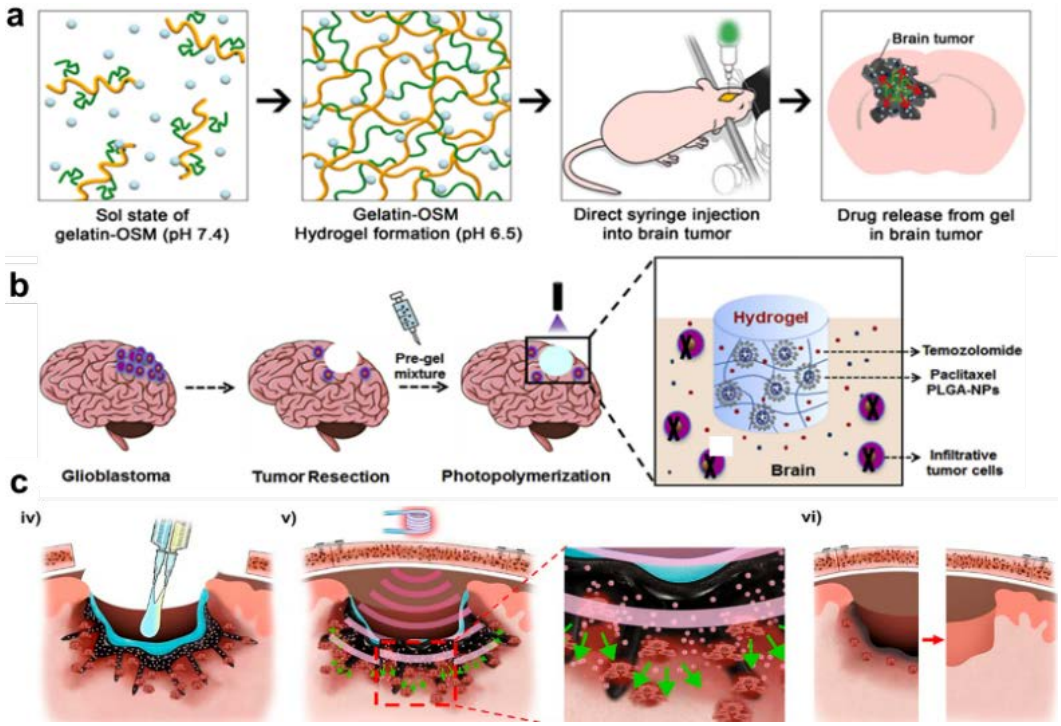

Figure 4. Schematic representation of smart hydrogels for the treatment of brain tumors. (a) In situ injection of gelatin-OSM hydrogel to inhibit tumor recurrence. (b) Codelivery of PTX and TMZ through a photoresponsive hydrogel for the postresection therapy of GBM. (c) The magnetic responsive hydrogel delivers wFIONs precisely deep into the brain tumor.

3.2. Photoresponsive Hydrogels

In the near infrared-ultraviolet/visible (NIR-UV/VIS) spectrum, water is nearly transparent [67,68]. Photoresponsive hydrogels alter their morphology in response to light irradiation, through the absorption or release of water [21,69–71]. Consequently, hydrogels are well-suited as light-responsive biomaterials. The chemical and physical versatility of hydrogels, combined with their photoresponsiveness, makes them ideal for a range of applications, spanning from biomaterials to biomedicine [72]. Zhao and colleagues explored a local DDS based on photopolymerizable hydrogels for postoperative GBM treatment Figure 4(b) [73]. Upon light irradiation, the hydrogel not only forms rapidly but also exhibits low swelling, thereby preventing an increase in intracranial pressure. To enhance the therapeutic efficacy against GBM, they incorporated paclitaxel (PTX) and temozolomide

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(TMZ) into the hydrogels to create a combined DDS. In a U87MG orthotopic transplantation tumor model, the hydrogel proved suitable for implantation post-tumor resection, demonstrating excellent sustained-release capabilities for the drug.

There has been a marked increase in the development of photoresponsive hydrogels in recent years [74]. These hydrogels possess physical and chemical characteristics akin to the flexible materials found in living systems [75]. One of the primary advantages of photoresponsive hydrogels is their cost-effectiveness, coupled with the capability for non-contact and spatiotemporal control. These properties render them excellent candidates for applications in biomaterials and biomedicine [76].

3.3. Magnetic Responsive Hydrogels

Magnetic responsive hydrogels are typically fabricated by incorporating micron or nanometre-sized magnetic particles, such as Fe_2O_3 and Fe_3O_4 [77,78]. When subjected to an external magnetic field, the hydrogel's magnetic nanoparticles can be released with precision [79]. Magnetic fields offer advantages over other stimuli as they are contactless and relatively straightforward to manipulate, making them particularly suitable for biomedical applications [67,80]. Kang and colleagues have recently reported the use of magnetically responsive hydrogels in the treatment of brain tumors Figure 4(c) [32]. Following surgical intervention, the hydrogel, injected into the site of the excised brain tumor, rapidly transitions to a gel state at body temperature. Under alternating magnetic fields, the hydrogel, mixed with water-dispersible ferrimagnetic iron oxide nanocubes (wFIONs), generates heat, accelerating the micelle process. Consequently, the release and diffusion of the drug can penetrate centimeter deep, facilitating precise drug delivery for brain tumor treatment. Magnetic responsive hydrogels hold significant potential for targeted tumor therapy, with diverse applications including magnetically controlled drug release, magnetic hyperthermia, and magnetic targeting [81].

4. Advantages of Hydrogels in the Treatment of Brain Tumors

The Despite significant advances in biomedicine, malignant brain tumors remain a formidable challenge, with cure remaining elusive. The BBB significantly impedes therapeutic efficacy, primarily by restricting the entry of large molecules and over 90% of small molecular drugs into the brain [82–85]. Additionally, the invasive nature of brain tumors further complicates treatment, with tumor cells infiltrating surrounding healthy brain parenchyma and developing mechanisms of multidrug resistance. These factors collectively pose substantial challenges in brain tumor therapy [86].

Hydrogels exhibit remarkable properties stemming from their crosslinked polymer networks, which enable them to retain substantial amounts of water within their structure [87,88]. As depicted in Figure 5, hydrogels can be classified into physical, chemical, and dual network hydrogels based on their crosslinking mechanisms [89]. The crosslinking in physical hydrogels primarily occurs through physical interactions such as hydrophobic association, chain aggregation, crystallization, polymer chain complexation, and hydrogen bonding [90]. Chemical hydrogels, on the other hand, are synthesized through covalent crosslinking or post- polymerization [91–93]. Dual network hydrogels are formed by combining both physical and chemical crosslinking methods [94–96]. Each type of crosslinked hydrogel possesses unique properties, making them versatile for a range of biomedical applications [97].

As exemplary biocompatible materials, hydrogels not only emulate the extracellular matrix in the brain but also establish ideal DDSs for the local treatment of brain tumors [98,99]. Hydrogels offer the following advantages as DDSs: (1) Biocompatibility: Hydrogels closely resemble human tissues in their properties. When drugs are encapsulated within hydrogels, they not only avert the rapid degradation of chemotherapy drugs in the body but also shield the brain from drug-related toxicity [100–102]. (2) Biodegradability: Ideally, the interaction between the host tissue and the hydrogel should orchestrate and fine-tune the degradation process, leading to its eventual disappearance [103]. (3) Intelligent drug release control: Smart hydrogels are particularly effective for targeting tumors due to their capacity to respond to various external stimuli and precisely regulate drug release [104–106]. (4) Accessibility: Hydrogels can be easily synthesized and mass-produced through chemical methods with a low ecological impact [107–109]. Currently, researchers in the field of hydrogels are

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developing multiple types and modes of hydrogel drug delivery systems, aiming to significantly contribute to the clinical treatment of brain tumors [110–112].

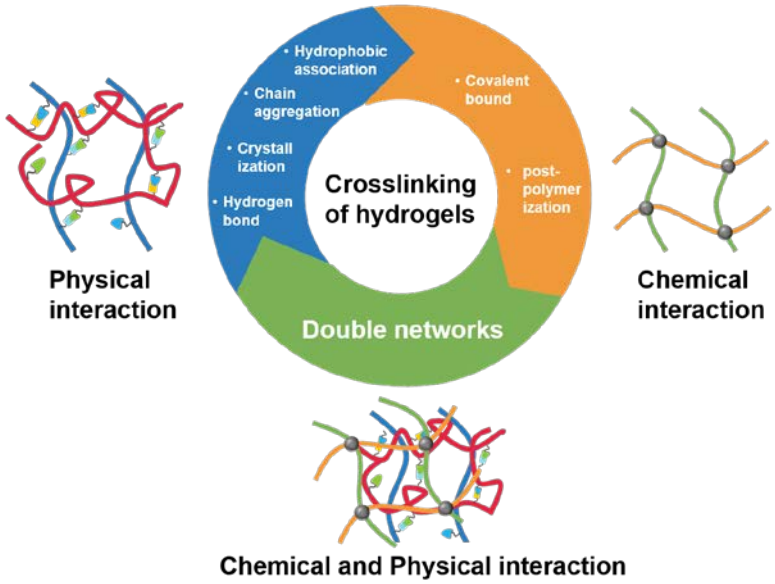

Figure 5. Hydrogels are prepared by physical cross-linking, chemical cross-linking and dual networks.

5. Conclusions and Prospectives

Owing to the BBB, the unique location and complex structure of the brain, the transportation of therapeutic drugs from the vessels to brain tumors is challenging. This paper summarizes four key aspects: (1) The challenges encountered in brain tumor treatment; (2) An overview of different administration methods, hydrogel materials, and administration characteristics of hydrogels; (3) Smart hydrogels with various responses in the treatment of brain tumors; (4) The advantages of hydrogels in the local treatment of brain tumors. Hydrogels for local administration are expected to be utilized in GBM treatment post-excision surgery, where the drug is passively diffused through multiple stimuli responses to achieve precise drug release and sustained drug administration. Moreover, smart hydrogels hold significant potential to enhance treatment outcomes and reduce side effects. The development of more sophisticated hydrogels and their optimization for various medical applications is an area of active exploration, heralding promising prospects for the future of personalized medicine.

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Data Availability Statement: The original data presented in the study are openly available in Figure 2a at [15], Figure 2b at [17], Figure 2c at [18], Figure 3a at [19], Figure 3b at [21], Figure 4a at [26], Figure 4b at [31] and Figure 4c at [32].

Conflicts of Interest: The authors declare that they have no competing interests.

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