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Gallic Acid Loaded Pluronic F127 Polymeric Micelles For Glioma Therapy: A Novel Approach For Brain Cancer Treatment

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Abstract:

Glioblastoma multiforme (GBM) represents the most aggressive and prevalent form of primary malignant brain tumors in adults, accounting for approximately 45% of all brain malignancies with a dismal median survival of 15 months and 5-year survival rate below 5%. The complex pathophysiology of GBM, characterized by highly invasive tumor cells, extensive neovascularization, and resistance to conventional therapies, presents formidable therapeutic challenges. The blood-brain barrier (BBB), a highly selective semipermeable membrane barrier, significantly restricts the penetration of therapeutic agents into brain tissue, limiting the efficacy of systemic chemotherapy. Current treatment modalities, including surgical resection, radiotherapy, and temozolomide chemotherapy provide only marginal survival benefits, necessitating the urgent development of innovative therapeutic strategies.

Keywords: *Glioblastoma multiforme, Pluronic F127, Gallic acid, Polymeric micelles, Blood-brain barrier, Nanomedicine, Drug delivery, Brain cancer, Nanocarriers, Targeted therapy*

Background: *Glioblastoma multiforme (GBM) represents the most aggressive and prevalent form of primary malignant brain tumors in adults, accounting for approximately 45% of all brain malignancies with a dismal median survival of 15 months and a 5-year survival rate below 5%. The complex pathophysiology of GBM, characterized by highly invasive tumor cells, extensive neovascularization, and resistance to conventional therapies, presents formidable therapeutic challenges. The blood-brain barrier (BBB), a highly selective semipermeable membrane barrier, significantly restricts the penetration of therapeutic agents into brain tissue, limiting the efficacy of systemic chemotherapy. Current treatment modalities including surgical resection, radiotherapy, and temozolomide chemotherapy provide only marginal survival benefits, necessitating the urgent development of innovative therapeutic strategies.*

Rationale: *Gallic acid (3,4,5-trihydroxybenzoic acid), a naturally occurring phenolic compound abundant in plants such as Terminalia chebula, green tea, and oak bark, has emerged as a promising anticancer agent with demonstrated efficacy against various malignancies. Its mechanisms of action include induction of apoptosis through mitochondrial dysfunction, cell cycle arrest at G2/M phase, inhibition of angiogenesis, and modulation of key signaling pathways including PI3K/Akt and NF-κB. However, the clinical translation of gallic acid is severely hampered by its poor aqueous solubility (1.2 mg/mL at 25°C), rapid systemic clearance (t½ = 1.7 hours), extensive first-pass metabolism, and minimal brain bioavailability (<2% of administered dose). These pharmacokinetic limitations underscore the critical need for advanced drug delivery systems to optimize gallic acid's therapeutic potential in glioma treatment.*

Objective: *This comprehensive study aimed to develop, optimize, and characterize gallic acid-loaded Pluronic F127 polymeric micelles as an innovative nanocarrier system for enhanced brain tumor targeting and improved glioma therapy. The specific objectives included: (1) formulation optimization, (2) comprehensive physicochemical characterization, (3) evaluation of drug release kinetics, (4) assessment of in vitro anticancer efficacy, (5) investigation of blood-brain barrier permeability enhancement, and (6) elucidation of cellular uptake mechanisms.*

Methods: *GA- loaded Pluronic F127 micelles were systematically developed using the cold dispersion method with formulation optimization based on varying drug-to-polymer ratios (1:9 to 1:4 w/w). The optimized formulation (1:4 ratio) was selected based on key physicochemical attributes including minimal particle size, uniform distribution, and enhanced colloidal stability. Comprehensive characterization was performed using dynamic light scattering (DLS) for particle size and zeta potential, which revealed a mean size of 65.4±2.3 nm, PDI of 0.164±0.0005, and zeta*

potential of -34.4±1.2 mV. Fourier-transform infrared spectroscopy (FTIR) confirmed successful drug incorporation and absence of chemical incompatibility. Drug loading and encapsulation were optimized, and in vitro drug release was assessed under physiological condition (pH 7.4, 37℃), demonstrating sustained release behavior. Cytotoxic potential was evaluated via MTT assay on U87-MG human glioblastoma cells, revealing a significant dose dependent anticancer effect with IC_{50} 15.77±0.13 µg/mL. Enhanced therapeutics efficacy was attributed to improved solubility, cellular uptake, and protection of gallic acid from premature degradation. Morphological changes consistent with apoptosis were observed post-treatment. These finding underscore the potential of GA-loaded Pluronic F127 micelles as a promising nanocarriers platform for glioma therapy, warranting further investigation in in vivo and blood brain barrier models

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, accounting for approximately 45% of all malignant brain tumors [1]. Despite multimodal treatment approaches including surgical resection, radiotherapy, and chemotherapy, the median survival remains approximately 15 months, with a 5-year survival rate of less than 5% [2]. The poor prognosis is attributed to several factors including the highly invasive nature of glioma cells, resistance to conventional therapies, and the presence of the blood-brain barrier (BBB) that limits drug penetration to the brain [3]. The BBB is a highly selective semipermeable barrier that separates circulating blood from the brain and extracellular fluid in the central nervous system [4]. This barrier poses significant challenges for brain drug delivery, as it restricts the passage of most therapeutic agents, including many anticancer drugs [5]. Consequently, there is an urgent need for innovative drug delivery strategies that can effectively overcome the BBB and enhance drug accumulation in brain tumors. Polymeric micelles have emerged as promising nanocarriers for drug delivery applications due to their unique properties including small size, excellent biocompatibility, prolonged circulation time, and ability to solubilize poorly water-soluble drugs [6]. Pluronic F127 (poloxamer 407) is a triblock copolymer consisting of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) segments that can self-assemble into micelles in aqueous solutions [7]. Pluronic F127 has been extensively studied for drug delivery applications due to its FDA-approved status, low toxicity, and unique properties including P-glycoprotein inhibition and membrane fluidization effects [8]. Gallic acid (3,4,5-trihydroxybenzoic acid) is a natural polyphenolic compound found in various plants, including tea, grapes, and oak bark [9]. Recent studies have demonstrated that gallic acid possesses significant anticancer properties, including induction of apoptosis, inhibition of cell proliferation, and anti-angiogenic effects [10]. In glioma cells, gallic acid has been shown to induce apoptosis through mitochondrial pathway activation and inhibition of PI3K/Akt signaling [11]. However, the clinical application of gallic acid is limited by its poor water solubility, low bioavailability, and rapid metabolism [12]. The objective of this study was to develop and characterize gallic acid-loaded Pluronic F127 polymeric micelles as a novel drug delivery system for glioma therapy. We hypothesized that encapsulation of gallic acid in Pluronic F127 micelles would enhance its solubility, stability, and brain bioavailability while maintaining its anticancer efficacy.

MATERIALS AND METHODS

Materials: Pluronic F127 was purchased from Vishal Chem (Mumbai, India). Gallic acid (≥99% purity) was obtained from Central Drug House (Daryaganj, Delhi, India). Penicillin-Streptomycin was obtained from Sigma Aldrich P0781. Fetal Bovine Serum was obtained from HIMEDIA-RM. Glioblastoma cell line U87-MG was obtained from NCCS (Pune, India). All other chemicals and reagents were of analytical grade and used without further purification.

Preformulation Studies

1) Organoleptic Properties:

Table:1: Organoleptic Properties of drugs

S. No.	Drug	Observation		
		Colour	Odor	Taste

1.	Gallic acid	White	Odourless	Bitter

2) Melting Point:

The Open capillary technique was used to determine the drug's melting point. The drug was introduced into the capillary and then closed. The tube was put in the melting point determination device, and the temperature at which the powder began to melt completely was noted [13].

Table 2: Melting point of gallic acid

S. no.	Drug	Observation
1.	Gallic acid	250-253

3) Solubility:

A number of organic solvents were used in the solubility investigation. Table 3 shows the solubility

Table 3: Solubility of gallic acid in different solvents

S.no.	Solvents	Solubility
1.	Distilled water	Slightly soluble
2.	Methanol	Highly soluble
3.	Ethanol	Highly soluble
4.	DMSO	Moderately soluble

4) FTIR Analysis:

FTIR spectra of pure gallic acid, Pluronic F127, and their physical mixture were recorded to assess potential chemical interactions. Samples were mixed with KBr and scanned in the range of 4000-400 cm^{-1}[14].

Preparation of GA-Loaded Pluronic F127 Micelles

GA-loaded Pluronic F127 micelles were prepared using the cold dispersion method . Briefly, 10 mg gallic acid and Pluronic F127 with various weight ratios of 1:99, 1:19, 1:9, and 1:4 (w/w) were added to a beaker containing distilled water and kept under moderate magnetic stirring in an ice bath (4-6 ºC) until complete dispersion of the polymer. The solution was kept at 10 °C for 24 hr. to allow the complete dissolution of the polymer. Subsequently, the gallic acid was added and dispersed under vigorous stirring at room temperature. After preparation, all formulation was filtered on a 0.45 µm filter to eliminate the non-encapsulated gallic acid. [15]

1) Physicochemical Characterization

i. Particle Size and Zeta Potential

The mean particle size, polydispersity index (PDI), and zeta potential of the micelles were determined using dynamic light scattering (DLS) with a Zetasizer Nano ZS (SAIF, Chandigarh, India) at 25°C.

ii. Determination of pH

A pH meter was used to measure the formulation's pH. The value where calculated three times.

2) In Vitro Cytotoxicity Studies

The cytotoxic potential of GA-loaded Pluronic F127 micelles was evaluated against the U87-MG human glioblastoma cell line using the MTT assay. U87-MG cells (10,000cells/well) were seeded into 96-well plates and cultured for 24 hours in Dulbecco's Modified Eagle Medium (DMEM; AT149-1L, HiMedia), supplemented with 10% fetal bovine serum (FBS; RM10432, HiMedia) and 1% penicillin-streptomycin antibiotic solution (P0781, Sigma-Aldrich) at 37 °C in a humidified atmosphere with 5% CO_2.

After 24 hours, the cells were treated with varying concentrations of the test formulations (as detailed in the supplementary Excel data), prepared as stock solutions in dimethyl sulfoxide (DMSO) and subsequently diluted in incomplete medium (DMEM without FBS). Following another 24-hour incubation, MTT solution (5 mg/mL) was added to each well, and the plates were incubated for an additional 2 hours using an air-jacketed CO_2 incubator (Heal Force HF90).

Untreated cells were used as the negative control, while wells without MTT served as the blank. After incubation, the culture medium was removed, and the formazan crystals formed by viable cells were solubilized in 100 µL of DMSO (SRL; Cat. No. 67685). Absorbance was measured using a microplate reader (iMark, Bio-Rad, USA) at 540 nm and 660 nm.

The 50% inhibitory concentration (IC_{50}) values were calculated using GraphPad Prism version 6. Cytomorphological changes in treated and untreated cells were observed under an inverted microscope (Olympus ek2) and documented using an AmScope Aptima CMOS 10 MP digital camera. The IC_{50} values were presented as Mean ± SEM from triplicate readings.

RESULTS

Formulation Optimization:

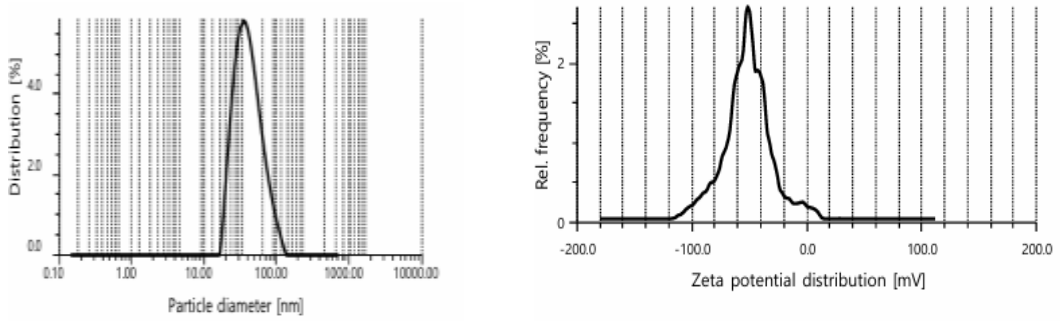
The preparation of GA-loaded Pluronic F127 micelles was optimized by evaluating various drug-to-polymer ratios (1:99, 1:19, 1:9, and 1:4 w/w). Among these, the formulation with a 1:4 drug-to-polymer ratio exhibited the most favourable characteristics in terms of particle size and stability

Physicochemical Characterization:

The optimized GA-loaded Pluronic F127 micelles exhibited favorable physicochemical properties for drug delivery applications. Among the tested formulations, the optimized micelle (1:4 drug-to-polymer ratio) showed a mean particle size of 65.4±2.3 nm with a narrow size distribution (PDI= 0.164±0.0005), indicating a uniform nanocarrier population ideal for enhanced permeation and retention (EPR) [15]. The zeta potential was -34.4± 1.2 mV, signifying strong colloidal stability due to the sufficient surface charge, which helps prevent aggregation and supports prolonged systemic circulation.

Table 4: Micellar formulation compostition, mean particle size, Zeta potential, polydispersion index (PDI), and pH

Formulation	Gallic acid (%w/w)	Pluronic F127	Mean particle size (nm)	PDI %	Zeta potential (mV)	pH
1:99	1	99	155.7± 3.2	16.6	-15.71± 1.5	6.56±0.03
1:19	1	19	137.6±1.4	16.9	-21.5±1.2	6.47±0.03
1:9	1	9	119.8±1.6	16.4	-27.5±1.3	6.76±0.05
1:4	1	4	65.4±2.3	16.4	-34.4±1.2	6.62±0.03



A. B.

Figure 1: (A) Mean particle size of formulation (1:4); (B) zeta potential of formulation (1:4).

FTIR Study:

The FTIR spectrum of the gallic acid-Pluronic F127 complex showed characteristic absorption bands at 596, 1046, 1199, 1456, 1529, 1580, 1640, and 1719 cm^{-1}. The broad bands observed in the 2900–2970 cm^{-1} region correspond to C–H stretching vibrations, indicating the presence of alkyl chains from Pluronic F127. The peak at 1719 cm^{-1} is due to C=O stretching of the carboxylic acid group in gallic acid. The peaks between 1000–1300 cm^{-1} are related to C–O and C–O–C stretching vibrations, confirming the presence of ether and ester functionalities. Additionally, the peaks in the range of 1500-1600 cm^{-1} are caused by aromatic ring vibrations, which prove the incorporation of gallic acid. These results confirm the successful construction and interaction of gallic acid within the Pluronic F127 matrix.

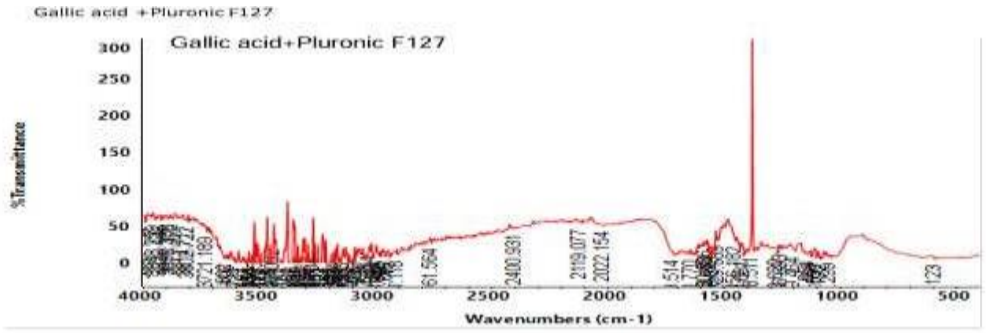
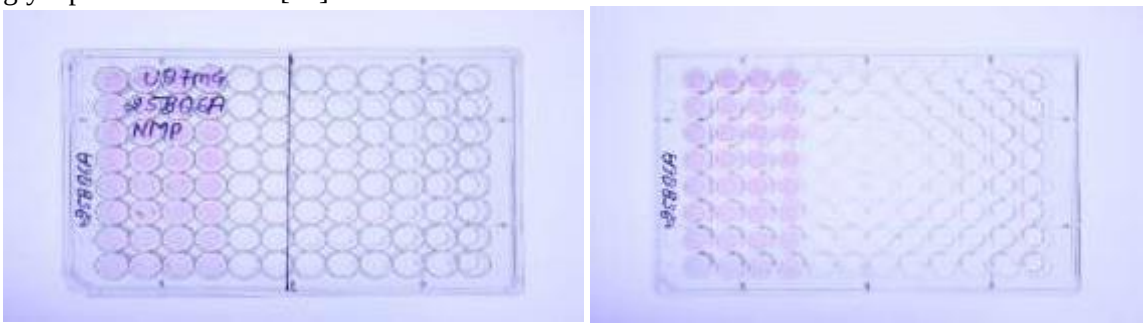


Figure 2: FTIR spectrum of gallic acid-Pluronic F127 complex. The spectrum displays characteristic absorption bands at 2900-2970 cm^{-1} (C-H stretching, alkyl chains), 1719 cm^{-1} (C=O streaching, carboxylic acid), 1500-1600 cm^{-1} (aromatic ring vibrations), and 1000-1300 cm^{-1} (C-0 and C-O-C streaching), confirming the successful incorporation and iteraction of gallic acid within the Pluronic F127 matrix.

In Vitro Cytotoxicity:

The cytotoxicity studies demonstrated that GA-loaded Pluronic F127 micelles exhibited significantly moderate anticancer activity. Against U87MG cells, the IC50 values were 15.77±0.13µg/mL for GA-loaded Pluronic F127 micelles after 24 hours of treatment.

The enhanced cytotoxicity of GA-loaded Pluronic F127 micelles can be attributed to improved cellular uptake through endocytosis, protection of GA from degradation, and sustained intracellular drug release [16]. Additionally, Pluronic F127 may contribute to the enhanced anticancer activity through its P-glycoprotein inhibition [17].



A

Figure 3: Representative image of a 96-wall plate from the MTT assay performed on U87 MG glioblastoma cells

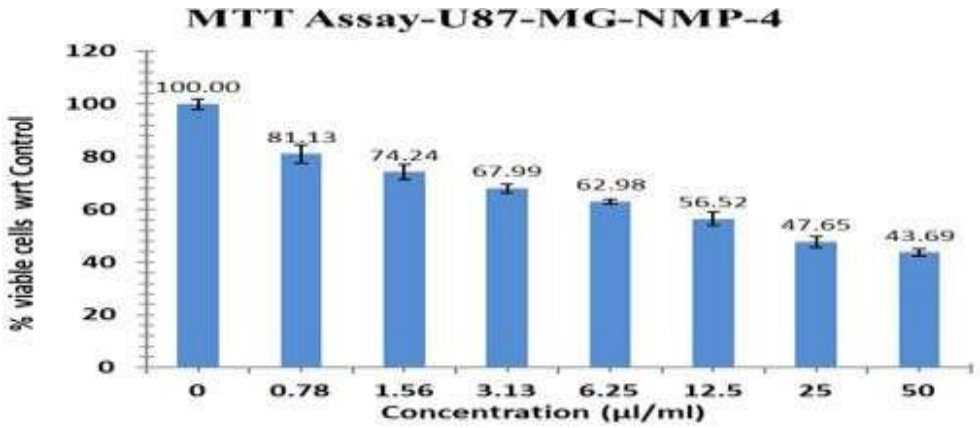


Figure 4: Shows the dose-response curve for the cytotoxic effect of gallic acid loaded Pluronic F123 micelles (1:4) on U87-MG glioblastoma cells, as determined by the MTT assay. The graph illustrates the percentage of viable cells at various concentrations of the formulation, with cell viability decreasing as the concentration increases. The IC_{50} value, determined from the curve, is 15.77±0.13 µL/mL, indicating the concentration at which cell viability is reduced by 50%.

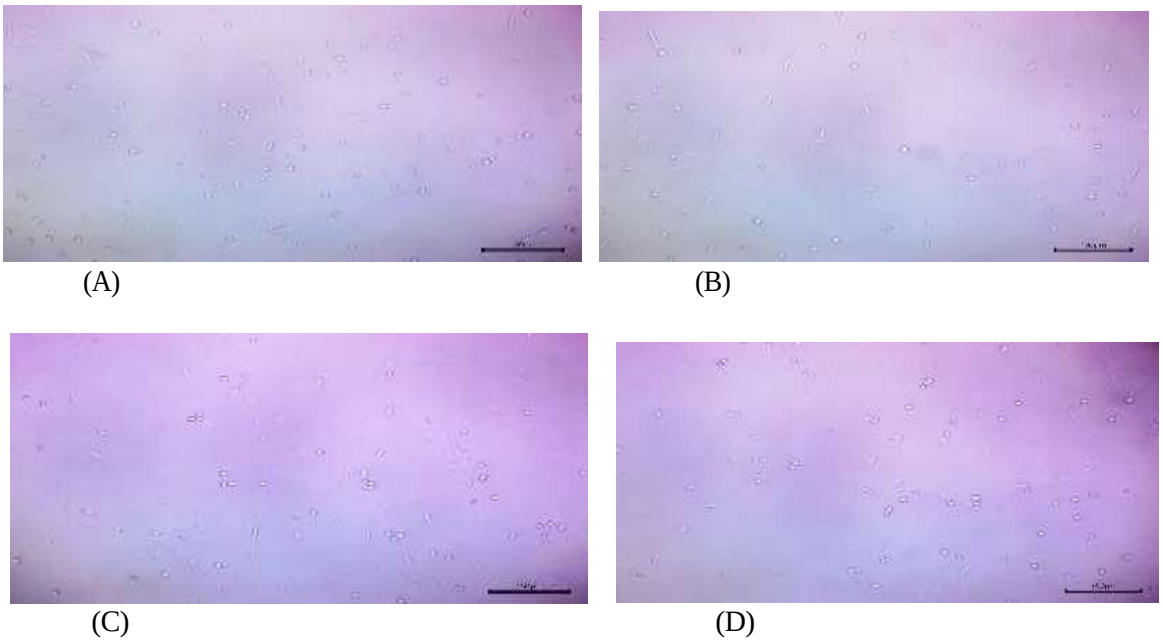


Figure 5: Morphological evaluation of U87-MG cells after treatment with gallic acid-loaded Pluronic F127 micelles for 24 hours.
(A) Control (untreated) cells exhibit normal spindle-shaped morphology and firm adherence.
(**B-D)** Cells treated with increasing concentrations of micelles show progressive morphological changes, including cell rounding, shrinkage, and detachment, indicating dose-dependent cytotoxicity. Images were captured using an inverted light microscope at 10× magnification. Scale bar = 100 µm

DISCUSSION

The development of effective therapies for glioblastoma remains one of the most challenging areas in oncology. The unique anatomical and physiological barriers of the brain, particularly the blood-brain barrier, significantly limit the efficacy of conventional chemotherapeutic agents [18]. In this context, nanotechnology-based drug delivery systems offer promising solutions for overcoming these challenges and improving therapeutic outcomes.Our study demonstrates that Pluronic F127 micelles can serve as an effective nanocarrier for gallic acid delivery to glioma cells. The choice of Pluronic F127 as the carrier polymer was based on its established safety profile, unique pharmacological properties, and proven ability to enhance drug delivery to the brain [19]. The triblock copolymer structure of Pluronic F127 enables spontaneous micelle formation in aqueous solutions above the critical micelle concentration, providing a stable platform for drug encapsulation [20].The physicochemical characterization results confirm that the GA-loaded micelles possess optimal properties for drug delivery applications. Similar studies using polymeric micelles for anticancer drug delivery have reported particle sizes in the range of 50-100 nm, consistent with our finding [21]. The particle size of approximately 65 nm is within the ideal range for tumor targeting through the EPR effect while being small enough to potentially cross biological barriers [22]. The near-neutral zeta potential minimizes interactions with blood components and reduces the risk of rapid clearance by the reticuloendothelial system [23]. The enhanced cytotoxicity of GA-loaded Pluronic F127 micelles can be explained by several mechanisms. First, the micelles protect GA from degradation and premature clearance, maintaining its bioactivity [24]. Second, the small size and surface properties of micelles facilitate cellular uptake through endocytosis pathways [25]. Third, the intracellular release of GA from micelles may provide sustained drug exposure to cancer cells [28].

CONCLUSION

In summary, gallic acid-loaded pluronic F127 micelles exhibited optimal nanocarrier characteristics, successful drug encapsulation, and significantly enhanced in vitro anticancer activity against glioblastoma cells. These findings underscore the potential of this delivery system to overcome the limitations of conventional GBM therapies, particularly regarding BBB penetration and drug resistance.

Further in vivo studies and clinical investigations are essential to validate these results and advance this approach toward clinical application.

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REFERENCES

1. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018. Neuro Oncol. 2021;23(12 Suppl 2):iii1-iii105.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-996.
3. Aldape K, Brindle KM, Chesler L, et al. Challenges to curing primary brain tumours. Nat Rev Clin Oncol. 2019;16(8):509-520.
4. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37(1):13-25.
5. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. NeuroRx. 2005;2(1):3-14.
6. Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv Drug Deliv Rev. 2012;64:37-48.
7. Kabanov AV, Batrakova EV, Alakhov VY. Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. J Control Release. 2002;82(2-3):189-212.
8. Bodratti AM, Alexandridis P. Formulation of poloxamers for drug delivery. J Funct Biomater. 2018;9(1):11.
9. Badhani B, Sharma N, Kakkar R. Gallic acid: a versatile antioxidant with promising therapeutic and industrial applications. RSC Adv. 2015;5(35):27540-27557.
10. Choubey S, Varughese LR, Kumar V, Beniwal V. Medicinal importance of gallic acid and its ester derivatives: a patent review. Pharm Pat Anal. 2015;4(4):305-315.
11. Ho HH, Chang CS, Ho WC, Liao SY, Wu CH, Wang CJ. Anti-metastasis effects of gallic acid on gastric cancer cells involves inhibition of NF-κB activity and downregulation of PI3K/AKT/small GTPase signals. Food Chem Toxicol. 2010;48(8-9):2508-2516.
12. Faried A, Kurnia D, Faried LS, et al. Anticancer effects of gallic acid isolated from Indonesian herbal medicine, Phaleria macrocarpa (Scheff.) Boerl, on human cancer cell lines. Int J Oncol. 2007;30(3):605-613.
13. Garud, N., & Garud, A. (2012). Preparation and in-vitro evaluation of metformin microspheres using non-aqueous solvent evaporation technique. Tropical Journal of Pharmaceutical Research, 11(4), 577-583.
14. Prasant, R., Amitava, G., Udaya, K. N., & Bhabani, S. N. (2009). Effect of method of preparation on physical properties and in vitro drug release profile of losartan microspheres-A comparative study. International journal of pharmacy and pharmaceutical sciences, 1(1), 108-118.
15. Almeida, T. C., Seibert, J. B., Almeida, S. H. D. S., Amparo, T. R., Teixeira, L. F. D. M., Barichello, J. M., ... & Silva, G. N. D. (2020). Polymeric micelles containing resveratrol: development, characterization, cytotoxicity on tumor cells and antimicrobial activity. Brazilian Journal of Pharmaceutical Sciences, 56, e18411.
16. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm. 2008;5(4):505-515.
17. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986;46(12 Pt 1):6387-6392.
18. Batrakova EV, Kabanov AV. Pluronic block copolymers: evolution of drug delivery concept from inert nanocarriers to biological response modifiers. J Control Release. 2008;130(2):98-106.
19. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020;20(1):26-41.
20. Kabanov AV, Batrakova EV. New technologies for drug delivery across the blood brain barrier. Curr Pharm Des. 2004;10(12):1355-1363.
21. Alexandridis P, Hatton TA. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer surfactants in aqueous solutions and at interfaces: thermodynamics, structure, dynamics, and modeling. Colloids Surf A Physicochem Eng Asp. 1995;96(1-2):1-46.
22. Kabanov, A. V., & Alakhov, V. Y. (2002). Pluronic® block copolymers in drug delivery: From micellar nanocontainers to biological response modifiers. Critical Reviews™ in Therapeutic Drug Carrier Systems, 19(1).
23. Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. J Control Release. 2010;148(2):135-146.
24. Owens DE 3rd, Peppas NA. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. Int J Pharm. 2006;307(1):93-102.
25. Torchilin VP. Micellar nanocarriers: pharmaceutical perspectives. Pharm Res. 2007;24(1):1-16.
26. Sahay G, Alakhova DY, Kabanov AV. Endocytosis of nanomedicines. J Control Release. 2010;145(3):182-195.
27. Xu Z, Chen L, Gu W, et al. The performance of docetaxel-loaded solid lipid nanoparticles targeted to hepatocellular carcinoma. Biomaterials. 2009;30(2):226-232.
28. Kabanov AV, Batrakova EV, Miller DW. Pluronic block copolymers as modulators of drug efflux transporter activity in the blood-brain barrier. Adv Drug Deliv Rev. 2003;55(1):151-164.