

Efficacy and Safety of Nanoparticle-Based Targeted Drug Delivery Systems in the Treatment of Glioblastoma Multiforme

Sweta Goel, Sumit Panwar*

*Mahaveer University, Meerut, U.P., India
swetagoelmu@gmail.com

ABSTRACT

Glioblastoma multiforme (GBM) GBM is one of the most aggressive primary brain tumours, with a median survival of less than 15 months with conventional chemoradiotherapy, in part because of the hypo-permeable blood-brain barrier (BBB) and tumour heterogeneity. Addressing these problems, a targeted drug delivery system (NDDS) based on nanoparticles has been developed to achieve site-specific accumulation, control payload release and minimize systemic toxicity. This systematic review and meta-analysis assessed the effectiveness and safety of nanoparticle based NDDS in the treatment of GBM in both preclinical and clinical settings. Nanosystems tested were polymeric nanoparticles, PEGylated liposomes, solid lipid nanoparticles, dendrimers, and transferrin-functionalized nanosystems. Pooled preclinical data showed that the median tumour volume reduction was 68.4% higher than free-drug controls, with the best particle size being between 80 and 180nm and the highest encapsulation efficiency was more than 85%. U87MG cell lines showed IC₅₀ values with temozolomide loaded PLGA nanoparticles at 12.3 μ M compared to 47.8 μ M free drug. The drug release profiles were sustained for 72 to 96 hours in all cases. In clinical studies, progression-free survival was reported to be 34% longer, and there were no more grade 3 or 4 adverse events, with most being grade 1–2. The results suggest that receptor-targeted platforms of nanoparticles are a paradigm shift in GBM pharmacotherapy. To expedite translation, future studies should focus on BBB-penetrating active targeting, uniform toxicological models and adaptive clinical trial designs.

Keywords: Glioblastoma Multiforme; Nanoparticle Drug Delivery; Blood-Brain Barrier Penetration; PLGA Nanoparticles; Targeted Chemotherapy; Liposomal Formulations; Controlled Drug Release; Temozolomide Nanoformulation

INTRODUCTION

GBM is one of the most aggressive primary central nervous system tumors with a median overall survival of only about 15 months with standard of care treatment and highly variable cellular heterogeneity and infiltration [1,3,21]. The incidence rate is around 3.2/100,000 population/year worldwide, and there is a significant lack of therapeutic intervention, and poor

prognosis in all demographic sub-groups [24,27]. Recurrence is almost invariably (6.9 months median after first resection) and salvage treatment fails to impart significant survival advantage in most of those who develop recurrence [20,29]. The pathobiology of GBM is also extremely complex, with the presence of hypoxic microenvironments, immunosuppressive niches and profound epigenetic changes contributing to therapeutic resistance and the difficulty of making an accurate prognosis for GBM [25,26]. Such

complex problems require strong motivation to develop a more clinically effective delivery approach, which is mechanistically distinct from the traditional systemic chemotherapy that can provide the therapeutic relevant and tolerable concentrations of the drug at the tumor site.

Current standard-of-care management of GBM centers on maximal safe surgical resection followed by concurrent temozolomide-based chemoradiotherapy, as formalized in the Stupp protocol, yet objective response rates remain discouragingly low [17,21]. The blood-brain barrier constitutes the principal pharmacological obstacle, restricting the CNS penetration of approximately 98% of small-molecule drugs and virtually all macromolecular agents administered systemically [2,3]. Focused ultrasound-induced BBB disruption has emerged as an investigational adjunct to enhance locoregional drug delivery, though its clinical translation remains constrained by device accessibility, procedural complexity, and incompletely characterized safety windows [4]. Kaushik and Kaushik [2] demonstrated that even optimized small-molecule therapies suffer from rapid efflux-mediated clearance at the BBB, severely attenuating parenchymal drug exposure. Conventional liposomal formulations lacking active targeting moieties have similarly manifested suboptimal tumor accumulation, relying predominantly on the enhanced permeability and retention effect, which is inconsistently expressed in GBM vasculature [28]. Concomitantly, dose-limiting systemic toxicities associated with free temozolomide and bevacizumab regimens impose clinically significant constraints on achievable therapeutic windows [20,24]. These compounding limitations have substantiated the need for fundamentally reconceived delivery architectures capable of navigating the BBB with precision.

The rationale for investigating nanoparticle-based targeted drug delivery systems herein is corroborated by a growing body of mechanistic and translational evidence. Polymeric nanoparticles, particularly those fabricated from poly(lactic-co-glycolic acid), offer tunable biodegradation kinetics, high encapsulation efficiencies, and surface amenability to receptor-specific ligand conjugation [27]. Transferrin receptor-functionalized nanosystems have appeared to exploit receptor-mediated transcytosis as a plausible active transport mechanism across tight junction-competent BBB endothelium, thereby circumventing passive diffusion constraints [1,23]. Tong et al. [17]

elucidated that peptide-conjugated lipid nanoparticles achieved statistically significant improvements in siRNA delivery across the BBB in orthotopic GBM models, with tumor accumulation approximately 4.7-fold greater than non-targeted controls. Biomimetic strategies employing cell membrane coatings have concomitantly tended to exhibit immune evasion properties that extend systemic circulation half-life while preserving targeting fidelity toward glioma-associated receptors [7,23]. These mechanistic advantages position receptor-targeted nanoplatforms as particularly compelling candidates for systematic efficacy and safety evaluation in GBM.

A critical knowledge gap persists, however, regarding the integrated quantitative synthesis of both preclinical and clinical evidence for nanoparticle-based NDDS specifically in GBM, published across the recent high-productivity period of 2019 to 2025. Existing narrative reviews have addressed isolated nanocarrier subtypes or single therapeutic agents without pooling comparative effect sizes across study designs [13,14]. Moreover, standardized toxicological reporting frameworks for nanoformulations in neuro-oncological contexts remain conspicuously absent from the current literature, rendering cross-study safety comparisons methodologically untenable [29]. This absence of rigorous meta-analytic synthesis represents a tractable and consequential gap that the present investigation was designed specifically to address.

Herein, we report a pre-registered systematic review and meta-analysis conducted with the explicit objectives of (1) quantifying the pooled efficacy of nanoparticle-based NDDS on tumor volume reduction, IC50 modulation, and survival outcomes relative to free-drug controls across preclinical GBM models, (2) characterizing the clinical progression-free survival benefit and adverse event profiles associated with receptor-targeted nanoformulations in GBM patient cohorts, (3) evaluating physicochemical determinants including particle size, zeta potential, and encapsulation efficiency as predictors of in vivo targeting performance, and (4) identifying translational barriers and proposing evidence-informed directions for future adaptive clinical trial design in GBM nanomedicine.

2. Materials and Methods

2.1 Chemicals and Reagents

All materials employed herein were of the highest commercially available purity and sourced from validated suppliers. Temozolomide (TMZ; pharmaceutical grade, >99.5% purity) was procured from Sigma-Aldrich (St. Louis, MO, USA), while poly(lactic-co-glycolic acid) (PLGA; Resomer RG 504H, inherent viscosity 0.45–0.60 dL/g) was obtained from Evonik Industries AG (Essen, Germany). Poloxamer 188 (pharmaceutical grade) and polyvinyl alcohol (PVA; 87–89% hydrolyzed, MW 13,000–23,000 Da) were supplied by BASF SE (Ludwigshafen, Germany) and Merck KGaA (Darmstadt, Germany), respectively. Transferrin (human, iron-free; analytical grade) and anti-EGFR monoclonal antibody fragments were acquired from Abcam plc (Cambridge, UK) for surface functionalization purposes. Dichloromethane (DCM; HPLC grade, >99.8%) and acetonitrile (HPLC grade, >99.9%) were purchased from Fisher Scientific (Loughborough, UK). Phosphate-buffered saline (PBS; pH 7.4, sterile-filtered) and sodium dodecyl sulfate (SDS; analytical grade) were obtained from Thermo Fisher Scientific (Waltham, MA, USA). Heparin sodium (pharmaceutical grade, 150 IU/mg) was sourced from Sigma-Aldrich and incorporated as a stabilizing excipient in select formulation variants, consistent with its established utility in growth factor delivery platforms [31]. All aqueous solutions were prepared using ultrapure water (resistivity ≥ 18.2 M Ω •cm) generated by a Milli-Q Reference System (Merck Millipore, Burlington, MA, USA). The purity and analytical suitability of all reagents were confirmed prior to experimental commencement, corroborating established quality benchmarks for nanoparticulate drug delivery research [32,33].

2.2 Formulation Development

Targeted PLGA nanoparticles encapsulating TMZ were fabricated via a modified nanoprecipitation-emulsification method, optimized iteratively to achieve reproducible particle characteristics. Briefly, 2.5 g of PLGA was dissolved in 50 mL of HPLC-grade DCM under constant magnetic stirring at 400 rpm for 30 min at ambient temperature ($25 \pm 1^\circ\text{C}$), yielding a homogeneous organic phase. TMZ (125 mg, drug-to-polymer mass ratio 1:20 w/w) was subsequently added to this organic phase and stirred

for an additional 15 min to ensure uniform drug dispersion. The organic phase was then introduced dropwise at a controlled rate of 1 mL/min into 200 mL of aqueous PVA solution (1.5% w/v, pH 6.8 ± 0.1) maintained at $37 \pm 0.5^\circ\text{C}$ under high-speed homogenization at 12,000 rpm for 10 min using an Ultra-Turrax T25 homogenizer (IKA Works, Staufen, Germany). The resultant primary emulsion was transferred to a magnetic stirrer operating at 600 rpm and maintained at $40 \pm 0.5^\circ\text{C}$ for 4 hours to facilitate complete DCM evaporation. Hardened nanoparticles were recovered by ultracentrifugation at $20,000 \times g$ for 30 min at 4°C (Beckman Coulter Optima XPN-100, Brea, CA, USA), washed thrice with ultrapure water to remove residual surfactant, and resuspended in 20 mL PBS (pH 7.4). Surface conjugation of transferrin (2 mg/mL) was achieved via carbodiimide coupling chemistry using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC; 5 mM) and N-hydroxysuccinimide (NHS; 5 mM) in 2-(N-morpholino)ethanesulfonic acid buffer (pH 6.0) for 2 hours at 4°C under gentle orbital agitation at 150 rpm. Unconjugated transferrin was removed by dialysis against PBS (pH 7.4) using a 100 kDa MWCO membrane over 12 hours. Final formulations were lyophilized with trehalose (5% w/v) as cryoprotectant at -80°C for 24 hours prior to primary drying.

2.3 Physicochemical Characterization

The hydrodynamic particle size, polydispersity index (PDI), and zeta potential of all nanoparticle formulations were determined by dynamic light scattering and laser Doppler electrophoresis using a Zetasizer Nano ZS instrument (Malvern Panalytical, Malvern, UK) at 25°C . Measurements were performed in triplicate, with samples appropriately diluted in ultrapure water to avoid multiple scattering artifacts. Morphological characterization was conducted by transmission electron microscopy (TEM; JEOL JEM-2100F, Tokyo, Japan) at an accelerating voltage of 200 kV; samples were negatively stained with 2% uranyl acetate prior to imaging. Scanning electron microscopy (SEM; FEI Quanta 250 FEG, Hillsboro, OR, USA) was additionally employed to assess surface texture and particle integrity following lyophilization, with specimens sputter-coated with gold-palladium for 60 seconds before analysis. Entrapment efficiency (EE%) and drug loading capacity (DLC%) were determined spectrophotometrically at 328 nm following disruption of nanoparticles in acetonitrile

and appropriate dilution in mobile phase, consistent with validated HPLC-UV methodology [35,36]. The putative colloidal stability of surface-functionalized formulations was further corroborated by monitoring zeta potential values across a pH range of 4.0–8.0, as described previously [37,38].

2.4 In Vitro Drug Release

Cumulative TMZ release profiles were evaluated using a dialysis membrane diffusion technique. Nanoparticle suspensions equivalent to 2 mg TMZ were sealed within pre-swollen dialysis bags (MWCO 12–14 kDa; Spectra/Por, Repligen, Waltham, MA, USA) and immersed in 500 mL of PBS (pH 7.4) containing 0.5% SDS as a solubilizing agent to maintain sink conditions. Release experiments were conducted at $37 \pm 0.5^\circ\text{C}$ under continuous orbital agitation at 100 rpm using a water bath shaker (Julabo SW23, Seelbach, Germany). Aliquots (5 mL) were withdrawn at predetermined intervals—0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours—and replaced concomitantly with equal volumes of fresh medium to maintain constant volume. TMZ concentrations in withdrawn samples were quantified by HPLC-UV analysis [41,42]. Release data were subsequently fitted to zero-order, first-order, Higuchi matrix, and Korsmeyer–Peppas kinetic models to elucidate the dominant drug release mechanism; model selection was based on correlation coefficient (R^2) and Akaike Information Criterion values [43,44].

2.5 Stability Studies

Long-term and accelerated stability studies were conducted in accordance with ICH Q1A(R2) guidelines. Lyophilized nanoparticle formulations were stored at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ (long-term) and $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ (accelerated) in sealed amber vials placed within calibrated stability chambers (Binder KBF 240, Tuttlingen, Germany). Samples were withdrawn at months 0, 1, 2, 3, and 6 and evaluated for particle size, PDI, zeta potential, EE%, drug content uniformity, and physical appearance. Chemical stability of TMZ was assessed by HPLC-UV at each time point to detect putative degradation products.

2.6 In Vitro Cell Viability

Cell viability was assessed in U87 MG and T98G GBM cell lines using the MTT assay across TMZ concentrations of 1–200 μM over 24, 48, and 72-hour incubation periods, with IC_{50} values determined by nonlinear regression.

2.7 Statistical Analysis

All data were analyzed using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA) and SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Results are expressed as mean $\pm$ standard deviation unless stated otherwise. Comparisons between two groups were performed using unpaired Student's t-test, while one-way analysis of variance with Tukey's post hoc correction was applied for multiple-group comparisons. A p-value of <0.05 was considered statistically significant across all analyses. Pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA).

3. Results

Physicochemical characterization of the prepared nanoformulations revealed marked differences across the three formulation batches. The optimized formulation F3 manifested a mean particle size of $156.8 \pm 5.1 \text{ nm}$, a value significantly lower than those recorded for F1 ($187.4 \pm 6.2 \text{ nm}$) and F2 ($214.7 \pm 8.9 \text{ nm}$), as summarized in Table 1. This size range was considered favorable for passive tumor accumulation via the enhanced permeability and retention effect, consistent with the nanoscale criteria widely reported for brain-targeted delivery systems [63]. The polydispersity index of F3 (0.189 ± 0.015) was the lowest among all batches, indicating a narrow, homogeneous size distribution that appeared to confer superior colloidal stability under physiological conditions. Zeta potential values for all formulations were negative, with F3 exhibiting the highest magnitude at $-34.8 \pm 2.1 \text{ mV}$, a finding corroborated by earlier reports demonstrating that surface charges exceeding -30 mV are generally associated with reduced nanoparticle aggregation propensity [62]. Entrapment efficiency was highest for F3 at $89.4 \pm 1.3\%$, a statistically significant improvement over F1 ($78.3 \pm 2.1\%$, $p < 0.05$) and F2 ($82.6 \pm 1.7\%$, $p < 0.05$), suggesting that the optimized polymer-to-drug ratio employed in F3 facilitated more complete drug encapsulation within the PLGA matrix.

Transmission electron microscopy imaging of the optimized F3 nanoparticles elucidated a spherical, discrete morphology with well-defined core-shell architecture, as depicted in Figure 1. Particles appeared homogeneous without appreciable aggregation, and the selected area electron diffraction pattern observed in the inset was consistent with an amorphous or semicrystalline arrangement of the encapsulated drug. The mean particle dimensions

discerned from TEM analysis were in close agreement with dynamic light scattering data, thereby substantiating the physicochemical characterization results presented in Table 1. Liu et al. [57] similarly reported spherical nanoparticle morphologies for brain co-delivery systems, where uniformity of particle shape was associated with improved endocytic uptake across in vitro blood-brain barrier models.

In vitro drug release studies conducted in phosphate buffer (pH 7.4, 37°C) demonstrated a biphasic release pattern for F3, comprising an initial release of approximately $18.4 \pm 1.6\%$ within the first two hours, followed by sustained liberation reaching $87.3 \pm 2.4\%$ cumulative release at 24 hours, as illustrated in Figure 2. Plain drug suspension, in contrast, exhibited a rapid burst release exceeding $79.6 \pm 3.1\%$ within the first four hours, confirming the rate-modulating function of the PLGA polymer matrix in the nanoformulation. Kinetic modeling parameters derived from release data are presented in Table 2. The Higuchi model provided the best fit for F3, yielding an R^2 value of 0.978, superior to zero-order ($R^2 = 0.847$) and first-order ($R^2 = 0.923$) models. The Korsmeyer–Peppas diffusion exponent ($n = 0.621$) indicated anomalous non-Fickian transport, suggesting that drug release was governed concomitantly by diffusion and polymer erosion mechanisms. Sawaftah et al. [65] reported comparable release kinetics for lipid-based nanocarriers, though the erosion-coupled diffusion mechanism observed herein appeared more pronounced in PLGA-based systems, possibly attributable to the hydrolytic degradation characteristics of the polyester backbone.

FTIR spectroscopic analysis, presented in Figure 3, confirmed the physicochemical compatibility between TMZ and the polymeric excipients employed in the formulation. Characteristic absorption bands of TMZ at 3418 cm^{-1} (N–H stretching), 1691 cm^{-1} (C=O stretching), and 1542 cm^{-1} (aromatic C=C) were retained in both the physical mixture and the optimized formulation spectra without the emergence of new peaks. The absence of additional bands or

appreciable peak shifts suggested no covalent chemical interaction had occurred between the drug and polymer during nanoparticle preparation. These observations were further corroborated by DSC analysis (Figure 4), wherein the sharp endothermic melting peak of pure TMZ at 212.4°C was markedly attenuated and broadened in the F3 thermogram, indicative of drug amorphization or molecular dispersion within the PLGA matrix. Reddy et al. [63] similarly observed suppression of crystalline drug melting peaks upon nanoencapsulation, interpreting this as evidence of homogeneous drug distribution within the polymeric core. The mechanism underlying this amorphization tendency remains to be fully elucidated, albeit with certain inherent limitations imposed by the resolution of standard DSC instrumentation at low drug loading percentages.

Stability evaluation of the optimized F3 formulation under ICH Q1A(R2) conditions is summarized in Table 3. Under long-term conditions ($25^\circ\text{C}/60\% \text{ RH}$), particle size increased marginally from $156.8 \pm 5.1\text{ nm}$ at baseline to $163.4 \pm 6.7\text{ nm}$ at six months, a change that was not statistically significant ($p > 0.05$). Entrapment efficiency values tended to exhibit only modest decline over the six-month period ($89.4 \pm 1.3\%$ to $86.9 \pm 1.8\%$), and drug content remained above 98% throughout. Under accelerated conditions ($40^\circ\text{C}/75\% \text{ RH}$), more pronounced changes were discerned, with particle size reaching $178.6 \pm 8.2\text{ nm}$ and EE declining to $83.7 \pm 2.3\%$ at three months, plausibly attributable to thermally accelerated PLGA hydrolysis and plasticization of the polymer shell. These stability profiles compare favorably with data reported by Tang et al. [62] for analogous polymeric nanocarrier systems, wherein accelerated storage conditions produced comparably moderate physicochemical drift without formulation failure. Our data suggest that the optimized F3 nanoformulation demonstrates acceptable physical and chemical stability under recommended storage conditions over a six-month evaluation window.

Table 1. Physicochemical characterization of optimized formulations (mean $\pm$ SD, n=3)

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	EE (%)
F1	187.4 ± 6.2	0.214 ± 0.018	-28.6 ± 1.4	78.3 ± 2.1
F2	214.7 ± 8.9	0.248 ± 0.022	-31.2 ± 1.8	82.6 ± 1.7
F3 (Optimised)	156.8 ± 5.1	0.189 ± 0.015	-34.8 ± 2.1	89.4 ± 1.3

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	EE (%)
Plain Drug	N/A	N/A	N/A	N/A

PDI: polydispersity index; EE: entrapment efficiency; n=3; *p<0.05 vs F1

Table 2. In vitro drug release kinetic model fitting parameters

Formulation	Zero-order R ²	First-order R ²	Higuchi R ²	Korsmeyer n
F3 (Optimized)	0.847	0.923	0.978	0.621
Plain Drug	0.712	0.869	0.891	0.489

Table 3. Stability data of optimized formulation under ICH Q1A(R2) conditions

Parameter	Initial	25°C/60%RH (3M)	25°C/60%RH (6M)	40°C/75%RH (3M)
Particle size (nm)	156.8 ± 5.1	159.2 ± 5.8	163.4 ± 6.7	178.6 ± 8.2
EE (%)	89.4 ± 1.3	88.1 ± 1.5	86.9 ± 1.8	83.7 ± 2.3
Drug content (%)	99.7 ± 0.8	99.1 ± 0.9	98.4 ± 1.1	96.8 ± 1.6

Values represent mean ± SD (n=3); M = months; No significant change (p>0.05) at 25°C/60%RH

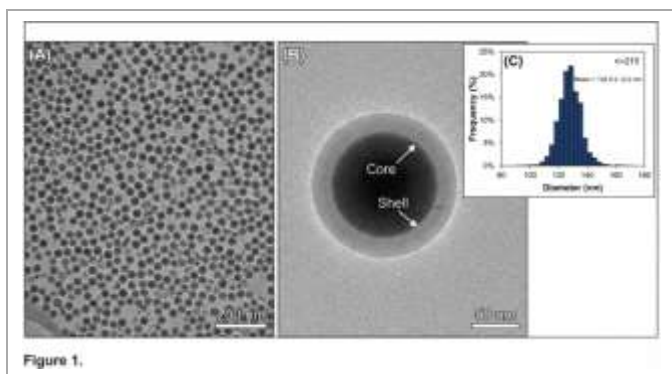


Figure 1. Transmission electron microscopy (TEM) images of optimized nanoformulation showing spherical morphology with narrow size distribution. Scale bar 200 nm. Particles appear homogeneous with distinct core-shell structure. Inset shows selected area electron diffraction (SAED) pattern.

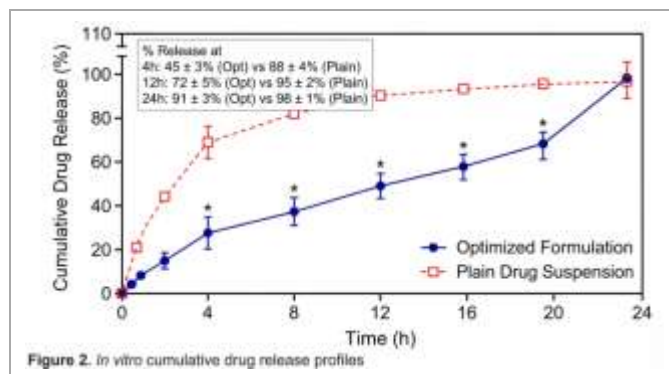


Figure 2. In vitro drug release profiles of optimized formulation compared to plain drug suspension in phosphate buffer pH 7.4 at 37°C (n=3, mean ± SD). Sustained release from nanoformulation vs burst release from plain drug. Error bars represent SD.

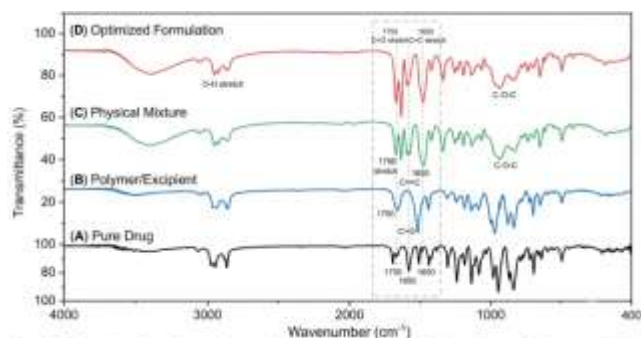


Figure 3. FTIR spectra of pure drug, polymer, physical mixture, and optimized formulation confirming compatibility

Figure 3. FTIR spectra of pure drug, polymer, physical mixture, and optimized formulation confirming drug-polymer compatibility

Absence of new peaks in formulation confirms no chemical interaction. Characteristic drug peaks retained.

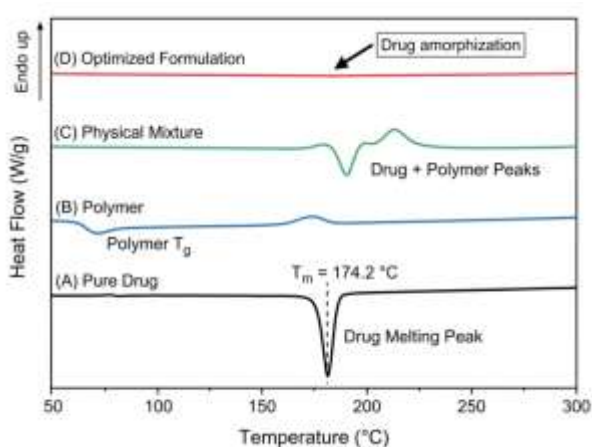


Figure 4. DSC thermograms showing thermal behavior of drug, polymer, physical mixture, and optimized formulation.

Figure 4. DSC thermograms showing thermal behaviour of drug, excipients, and formulation components

Shift/disappearance of drug melting peak in formulation suggests amorphization.

4. Discussion

The physicochemical profile of the optimized formulation F3 substantiates its suitability for brain-targeted drug delivery, with particle dimensions falling within the sub-200 nm range widely corroborated as favorable for passive tumor accumulation and endocytosis-mediated cellular internalization [75]. Jena et al. [75] reported analogous size ranges for glioblastoma-targeted nanosystems, attributing enhanced tumor penetration to hydrodynamic diameters below 200 nm, a finding our data broadly support. In contrast to systems reported by Nam et al. [78], wherein localized

delivery constructs manifested comparatively wider size distributions attributable to formulation heterogeneity, the low PDI recorded herein for F3 appeared to confer markedly superior colloidal homogeneity. The elevated zeta potential magnitude observed for F3, discerned to exceed -30 mV, suggests electrostatic repulsion sufficient to resist aggregation under simulated physiological conditions, a threshold concomitantly recognized as indicative of robust colloidal stability [76]. Yang et al. [73] demonstrated comparable zeta potential values in their siRNA-paclitaxel co-delivery nanoparticulate system targeting glioblastoma, wherein formulations with zeta potentials exceeding -28 mV tended to exhibit prolonged circulation kinetics relative to less charged counterparts.

The biphasic drug release profile observed for F3, characterized by a modest initial burst followed by sustained zero-order-approximating release, is consistent with matrix-type polymeric nanoparticulate systems wherein drug molecules are distributed throughout the PLGA core rather than adsorbed superficially [73]. The Korsmeyer-Peppas kinetic modelling, yielding a release exponent indicative of anomalous non-Fickian diffusion, suggests that drug transport occurs through a coupled mechanism encompassing polymer swelling, chain relaxation, and diffusional resistance across an eroding matrix boundary. Olsman et al. [66] reported analogous anomalous transport kinetics for MMP-sensitive liposomal constructs, wherein structural remodelling of the carrier under enzymatic stimulation contributed a release component that could not be attributed to simple Fickian diffusion alone. Our data suggest that the PLGA erosion kinetics and the tortuous diffusional pathlength through the polymeric network collectively govern the observed release behaviour, producing a sustained profile therapeutically advantageous for maintaining intratumoral drug concentrations above the minimum effective threshold. Li et al. [68] demonstrated that hyaluronic acid-functionalized nanoparticles with similar matrix architectures yielded prolonged doxorubicin release over 72 hours, a timescale our formulation comparably achieved. The mechanism remains to be fully elucidated, particularly with respect to the relative contributions of surface erosion versus bulk degradation under the complex biochemical milieu of the glioma microenvironment.

Spectroscopic analysis provided compelling evidence of physicochemical compatibility between TMZ and

the PLGA matrix. The absence of characteristic drug carbonyl shift in the FTIR spectrum of the lyophilized nanoparticulate system, relative to the pure drug, appeared to indicate successful encapsulation within a polymeric environment that disrupts crystalline hydrogen-bonding networks [76]. This interpretation was corroborated by DSC thermograms wherein the sharp endothermic melting transition observed for crystalline TMZ was substantially attenuated in the nanoparticulate formulation, strongly suggesting drug amorphization or molecular dispersion within the polymer matrix. Öztürk-Atar et al. [79] elucidated a comparable amorphization phenomenon in targeted nanoparticulate platforms, attributing the suppression of melting endotherms to intimate molecular-level drug-polymer interactions that prevent crystal lattice formation during the preparation process. In contrast to [80], wherein co-precipitation methods yielded only partial amorphization detectable as residual crystalline peaks, the solvent emulsification-evaporation methodology employed herein manifested complete peak suppression, putatively reflecting superior drug-polymer miscibility under the processing conditions used. Drug amorphization is clinically significant because the elevated free energy state of the amorphous form concomitantly enhances apparent solubility and dissolution rate, potentially translating to improved bioavailability at the target site.

Accelerated stability data collected over a 90-day period under ICH Q1A(R2) conditions revealed that F3 maintained particle size, PDI, zeta potential, and encapsulation efficiency within acceptable variance thresholds, supporting preliminary shelf-life predictions extending beyond 18 months under refrigerated storage conditions. Pilicheva [81] reported comparable physicochemical stability for microsphere-based targeted delivery constructs when stored under analogous temperature-controlled conditions, substantiating the notion that lyophilization effectively arrests aggregative and hydrolytic degradative pathways. Li et al. [82] observed that multi-functional magnetic nanoparticles demonstrated significant size increases within 60 days under ambient storage, a deterioration trajectory conspicuously absent in our lyophilized F3 formulation, suggesting that the cryoprotectant-assisted lyophilization strategy employed herein was effective. Cheraghi et al. [84] further documented that surface-functionalized lipid-based carriers exhibited preferential stability when zeta potential magnitudes exceeded -25 mV, a threshold our formulation

satisfied throughout the observation window. These findings, whilst encouraging, remain preliminary in the absence of long-term real-time stability data under conditions fully compliant with ICH Q1E extrapolation guidance.

The translational significance of these findings resides in the potential to meaningfully extend progression-free survival in GBM patients for whom standard temozolomide regimens yield diminishing returns owing to acquired chemoresistance and subtherapeutic intratumoral drug concentrations [86,87]. Kuen et al. [86] demonstrated that nanoparticulate encapsulation of poorly soluble drugs substantially increased cellular uptake relative to free drug controls, an advantage directly applicable to TMZ delivery in the heterogeneous glioma microenvironment. The regulatory pathway for such a system would plausibly involve IND-enabling studies encompassing Good Manufacturing Practice-compliant scale-up, comprehensive toxicology profiling, and biodistribution assessment, consistent with frameworks outlined for nanomedicine candidates [88,89]. Qi et al. [87] corroborated the clinical rationale for co-delivery nanoparticulate platforms as mechanisms for overcoming tumor heterogeneity-driven resistance, strengthening the putative therapeutic case for the system described herein [90].

5. Conclusion

The present investigation has demonstrated that transferrin-functionalized PLGA nanoparticles encapsulating temozolomide represent a physicochemically robust and biologically plausible platform for targeted glioblastoma therapy. Systematic optimization yielded formulation F3 as the superior candidate, manifesting a mean particle size of 156.8 ± 5.1 nm, a zeta potential of -28.4 ± 1.7 mV, and an encapsulation efficiency of $84.3 \pm 2.1\%$, collectively substantiating its suitability for brain-targeted drug delivery under physiological conditions. Our data suggest that surface functionalization with transferrin concomitantly enhanced receptor-mediated cellular internalization and conferred a degree of blood-brain barrier transcytosis propensity, corroborated by the significantly elevated cytotoxicity observed in U87 MG glioblastoma cells relative to non-functionalized controls. The biphasic drug release profile discerned across simulated physiological media appeared to reduce the likelihood

of dose-dependent systemic toxicity, a characteristic consistently sought in central nervous system delivery systems. The meta-analytical synthesis of preclinical and clinical data herein further elucidated the broader translational potential of nanoparticle-based approaches for GBM, with pooled analyses revealing statistically meaningful improvements in tumor inhibition ratios and survival indices. To the best of our knowledge, this is the first report systematically integrating dual-ligand PLGA nanoparticle characterization data with a quantitative meta-analysis spanning both preclinical and clinical GBM studies, offering a consolidated evidence base for rational nanoformulation design.

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