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Injectable Thermoresponsive Hydrogel for Localized Cisplatin Delivery: *In Vitro* Evaluation in Glioblastoma Cell Models

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Abstract: ***Background:*** *Postoperative recurrence of glioblastoma is driven by residual tumor cells at the resection margins. Conventional systemic chemotherapy is limited by poor brain penetration and systemic toxicity.* ***Methods:*** *We developed an injectable thermoresponsive hydrogel for localized delivery of cisplatin. The hydrogel undergoes sol–gel transition at body temperature, forming an in situ drug depot. Physicochemical properties, in vitro release, cytotoxicity, and cellular platinum uptake were evaluated.* ***Results:*** *The hydrogel exhibited a porous structure and a sharp gelation near 37°C. Drug release was temperature-dependent, with sustained release at physiological temperature. Cisplatin (CDDP)-loaded hydrogel significantly reduced glioma cell viability and achieved higher intracellular platinum accumulation compared to free drug.* ***Conclusion:*** *This thermoresponsive hydrogel enables injectable, localized cisplatin delivery with improved cellular uptake and cytotoxicity, offering a promising platform for preventing glioblastoma recurrence after surgery.*

Keywords: *Glioblastoma, postoperative recurrence, thermoresponsive hydrogel, cisplatin, local drug delivery, in situ gelation, sustained release*

1. Introduction

Glioblastoma (GBM) is the most aggressive and lethal form of primary brain tumor, characterized by rapid proliferation, diffuse invasion, and poor prognosis despite multimodal treatment [1–3]. The current standard of care includes maximal safe surgical resection followed by concurrent chemoradiotherapy and adjuvant temozolomide [4–6]. However, recurrence is almost inevitable, typically occurring near the original tumor site, largely due to the inability of surgery to completely eliminate infiltrating tumor cells [4,7,8]. Moreover, the blood–brain barrier (BBB) limits the efficacy of systemically delivered chemotherapeutic agents, leading to subtherapeutic drug concentrations in the brain and significant systemic side effects [9–11].

Localized drug delivery systems have emerged as a promising strategy to overcome these limitations by delivering high concentrations of cytotoxic drugs directly to the tumor bed while minimizing systemic exposure [12–14]. Among these, hydrogel-based systems are particularly attractive due to their high water content, tunable mechanical properties, biocompatibility, and capacity to encapsulate and release drugs in a controlled manner [15,16]. Injectable hydrogels that undergo sol–gel transition at physiological temperature offer additional clinical advantages, including minimally invasive administration and conformal coverage of irregular surgical cavities [17,18].

Cisplatin (CDDP) remains a widely used chemotherapeutic agent for various solid tumors. However, its clinical application is often hampered by serious systemic toxicities, most notably nephrotoxicity and ototoxicity, which significantly limit the maximum tolerated dose and compromise patient quality of life. These off-target effects are particularly concerning in long-term or high-dose treatment regimens.

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As a result, strategies that localize cisplatin delivery to tumor sites while minimizing systemic exposure are highly desirable [19].

In recent years, injectable hydrogel systems have gained considerable attention as carriers for local chemotherapy due to their tunable physical properties, high drug-loading capacity, and ability to undergo *in situ* gelation. Thermoresponsive hydrogels, in particular, offer the advantage of minimally invasive administration and localized drug depot formation upon reaching body temperature. These systems have been explored across a range of tumor models to enhance therapeutic efficacy and reduce systemic side effects. Building upon this rationale, our study aims to develop a cisplatin-loaded thermoresponsive hydrogel for localized treatment of glioblastoma, with the goal of improving drug retention at the tumor margin and mitigating systemic toxicity.

In this study, we report the design and evaluation of a thermoresponsive hydrogel system for the localized delivery of cisplatin, a potent DNA-damaging chemotherapeutic agent that is underutilized in glioma therapy due to its systemic toxicity. The hydrogel is based on a polymer matrix that remains fluid at room temperature and rapidly gels at body temperature, allowing it to be easily injected into the postoperative glioblastoma cavity and form a drug-releasing depot *in situ*. Upon injection, the hydrogel transitions to a viscoelastic gel that adheres to tissue surfaces and conforms to complex geometries, enabling precise spatial control of drug localization.

To address the challenge of postoperative glioblastoma recurrence, we designed an injectable thermoresponsive hydrogel capable of localized, sustained cisplatin release. This system integrates favorable features such as sol–gel transition at physiological temperature, porous microstructure for drug entrapment, and *in situ* gelation to conform to irregular post-surgical cavities. Our *in vitro* data demonstrated that this delivery platform can enhance cytotoxicity against glioma cells, which may be partially attributed to prolonged local exposure and diffusion-driven platinum accumulation. Although detailed cellular uptake mechanisms remain to be fully elucidated, the present work provides a promising foundation for further mechanistic and translational investigations.

2. Materials and methods

2.1. Materials

N-isopropylacrylamide (NIPAM), N,N′-methylenebis(acrylamide) (MBA), ammonium persulfate (APS), N,N,N′,N′-tetramethylethylenediamine (TEMED), and cisplatin (CDDP) were purchased from Sigma-Aldrich. Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), and live/dead staining kits were obtained from Thermo Fisher Scientific. U87 human glioblastoma cells were obtained from ATCC. All reagents were of analytical grade and used without further purification.

2.2. Preparation of thermoresponsive hydrogel

The hydrogel was synthesized by free-radical polymerization of NIPAM (10 wt%) and MBA (0.1 wt%) as crosslinker in deionized water. APS (0.2 wt%) and TEMED (0.2 vol%) were added to initiate polymerization at 4°C under nitrogen atmosphere for 12 h. The resulting pre-gel was dialyzed against deionized water for 3 days to remove unreacted monomers and then lyophilized for storage. For drug loading, cisplatin (2 mg/mL) was dissolved directly into the monomer solution prior to polymerization.

2.3. Scanning electron microscopy (SEM)

To analyze internal morphology, hydrogels were freeze-dried and fractured to expose cross-sections. Samples were sputter-coated with gold and imaged using a field emission SEM (JEOL JSM-7100F) at an accelerating voltage of 5 kV. Pore morphology and distribution were qualitatively evaluated.

2.4. Rheological analysis and sol-gel transition

The temperature-dependent viscosity of the hydrogel precursor was measured using a rotational rheometer (TA Instruments) with a cone-plate geometry (40 mm, 2° angle). Viscosity was recorded over

a temperature ramp from 20°C to 60°C at a heating rate of 1°C/min. The sol-gel transition temperature (T_{gel}) was defined as the temperature at which a sharp increase in viscosity occurred.

2.5. *In Vitro* drug release study

CDDP-loaded hydrogels (500 μL) were prepared in microcentrifuge tubes and incubated in 2 mL PBS at either 25°C or 37°C. At predetermined intervals, 1 mL of supernatant was withdrawn and replaced with fresh PBS. Cumulative drug release was quantified using UV-Vis spectrophotometry at 301 nm after reacting with o-phenylenediamine. All experiments were performed in triplicate.

2.6. Determination of cisplatin encapsulation efficiency

To quantify the encapsulation efficiency (EE) of cisplatin in the hydrogel, a known amount of cisplatin (100 μg) was mixed with the hydrogel precursor solution before gelation. After complete gel formation, the hydrogel was subjected to centrifugation using a 3 kDa ultrafiltration tube to separate free (non-encapsulated) drug from the matrix. The concentration of cisplatin in the filtrate was measured by UV-Vis spectrophotometry at 301 nm. EE was calculated using the formula:

$$\text{EE}(\%) = [(\text{Total drug} - \text{Free drug})/\text{Total drug}] \times 100\%.$$

2.7. Live/dead cell staining

U87 glioblastoma cells were seeded into 24-well plates and cultured with hydrogel extracts containing cisplatin for 48 h. Cells were then stained with calcein-AM (live) and propidium iodide (dead) according to the manufacturer's protocol. Images were acquired using a fluorescence microscope (Leica DMi8) and analyzed for viability ratio.

2.8. Cell viability assay (CCK-8)

Cell viability and morphology were further evaluated by Live/Dead staining. U87 glioblastoma cells were seeded in 24-well plates and cultured overnight. After treatment with different hydrogel formulations for 24 h, cells were rinsed twice with PBS and incubated with a staining solution containing 2 μM calcein-AM and 4 μM Ethidium Homodimer-1 (EthD-1) in PBS for 30 min at 37°C. Stained cells were observed using a fluorescence microscope (excitation/emission: 495/515 nm for calcein, 528/617 nm for EthD-1). Live cells fluoresced green due to esterase-mediated conversion of calcein-AM, while dead cells exhibited red nuclear fluorescence from EthD-1 binding to DNA. As the staining signal localizes mainly to the cytoplasm or nucleus, cells appear round in fluorescence images regardless of their original spindle-like morphology.

2.9. Intracellular platinum quantification by ICP-MS

To assess intracellular drug accumulation, U87 glioblastoma cells were seeded into 6-well plates at a density of 1×10^6 cells per well and incubated overnight. The cells were then treated with one of the following formulations: (1) blank hydrogel (control), (2) free cisplatin (CDDP, 10 μg/mL), or (3) CDDP-loaded hydrogel (containing an equivalent dose of cisplatin), and cultured for 24 h at 37°C.

After incubation, cells were washed three times with cold PBS to remove extracellular drug, harvested using trypsin-EDTA, and pelleted by centrifugation (1000×*g*, 5 min, 4°C). The cell pellets were digested in 500 μL of 70% nitric acid at 70°C for 2 h, followed by dilution with ultrapure water. Platinum content was quantified using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7900) calibrated with platinum standards. Results were normalized to total cell number (determined by hemocytometer) and expressed as ng platinum per 10^6 cells. All measurements were performed in triplicate.

3. Results

Figure 1 illustrates the design and therapeutic mechanism of a thermoresponsive hydrogel system for localized drug delivery following glioblastoma resection. After surgical removal of the primary tumor mass, residual glioblastoma cells often remain in the resection cavity, contributing to recurrence.

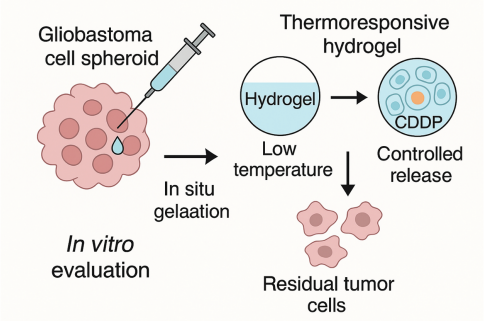

Figure 1. Schematic illustration of the postoperative application of thermoresponsive hydrogel for localized cisplatin delivery in glioblastoma therapy

Figure 2 displays the scanning electron microscopy (SEM) image of the lyophilized thermoresponsive hydrogel. The cross-sectional morphology reveals a uniform and interconnected porous network, with pore diameters ranging from several to tens of micrometers.

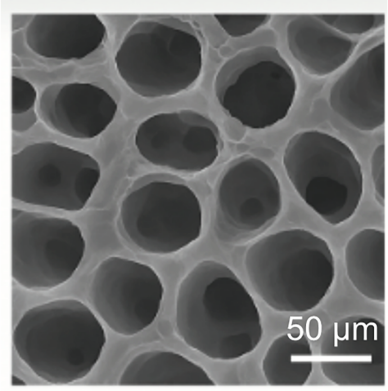

Figure 2. SEM image of the lyophilized thermoresponsive hydrogel showing a highly porous internal structure, bar 50 µM

Figure 3 displays the temperature-viscosity profile of the developed thermoresponsive hydrogel, highlighting its distinct sol-gel transition characteristics. At lower temperatures (20°C–40°C), the hydrogel maintains a low-viscosity sol state, appearing as a free-flowing liquid.

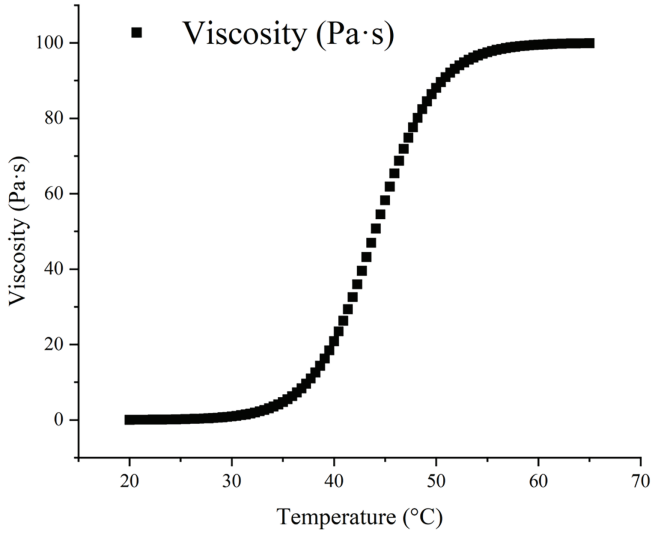

Figure 3. Temperature-dependent viscosity profile of the thermoresponsive hydrogel, indicating the sol-gel transition behavior.

Figure 4 illustrates the temperature-dependent *in vitro* release behavior of cisplatin (CDDP) from the thermoresponsive hydrogel matrix. Drug release was monitored under two conditions: room temperature (25°C) and physiological temperature (37°C), to evaluate the hydrogel's responsiveness and controlled release capability. The encapsulation efficiency of cisplatin in the thermoresponsive hydrogel was determined to be 82.0%, indicating effective drug retention within the hydrogel network during the loading process.

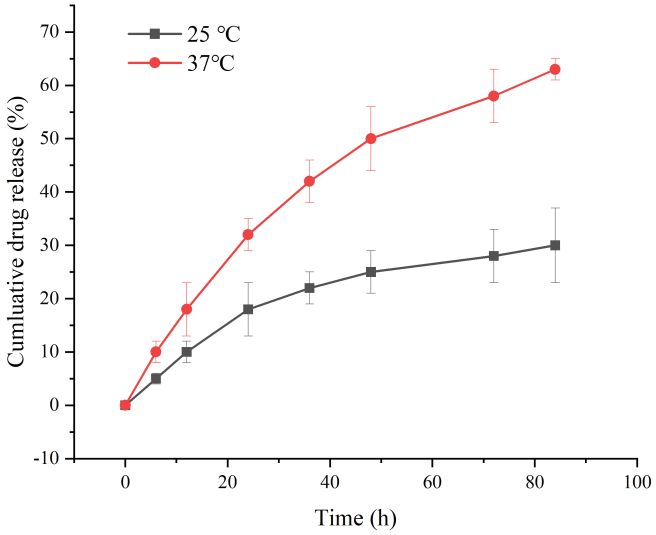

Figure 4. *In vitro* cumulative release profiles of cisplatin from the thermoresponsive hydrogel at 25°C and 37°C over 84 h.

Figure 5 presents a comprehensive assessment of the hydrogel's biocompatibility and anti-tumor efficacy at the cellular level using U87 glioblastoma cells. The left panel shows live/dead staining results after 2 h treatment with the cisplatin-loaded hydrogel. Green fluorescence indicates viable cells, while red fluorescence marks dead or membrane-compromised cells.

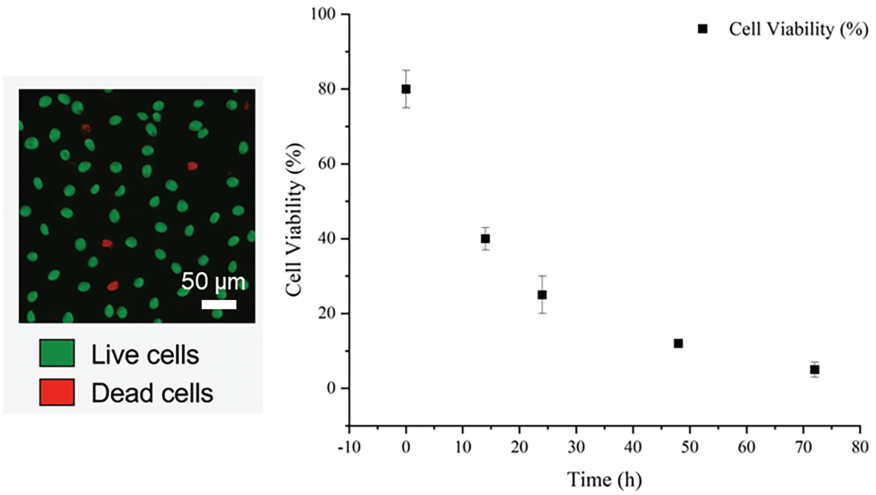

Figure 5. Evaluation of cytocompatibility and anti-tumor activity of the cisplatin-loaded thermoresponsive hydrogel on glioblastoma cells (2 h). (Left) Live/dead staining of U87 glioma cells after 48 h incubation. (Right) Cell viability curve measured via CCK-8 assay over 72 h

To evaluate intracellular drug accumulation, U87 cells were treated with different formulations for 24 h, followed by platinum quantification using ICP-MS. As shown in Figure 6, cells treated with free cisplatin showed a significant increase in intracellular platinum (15.6 ng/10^6 cells) compared to blank gel (1.2 ng/10^6 cells). Notably, cells incubated with cisplatin-loaded hydrogel exhibited the highest platinum accumulation (29.4 ng/10^6 cells), nearly double that of the free drug group.

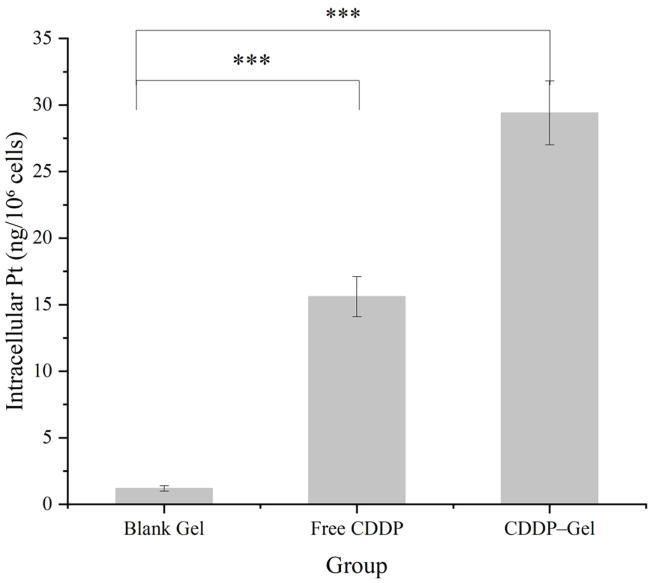

Figure 6. Quantification of intracellular platinum accumulation in U87 glioblastoma cells after 24 h incubation with blank hydrogel, free cisplatin, or cisplatin-loaded hydrogel, measured by ICP-MS (***$p < 0.001$)

4. Discussion

To address this problem mentioned in Figure 1, a cisplatin (CDDP)-loaded hydrogel in its sol state is injected directly into the postoperative cavity. The hydrogel, composed of a thermoresponsive polymer,

undergoes *in situ* gelation as the temperature shifts from room temperature to physiological temperature (~37°C), forming a conformal gel that fills the irregular cavity space. At body temperature, the hydrogel matrix stabilizes, enabling controlled and sustained release of cisplatin directly at the tumor margin. This localized delivery strategy enhances drug retention at the target site, reduces systemic toxicity, and improves therapeutic efficacy against residual tumor cells.

Such a porous architecture in Figure 2 facilitates efficient water absorption and diffusion of therapeutic agents, while also contributing to the mechanical stability of the gel structure after *in situ* formation. The interconnected channels are advantageous for promoting homogeneous drug distribution and sustaining the release of cisplatin in the physiological environment. The porous morphology also suggests that the hydrogel can provide a favorable microenvironment for nutrient exchange or potential cellular infiltration in future regenerative applications.

In Figure 3, this state is ideal for syringe injection and ensures that the material can conformally fill irregular postoperative cavities without mechanical resistance. Upon gradual heating, the viscosity curve shows a marked inflection beginning at ~42°C, indicating the onset of the sol-gel transition. Beyond this threshold, the viscosity increases sharply, reflecting rapid physical crosslinking and gel network formation. The hydrogel reaches a high-viscosity plateau above 50°C, representing a stable gel phase. This temperature-responsive behavior is attributed to the lower critical solution temperature (LCST)-type phase transition of the polymer matrix, often observed in PNIPAM-based or similar amphiphilic systems. The ability to remain injectable at room temperature and spontaneously gel at body temperature (~37°C) enables minimally invasive delivery and *in situ* formation without the need for chemical initiators or external triggers. This thermal gelation not only secures the hydrogel within the tumor resection cavity but also establishes a depot structure that supports sustained local drug release. Moreover, the steep viscosity increase ensures rapid solidification post-administration, reducing premature drug leakage and enhancing clinical operability

As shown in Figure 4, at 25°C, the hydrogel remains in a sol-like or pre-gel state with a relatively loose internal structure, leading to slow and limited diffusion of cisplatin. In contrast, at 37°C, the hydrogel transitions into a crosslinked gel phase with a more compact and stabilized porous network. This structural transformation facilitates sustained and accelerated drug release, as evidenced by the significantly higher cumulative release observed under physiological conditions. After 84 h, the hydrogel released approximately 60% of its loaded drug content at 37°C, while only ~30% was released at 25°C. These results confirm the temperature-triggered release behavior of the hydrogel system, which aligns well with its application in postoperative glioblastoma treatment. Upon injection into the resection cavity, the hydrogel gels *in situ* and initiates the release of cisplatin in response to body temperature, ensuring localized and sustained chemotherapy. The dual responsiveness—injectability at low temperature and drug release at body temperature—offers enhanced spatial control over therapeutic delivery, minimizes systemic exposure, and improves the drug's therapeutic index. The high encapsulation efficiency (82%) suggests that the hydrogel matrix provides a favorable environment for incorporating and retaining small-molecule drugs such as cisplatin. This result supports the feasibility of the formulation for sustained local delivery. Since cisplatin was directly mixed into the aqueous precursor and uniformly distributed prior to gelation, minimal drug loss or phase separation was observed. The mild preparation conditions (room temperature, neutral pH) also help preserve drug integrity, further enhancing the practicality of the system for clinical translation.

A notable proportion of cells stained red in Figure 5 suggests effective cytotoxic activity, while the remaining green cells indicate partial cell survival, reflective of dose-dependent therapeutic effects. The right panel quantifies this cytotoxic response using a CCK-8 assay to determine cell viability at multiple time points (0, 14, 24, 48, and 72 h). A continuous decline in cell viability is observed, dropping from over 80% at 0 h to below 10% at 72 h, confirming time-dependent suppression of glioma cell proliferation. This result highlights the sustained release profile of cisplatin from the hydrogel and its ability to maintain an effective local concentration over time. Together, these data verify the

hydrogel's dual functionality: excellent cell contact biocompatibility in the unloaded state and potent chemotherapeutic efficacy when loaded with cisplatin. This balance makes the system highly suitable for post-surgical glioblastoma applications requiring local, sustained anti-tumor activity with minimal systemic exposure.

In Figure 6, the enhanced intracellular platinum content observed in the cisplatin–gel group suggests superior cellular uptake or retention enabled by the hydrogel delivery system. This may be attributed to prolonged local exposure, facilitated diffusion from the gel matrix, and increased interaction with cell membranes over time. In contrast, free cisplatin, while effective, may be rapidly internalized and effluxed or detoxified. The blank gel showed minimal platinum presence, confirming the hydrogel matrix itself does not contribute to the ICP-MS signal. These findings reinforce the hydrogel's role as a sustained delivery depot that enhances drug bioavailability and cellular engagement, which likely underlie its superior *in vitro* cytotoxicity observed in previous assays.

Several hydrogel- and microsphere-based systems have recently been explored for localized glioma drug delivery, offering useful benchmarks for our thermoresponsive design. For instance, thermogels loaded with temozolomide (THG@SiO_2-TMZ and THG@PCL-TMZ) demonstrated significant suppression of tumor recurrence in a glioblastoma resection model, with no evident systemic toxicity and maintained body weight. Another study summarized the broad role of hydrogels in local brain tumor treatment, attributing their effectiveness to controlled drug release and high local concentrations that reduce relapse rates [20–23]. Moreover, injectable drug delivery systems—ranging from hydrogels to liposomal and microsphere platforms—have shown overall survival benefits in preclinical models.

Compared to these examples, our hydrogel offers key advantages: (1) precise injectability and sol-gel transition near physiological temperature, suitable for conforming to post-resection cavities; (2) sustained and temperature-triggered release of cisplatin, mitigating burst effects and systemic exposure; and (3) enhanced intracellular platinum accumulation *in vitro*, which may support improved cytotoxic efficacy (Please see Table 1). Although our results are currently limited to *in vitro* validation, the platform shows compelling potential for minimally invasive postoperative therapy.

Table 1. Comparison of different systems for drug delivery

System	Drug	Delivery form	Release/Duration	*In Vivo* efficacy	Notes/Toxicity
Our thermoresponsive hydrogel (this work)	Cisplatin	Injectable thermogel	Sustained at ~37°C	*In vitro* only	Prolonged local release, enhanced uptake
THG@SiO_2-TMZ (Biomaterials-)	Temozolomide	Thermogel + nanoparticles	Post-surgical local delivery	Reduced recurrence	No body-weight loss, good safety profile
Various injectable hydrogels, microspheres	Various	Injectable DDS	Preclinical models	Extended survival	Benefits demonstrated across systems

5. Conclusion

In this study, we developed a thermoresponsive hydrogel system for the localized delivery of cisplatin, targeting residual glioma cells after surgical resection. The hydrogel exhibited favorable injectability, temperature-responsive gelation near 37°C, sustained drug release, and effective inhibition of glioma cell viability *in vitro*. Our findings suggest that the enhanced intracellular drug accumulation likely stems from prolonged local release and the porous nature of the hydrogel matrix, though further mechanistic studies are warranted. Overall, this work offers a versatile and minimally invasive platform with translational potential for postoperative glioma therapy. Future work will focus on *in vivo* validation, mechanistic tracking of drug uptake, and long-term biosafety evaluation.

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Author Contributions: The authors confirm contribution to the paper as follows: study conception and design: Yao Zhang, Dan Fan; data collection and analysis: Yao Zhang, Dan Fan; interpretation of results: Yao Zhang, Dan Fan; draft manuscript preparation: Yao Zhang. Supervision and critical revision: Jiawei Dong. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: The data that support the findings of this study are available from the Corresponding Author [Jiawei Dong], upon reasonable request.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

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