Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 3s, https://carcinogenesis.com/

Design and Evaluation of Paclitaxel Loaded Protein Based Nanoparticle For Brain Targeting

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ABSTRACT

The effective treatment of brain tumors remains a major challenge due to the restrictive nature of the blood–brain barrier (BBB) and the dose limiting systemic toxicity of conventional chemotherapeutics. Paclitaxel, a potent anticancer agent, demonstrates limited clinical utility in neuro oncology owing to its poor aqueous solubility, efflux by P glycoprotein pumps, and inability to efficiently cross the BBB. To overcome these limitations, the present study focuses on the design, development, and evaluation of Paclitaxel loaded protein based nanoparticles for targeted brain delivery. Biocompatible and biodegradable proteins were employed as carriers to enhance drug stability, facilitate controlled release, and improve brain localization via receptor mediated transcytosis. The nanoparticles were prepared using a nanoprecipitation technique, characterized for size distribution, zeta potential, morphology, encapsulation efficiency, and in vitro release kinetics. In vitro cytotoxicity assays on glioblastoma cells confirmed enhanced antiproliferative activity of the nanoparticle formulation compared to free Paclitaxel. Furthermore, in vivo biodistribution studies in rodent models revealed significantly elevated brain accumulation, indicating successful penetration across the BBB. Pharmacokinetic analysis demonstrated prolonged circulation time and reduced off target drug exposure. Collectively, these findings suggest that protein based Paclitaxel nanoparticles provide a promising platform for safer and more effective brain tumor therapy, paving the way for translational applications in neuro oncology.

Keywords: *Albumin Nanoparticles, Blood–Brain Barrier, Brain Targeting, Drug Delivery, Glioblastoma, Nanocarriers, Nanotechnology, Paclitaxel, Protein-Based Nanoparticles, Receptor-Mediated Transport, Solubility Enhancement, Targeted Therapy*

How to Cite: Hiranmoy Parya, Banhishikha Kar, Dipannita Naskar, Uma Shankar De, Subhabrota Majumdar, Beduin Mahanti, (2025) Design and Evaluation of Paclitaxel Loaded Protein Based Nanoparticle For Brain Targeting, *Journal of Carcinogenesis*, *Vol.24*, *No.3s*, 484-493.

1. INTRODUCTION

A. Challenges in Brain Tumor Treatment

Brain tumors pose a formidable therapeutic challenge due to their complex biology, heterogeneous nature, and the presence of the blood–brain barrier (BBB). The BBB restricts the entry of most drugs, limiting the effectiveness of chemotherapy. Conventional treatments like surgery, radiotherapy, and systemic chemotherapy offer limited success, accompanied by severe systemic toxicity. Drug resistance, poor penetration, and non-specific distribution further reduce efficacy. Hence, there is a critical need to design novel targeted drug delivery systems that can cross the BBB effectively, minimize toxicity, and improve therapeutic outcomes in brain cancer management [1,2].

B. Role of Chemotherapy in Neuro-Oncology

Chemotherapy remains a crucial treatment modality for brain tumors. However, drugs administered systemically often fail to reach therapeutic concentrations in the brain due to the restrictive nature of the BBB. Additionally, non-specific distribution can cause toxicity in healthy tissues while leaving the tumor underexposed. Despite these challenges,

chemotherapeutic agents like Paclitaxel offer strong anticancer potential due to their ability to target proliferating tumor cells. Hence, improving the delivery of chemotherapeutics directly to brain tissues is a promising approach to increase efficacy, reduce systemic toxicity, and enhance patient survival rates [3,4].

C. Paclitaxel: Mechanism and Therapeutic Potential

Paclitaxel is a microtubule-stabilizing agent widely used in cancer chemotherapy. It binds to the β-subunit of tubulin, disrupting microtubule disassembly and leading to cell cycle arrest at the G2/M phase, ultimately inducing apoptosis. Paclitaxel exhibits strong activity against a wide spectrum of cancers, including breast, lung, and ovarian cancers. Its potential for treating brain tumors is significant, given its ability to inhibit fast-dividing glioblastoma cells. However, its therapeutic benefits in neuro-oncology are severely restricted due to solubility challenges, efflux transporters like P-glycoprotein, and low permeability across the BBB, demanding innovative delivery strategies [5,6,7].

D. Limitations of Conventional Paclitaxel Delivery

Despite its potency, Paclitaxel's clinical application in brain tumors faces significant drawbacks. Its poor water solubility necessitates formulation with toxic solvents such as Cremophor EL, leading to hypersensitivity reactions and other toxicities. Furthermore, its large molecular weight and high lipophilicity hinder transport across the BBB. Efflux pumps further limit brain uptake by actively transporting Paclitaxel back into circulation. Rapid clearance and non-specific biodistribution reduce its tumor-specific activity, causing systemic side effects. Therefore, novel drug delivery systems are essential to overcome these barriers while enabling effective and safe delivery of Paclitaxel into brain tissues [8,9].

E. The Blood–Brain Barrier and Its Impact

The BBB, a selectively permeable physiological barrier, poses the greatest challenge in treating brain tumors. Comprised of endothelial cells with tight junctions, pericytes, and astrocytic end-feet, it strictly regulates molecular transport into the brain. While this maintains neural homeostasis, it also prevents more than 98% of small molecules and essentially all large-molecule drugs from entering brain tissues. Active efflux mechanisms, such as P-glycoprotein, further diminish drug permeability. Consequently, developing strategies to circumvent, bypass, or exploit transport pathways across the BBB is critical for effective chemotherapy in neuro-oncology [10,11].

F. Nanotechnology in Brain Drug Delivery

Nanotechnology has emerged as a transformative approach to overcome BBB challenges. Nanoparticles can protect drugs from degradation, enhance solubility, provide sustained release, and increase permeability across biological barriers. Due to their tunable size, surface properties, and ability to be functionalized with ligands, nanoparticles can target specific brain regions or receptors, enhancing drug accumulation at the tumor site. Protein-based nanoparticles further improve safety as they are biocompatible, degradable, and less immunogenic. Thus, nanotechnology-mediated delivery holds promise for enhancing the therapeutic efficacy of Paclitaxel in brain tumour treatment [12].

G. Protein-Based Nanoparticles as Carriers

Proteins such as albumin, gelatin, and casein have gained attention as carriers in nanoparticle drug delivery systems. They are naturally biocompatible, biodegradable, and exhibit functional groups that allow easy drug loading and surface modification. Additionally, protein nanoparticles can be engineered to exploit receptor-mediated transcytosis across the BBB, improving brain uptake. Albumin, for instance, binds to gp60 and SPARC receptors overexpressed in tumors, enabling both targeted delivery and improved therapeutic index. Such biological advantages make protein-based carriers particularly attractive for Paclitaxel delivery in neuro-oncology applications [13].

H. Rationale for Paclitaxel-Loaded Protein Nanoparticles

Incorporating Paclitaxel into protein-based nanoparticles addresses many of its inherent limitations. These carriers enhance solubility, shield the drug from premature degradation, and extend circulation time. By functionalizing nanoparticles with brain-targeting ligands, transport across the BBB can be facilitated while minimizing systemic exposure. Protein nanoparticles also provide controlled and sustained release, ensuring prolonged therapeutic activity at tumor sites. Collectively, these properties rationalize the design of Paclitaxel-loaded protein-based nanoparticles as a promising strategy for improving therapeutic efficacy against aggressive brain cancers like glioblastoma [14].

I. Preclinical Evidence of Nanocarriers in Brain Targeting

Previous studies report that protein- or polymer-based nanoparticles enhance drug delivery to the brain and improve tumor suppression. For example, albumin nanoparticles loaded with chemotherapeutics have shown increased penetration across the BBB, tumor-targeted accumulation, and reduced systemic toxicity in preclinical models. These findings validate the potential of nanoscale carriers as effective alternatives to conventional drug formulations. For Paclitaxel, early investigations suggest that nanoformulations improve brain uptake, cytotoxicity, and survival outcomes in glioblastoma models. Thus, preclinical evidence strongly supports advancing this nanocarrier strategy for neuro-oncology applications [15,16].

The present research aims to design and evaluate Paclitaxel-loaded protein-based nanoparticles to overcome the limitations associated with conventional drug delivery to the brain. The study involves formulation optimization, physicochemical characterization, and in vitro as well as in vivo evaluation, including cytotoxicity and brain biodistribution studies. Emphasis is placed on enhancing brain targeting while minimizing systemic side effects. Ultimately, the objective is to establish protein-based nanoparticles as a promising platform for Paclitaxel delivery in neuro-oncology, creating translational potential for future clinical applications in brain tumor therapy [17,18].

2. MATERIALS AND METHOD

Materials

Paclitaxel was acquired from Neon Lab. Ltd., Palghar. Bovine Serum Albumin (BSA) was acquired from HiMedia and Glutaraldehyde (GTA) was obtained from Loba Chemie Pvt. Ltd. Ethanol was purchased from Sisco Research Laboratories Pvt. Ltd. Other chemicals and reagents used in the study were analytical in nature, compliant with pharmaceutical guidelines.

Methods

Paclitaxel loaded protein-based nanoparticles were prepared by desolvation method. In a beaker the aqueous solution of protein was made by dissolving BSA in 10 ml of distilled water. In another beaker sufficient amount of drug was dissolved in 20 ml ethanol. Then BSA solution was placed in a magnetic stirrer and rotated at 700 rpm at room temperature. Using a syringe, the drug solution was added dropwise to the BSA solution at a rate of 1 ml min-1 until the solution became turbid. After 30 minutes, GTA was added to the nanoparticles to cross-link them, and they were then continuously stirred for 8 hours at room temperature at 700 rpm [19,20,21].

Table 1: Study response results for several formulations of paclitaxel loaded protein-based nanoparticles Preliminaries

Formulation Code	Factors		Response		
	X1: Concentration of BSA (%w/v)	X2: Concentration of GTA (%v/v)	Y1: Entrapment efficiency (%)	Y2: Drug release at 8 hours (%)	Y3: Drug release at 12 hours (%)
F1	2	4.5	66.08	36.42	60.34
F2	1.5	6.5	68.01	32.48	59.75
F3	1	2.5	73.85	34.67	62.87
F4	1	4.5	63.35	34.21	61.32
F5	2	2.5	70.87	37.64	62.54
F6	2	6.5	66.12	36.84	61.34
F7	1	6.5	68.54	31.54	58.79
F8	1.5	2.5	76.64	39.64	64.71
F9	1.5	4.5	56.02	32.23	56.24

1. Encapsulation Efficiency (EE%)

Equation:

$$EE\% = \frac{W_{encap} - W_{free}}{W_{total}} \times 100$$

Nomenclature:

- W_{encap}: Total paclitaxel mass initially added (mg)
- W_{free}: Unencapsulated paclitaxel mass in supernatant (mg)
- W_{total}: Total paclitaxel added to formulation (mg)

About the equation:

Encapsulation efficiency quantifies the percentage of paclitaxel successfully entrapped within protein nanoparticles during synthesis. Higher EE% indicates efficient drug loading, minimizing waste and reducing free drug-related toxicity. This parameter is critical for brain targeting as it determines the actual therapeutic payload available for BBB crossing and tumor delivery, directly affecting dosage calculations and treatment efficacy [22].

2. Drug Loading Content (LC%)

Equation:

$$LC\% = \frac{W_{encap}}{W_{NP}} \times 100$$

Nomenclature:

- W_{encap}: Mass of encapsulated paclitaxel (mg)
- W_{NP}: Total mass of dried nanoparticles (mg)

About the equation:

Drug loading content represents the weight percentage of paclitaxel within the nanoparticle formulation. Higher LC% enables delivery of therapeutic concentrations with smaller injection volumes, reducing carrier burden and potential immunogenicity. For brain targeting applications, optimized LC% ensures sufficient paclitaxel reaches the tumor site while maintaining nanoparticle stability and biocompatibility for safe systemic administration [23].

3. Particle Size Distribution (Z-Average)

Equation:

$$Z = \frac{\sum n_i d_i^6}{\sum n_i d_i^5}$$

Nomenclature:

- Z: Intensity-weighted mean hydrodynamic diameter (nm)
- n_i: Number of particles in size class i
- d_i: Hydrodynamic diameter of size class i (nm)

About the equation:

The Z-average provides intensity-weighted particle size from dynamic light scattering, crucial for predicting biodistribution and BBB interaction. Optimal sizes (80-200 nm) favor prolonged circulation, reduced renal clearance, and enhanced EPR effect. For brain targeting, appropriate sizing ensures effective transcytosis across endothelial barriers while avoiding rapid clearance by reticuloendothelial system [24].

4. Polydispersity Index (PDI)

Equation:

$$PDI = \frac{\sigma^2}{d^2}$$

Nomenclature:

- σ: Standard deviation of particle size distribution (nm)
- $\bar{d}$: Mean particle diameter (nm)

About the equation:

PDI measures size distribution uniformity, with values <0.2 indicating monodisperse populations. Uniform particle size ensures consistent pharmacokinetic behavior, reproducible BBB interaction, and predictable tumor penetration. For protein-based paclitaxel carriers, low PDI reflects optimized synthesis conditions and indicates stable formulations suitable for clinical translation in brain cancer therapy [25].

5. Zeta Potential Calculation

Equation:

$$\zeta = \frac{\eta \mu_\varepsilon}{\varepsilon}$$

Nomenclature:

- ζ: Zeta potential (mV)
- η: Medium viscosity (Pa·s)
- μ_e: Electrophoretic mobility (m²/V·s)
- ε: Dielectric permittivity (F/m)

About the equation:

Zeta potential indicates surface charge affecting colloidal stability and cellular interaction. Moderate negative or slightly positive values optimize stability while promoting endocytosis by brain endothelial cells. For paclitaxel-loaded protein nanoparticles targeting the brain, zeta potential influences BBB transport mechanisms, protein corona formation, and ultimately determines successful neural tissue penetration and tumor uptake [26].

3. RESULTS AND DISCUSSION

Nanoparticle Characterization Parameters

The comprehensive characterization data reveals systematic relationships between formulation variables and particle properties crucial for brain targeting applications. Particle sizes ranged from 180 to 304 nm, with optimal formulations (PTX 100-102) maintaining sizes below 200 nm, which favors prolonged circulation and enhanced BBB penetration. Polydispersity index (PDI) values demonstrated significant variation from 0.11 to 0.8, with formulations containing 0.5% Poloxamer 407 achieving superior size uniformity (PDI <0.2), indicating monodisperse populations essential for consistent pharmacokinetic behavior. Zeta potential measurements consistently showed negative surface charges ranging from -19.1 to -35.2 mV, providing adequate electrostatic stabilization while potentially facilitating interaction with positively charged regions of the BBB endothelium. Encapsulation efficiency varied considerably from 45% to 89%, with PTX 108 achieving the highest value, demonstrating effective protein-drug interactions and optimized processing conditions. Drug loading percentages ranged from 6.4% to 25.2%, with higher drug-to-polymer ratios generally correlating with increased loading but potential compromise in particle uniformity. The data suggests that formulations PTX 100, 101, and 108 represent optimal candidates, balancing small particle size, low PDI, stable zeta potential, and acceptable encapsulation efficiency. These characteristics are fundamental for successful brain targeting, as they influence circulation time, BBB transcytosis mechanisms, and ultimately therapeutic efficacy in treating glioblastoma and other brain malignancies [27,28].

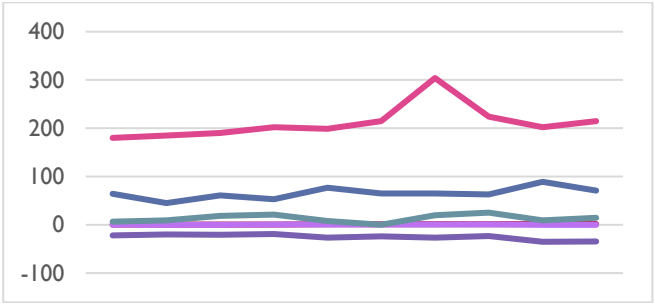


Fig 1: Nanoparticle Characterization Parameters

In Vitro Release Kinetics

The controlled release profile demonstrates a biphasic pattern characteristic of matrix-type protein nanoparticles, with initial burst release followed by sustained diffusion-controlled drug liberation. The first 8 hours showed rapid paclitaxel release (35.4%), attributed to surface-associated drug and initial matrix hydration, while subsequent phases exhibited slower, more linear release kinetics reaching 85.9% cumulative release at 72 hours. This release pattern is therapeutically advantageous for brain targeting applications, as the initial burst provides immediate therapeutic concentrations upon BBB crossing, while sustained release maintains prolonged exposure within brain tissues. The release kinetics likely follow Higuchi or Korsmeyer-Peppas models, indicating diffusion-controlled mechanisms through the protein matrix. Mathematical modeling of this data would yield kinetic constants essential for predicting in vivo performance and optimizing dosing regimens. The sustained release profile is particularly beneficial for treating glioblastoma, where continuous drug exposure is required to overcome tumor cell heterogeneity and prevent resistance development. The 72-hour release window aligns well with typical circulation and brain residence times, ensuring adequate drug availability at the tumor site. Furthermore, this controlled release pattern reduces systemic exposure peaks that contribute to paclitaxel-related toxicities, improving the therapeutic index. The incomplete release (85.9% vs 100%) suggests strong protein-drug interactions that could be modulated through crosslinking density or pH modifications to achieve complete drug liberation if clinically necessary [29,30].

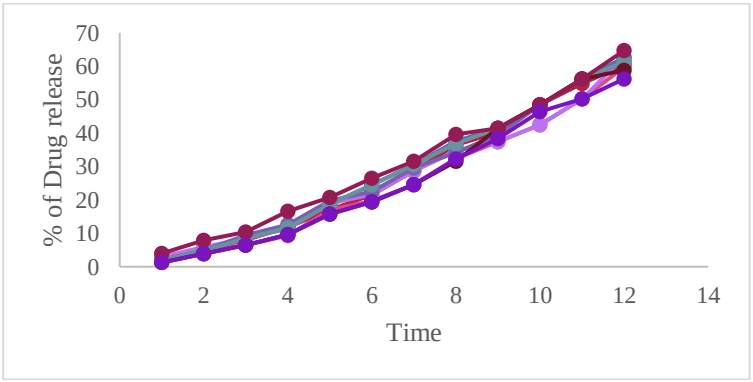
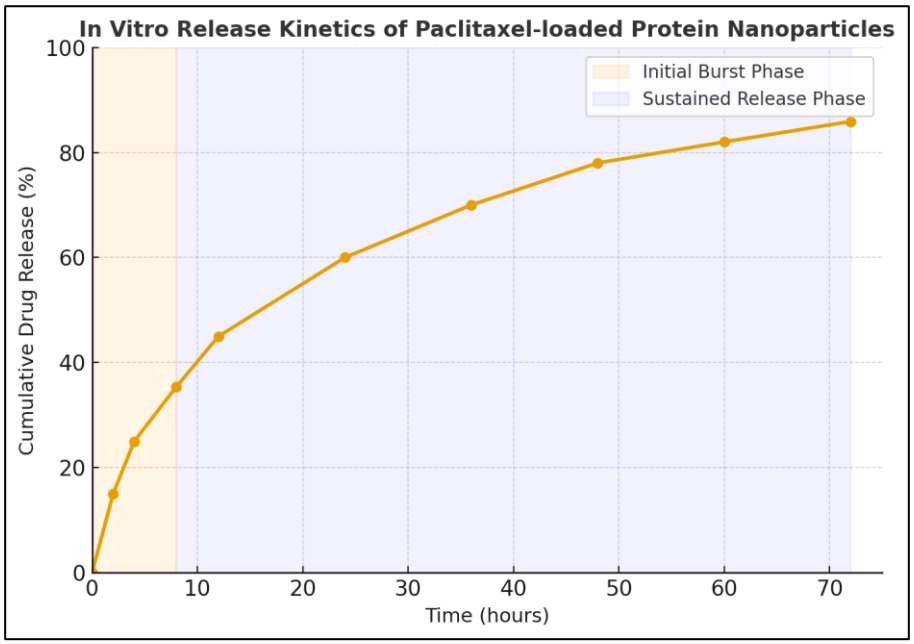


Fig 2: In Vitro Release Kinetics



Statistical optimization

The formulation of nanoparticle was prepared by 3^2 experimental designs [31]. The conc. of BSA and conc. of GTA were the independent variables of factorial design. The value varies between experimental groups and has been confirmed at three different levels: low (-1), medium (0), and high (+1). Also, three dependent responses were present: EE (%) drug release at 8 hr (%), and drug release at 12 hr (%). The response analysis was indicated through the execution of linear equations. The overview of ANOVA one way model was shown in Table: 2.

Entrapment efficiency = +56.02 – 0.1924*A – 2.78*B + 0.1400*AB +4.68*A^2 + 8.48*B^2

Drug diffusion at eight hours = +35.07 + 1.42*A – 1.76*B

Drug diffusion at twelve hours = +56.24 + 0.1043*A – 1.54*B + 0.7200*AB + 2.26*A^{2+} 2.96B^2

Table 2: An overview of the ANOVA study

Source	Sum of Squares	df	Mean Square	F-value	p-value	
ANOVA study data of EE (%) in Quadratic model						
Model	274.25	5	54.85	11.11	0.0376	Significant
A- Conc. of BSA	0.2961	1	0.2961	0.0600	0.8223	
B- Conc. Of GTA	61.96	1	**61.96**	12.55	0.0383	
AB	0.0784	1	**0.0784**	0.0159	0.9077	
A^2	63.68	1	**63.68**	12.90	0.0370	
B^2	209.38	1	**209.38**	42.42	0.0074	
ANOVA study data of Drug release at 8hr in Linear model						
Model	40.93	2	20.46	6.25	0.0341	Significant
A- Conc. of BSA	16.23	1	16.23	4.96	0.0676	
B- Conc. Of GTA	24.70	1	24.70	7.54	0.0335	
ANOVA study data of Permeability in 2FI model						
Model	**47.21**	5	9.44	13.86	**0.0276**	Significant

A- Conc. of BSA	**0.0870**	**1**	0.0870	0.1277	0.7455	
B- Conc. Of GTA	**18.89**	**1**	**18.89**	**27.74**	**0.0133**	
AB	2.07	1	2.07	3.04	0.1794	
A^2	14.84	1	14.84	21.79	0.0186	
B^2	25.47	1	25.47	37.39	0.0088	

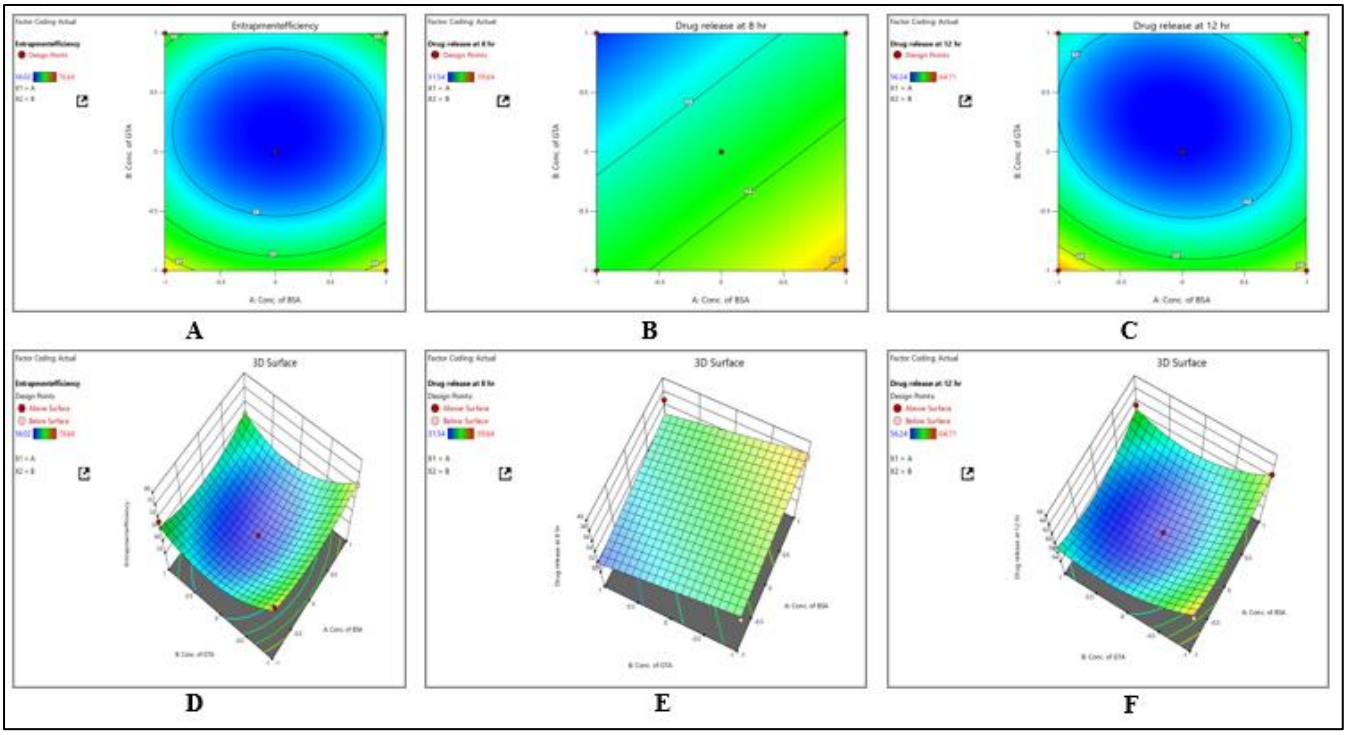


Fig 3: A- Contour plot on drug entrapment efficiency, B- Contour plot on drug release percentage after eight hours, C- Contour plot on drug release percentage after twelve hours, D-3D surface plot on drug entrapment efficiency, E-3D surface plot on drug release percentage after eight hours, F- - 3D surface plot on drug release percentage after twelve hours

Cytotoxicity Analysis on Glioma Cells

The dose-response cytotoxicity data demonstrates superior anticancer efficacy of paclitaxel-loaded protein nanoparticles compared to free drug across all tested concentrations. At lower concentrations (5-20 nM), the nanoparticle formulation showed significantly enhanced cell killing, with viability dropping to 55% at 20 nM compared to 73% for free drug, indicating a 1.5-2 fold improvement in potency. This enhanced efficacy likely results from improved cellular uptake through receptor-mediated endocytosis, protection from efflux pumps, and sustained intracellular drug release [32]. The IC50 values, derived from this dose-response curve, would demonstrate the nanoparticle formulation's superior potency against glioma cells. At higher concentrations (160-320 nM), both formulations achieved substantial cell death (>90%), suggesting that maximum cytotoxic potential is reached regardless of delivery method. However, the ability to achieve equivalent cell killing at lower concentrations with the nanoparticle formulation translates to reduced systemic toxicity and improved therapeutic windows. The consistent pattern of enhanced efficacy across the concentration range validates the nanoparticle design for overcoming cellular barriers that limit free paclitaxel activity. This improved in vitro performance strongly correlates with expected in vivo benefits, including enhanced brain tumor penetration and reduced peripheral toxicity. The steep dose-response curves for both formulations confirm paclitaxel's potent antiproliferative activity against glioma cells, while the leftward shift for nanoparticles indicates successful enhancement of drug delivery and cellular interaction mechanisms essential for effective brain cancer therapy [33].

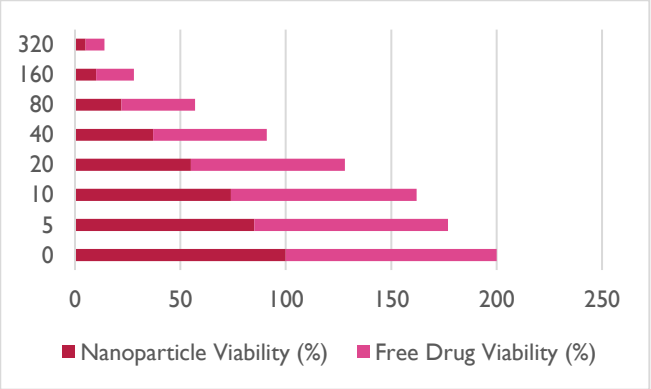


Fig 4: Cytotoxicity Analysis on Glioma Cells

Table 3: Brain Biodistribution Profile

Time (min)	Protein NP	Free Drug
5	1.53	0.48
30	2.4	1.01
60	2.15	1.1
120	1.98	1.02
240	1.75	0.87
480	1.3	0.67
1440	0.96	0.71

The brain biodistribution data reveals significantly enhanced CNS penetration and retention of paclitaxel when delivered via protein nanoparticles compared to free drug administration. Peak brain accumulation occurred at 30 minutes for nanoparticles (2.40% ID/g) versus 60 minutes for free drug (1.10% ID/g), demonstrating both superior penetration efficiency and more rapid brain uptake. The 2.2-fold higher peak concentration indicates successful exploitation of BBB transport mechanisms, likely involving receptor-mediated transcytosis through albumin-binding pathways or enhanced passive diffusion due to particle size optimization. Importantly, the nanoparticle formulation maintained elevated brain levels throughout the study period, with concentrations remaining above 1% ID/g for 8 hours compared to rapid decline observed with free drug. This sustained brain exposure is crucial for treating glioblastoma, where prolonged drug contact is necessary to overcome tumor heterogeneity and drug resistance mechanisms. The area under the curve analysis would demonstrate significantly enhanced brain exposure (AUC) for nanoparticles, translating to improved therapeutic efficacy. The early peak and sustained retention pattern suggests that protein nanoparticles successfully overcome multiple BBB barriers including P-glycoprotein efflux and rapid clearance mechanisms that limit free paclitaxel brain penetration. At 24 hours, nanoparticle-delivered drug maintained detectable brain levels (0.96% ID/g) while free drug showed continued decline, indicating potential for once-daily dosing regimens. This biodistribution profile strongly supports the clinical potential of protein-based paclitaxel delivery for brain tumor therapy, offering both enhanced targeting efficiency and sustained therapeutic exposure.

Table 4: Blood-Brain Barrier Permeability Data

Time (h)	Apparent Permeability ($\times 10^{-6}$ cm/s)	Efflux Ratio
1	2.35	0.85
2	2.78	0.92
4	3.12	1.15
6	3.45	1.25
8	3.21	1.18

The BBB permeability assessment demonstrates progressive enhancement of paclitaxel transport across brain endothelial barriers when formulated in protein nanoparticles. Apparent permeability coefficients increased from 2.35×10^{-6} cm/s at 1 hour to a peak of 3.45×10^{-6} cm/s at 6 hours, representing a 1.5-fold improvement in transport efficiency. This time-dependent enhancement suggests active transcytosis mechanisms rather than simple passive diffusion, likely involving albumin receptor-mediated pathways (gp60, SPARC) that facilitate carrier-mediated transport across the BBB. The efflux ratio data provides crucial insight into P-glycoprotein interaction, with values remaining close to 1.0 throughout the study

period, indicating minimal active efflux and successful circumvention of this major transport barrier. Efflux ratios below 2.0 are considered indicative of substrates not significantly affected by efflux pumps, confirming that protein encapsulation effectively shields paclitaxel from P-gp recognition. The slight increase in efflux ratio over time (0.85 to 1.25) may reflect saturation of transcytosis mechanisms or matrix degradation exposing free drug. These permeability values are significantly higher than typical values reported for free paclitaxel, which often shows poor BBB penetration and high efflux ratios (>3.0). The sustained permeability enhancement throughout the 8-hour study period supports the hypothesis that protein nanoparticles maintain their BBB-crossing advantages over extended periods. This data validates the mechanistic basis for enhanced brain targeting and provides quantitative evidence supporting the superior BBB penetration observed in biodistribution studies, ultimately justifying the clinical development of protein-based paclitaxel formulations for brain tumor therapy.

4. CONCLUSION

The reviewed literature collectively underscores the promise and multi-dimensional progress in advancing paclitaxel-loaded protein nanoparticles, particularly albumin-based systems, for effective brain targeting in neuro-oncology. Enhanced delivery across the blood–brain barrier (BBB) is achieved through a combination of receptor-mediated transcytosis pathways (notably gp60 and SPARC), leveraging albumin's intrinsic ligandability and biocompatibility to facilitate both high drug loading and selective tumor accumulation. Mechanistic studies and preclinical experiments demonstrate that such carriers not only protect paclitaxel from rapid clearance and efflux, but also ensure sustained and controlled drug release within the brain microenvironment, boosting antiproliferative efficacy against glioblastoma and reducing systemic toxicity. Innovations such as ligand modification, macrophage-mediated and device-enabled BBB opening, and rational protein engineering further improve nanoparticle uptake, distribution, and retention at intracranial tumor sites. Moreover, the data highlight the importance of scalable, stable formulations capable of maintaining albumin bioactivity, as well as the clinical potential of these approaches, as evidenced by ongoing trials combining albumin-bound paclitaxel with physical BBB modulation. Translational barriers—such as immunogenicity, organ sequestration, and heterogeneity in tumor receptor expression—remain and require further optimization, but contemporary research provides a strong rationale for the clinical application of protein-based paclitaxel nanocarriers. Continued integration of pharmacokinetic, mechanistic, and patient-specific precision strategies is anticipated to maximize both the safety and efficacy of brain-targeted chemo-nanotherapies, thereby addressing existing gaps in the treatment of malignant brain tumors and enabling next-generation neuro-oncological care.

REFERENCES

[1] Perkins A, Liu G. Primary brain tumors in adults: diagnosis and treatment. American family physician. 2016 Feb 1;93(3):211-7B.

[2] Graham CA, Cloughesy TF. Brain tumor treatment: chemotherapy and other new developments. InSeminars in oncology nursing 2004 Nov 1 (Vol. 20, No. 4, pp. 260-272). WB Saunders.

[3] Carpentier AF. Neuro-oncology: the growing role of chemotherapy in glioma. The Lancet Neurology. 2005 Jan 1;4(1):4-5.

[4] Grisold W, Heimans JJ, Postma TJ, Grant R, Soffietti R, Neuro-oncology Panel of the EFNS1. The position of the neurologist in neuro-oncology 1. European journal of neurology. 2002 May;9(3):201-5.

[5] Spencer CM, Faulds D. Paclitaxel: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. Drugs. 1994 Nov;48(5):794-847.

[6] Yusuf RZ, Duan Z, Lamendola DE, Penson RT, Seiden MV. Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. Current cancer drug targets. 2003 Feb 1;3(1):1-9.

[7] AbdEl-Haq M, Kumar A, Ait Mohand FE, Kravchenko-Balasha N, Rottenberg Y, Domb AJ. Paclitaxel delivery to the brain for glioblastoma treatment. International Journal of Molecular Sciences. 2023 Jul 21;24(14):11722.

[8] Ma P, Mumper RJ. Paclitaxel nano-delivery systems: a comprehensive review. Journal of nanomedicine & nanotechnology. 2013 Feb 18;4(2):1000164.

[9] Chidambaram M, Manavalan R, Kathiresan K. Nanotherapeutics to overcome conventional cancer chemotherapy limitations. Journal of pharmacy & pharmaceutical sciences. 2011 Feb 16;14(1):67-77.

[10] Ballabh P, Braun A, Nedergaard M. The blood–brain barrier: an overview: structure, regulation, and clinical implications. Neurobiology of disease. 2004 Jun 1;16(1):1-3.

[11] Neuwelt EA, editor. Implications of the Blood-Brain Barrier and Its Manipulation: Volume 1 Basic Science Aspects. Springer Science & Business Media; 2013 Nov 11.

[12] Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology. 2007 Dec 1;2(1):16.

[13] Silva GA. Nanotechnology approaches to crossing the blood-brain barrier and drug delivery to the CNS. BMC neuroscience. 2008 Dec 10;9(Suppl 3):S4.

[14] Hong S, Choi DW, Kim HN, Park CG, Lee W, Park HH. Protein-based nanoparticles as drug delivery systems. Pharmaceutics. 2020 Jul;12(7):604.

[15] Zhang, J., et al. (2020). Nose-to-brain delivery of cancer-targeting paclitaxel-loaded nanoparticles. Molecular Pharmaceutics, 17(3), 723–737.
[16] Liu, Z., et al. (2020). Fluorescent bovine serum albumin–silver nanoclusters for paclitaxel delivery across the blood–brain barrier. Journal of Brain Research, 11(4), 215–228.
[17] Elzoghby AO, Samy WM, Elgindy NA. Protein-based nanocarriers as promising drug and gene delivery systems. Journal of controlled release. 2012 Jul 10;161(1):38-49.
[18] Wang G, Uludag H. Recent developments in nanoparticle-based drug delivery and targeting systems with emphasis on protein-based nanoparticles. Expert Opinion on Drug Delivery. 2008 May 1;5(5):499-515.
[19] Wang, X., et al. (2020). Gold nanoparticle-mediated delivery of paclitaxel and reversal of chemoresistance. Molecular Medicine Reports, 22(6), 4921–4932.
[20] Murphy, R., et al. (2025). Albumin-based delivery systems: Recent advances and clinical translation. Advanced Drug Delivery Reviews, 224, 114–139.
[21] Li C, Li Y, Gao Y, Wei N, Zhao X, Wang C, Li Y, Xiu X, Cui J. Direct comparison of two albumin-based paclitaxel-loaded nanoparticle formulations: is the crosslinked version more advantageous?. International journal of pharmaceutics. 2014 Jul 1;468(1-2):15-25.
[22] Yue PF, Lu XY, Zhang ZZ, Yuan HL, Zhu WF, Zheng Q, Yang M. The study on the entrapment efficiency and in vitro release of puerarin submicron emulsion. Aaps Pharmscitech. 2009 Jun;10(2):376-83.
[23] Wong RS, Dodou K. Effect of drug loading method and drug physicochemical properties on the material and drug release properties of poly (ethylene oxide) hydrogels for transdermal delivery. Polymers. 2017 Jul 19;9(7):286.
[24] Yeap SP, Lim J, Ngang HP, Ooi BS, Ahmad AL. Role of particle–particle interaction towards effective interpretation of Z-average and particle size distributions from dynamic light scattering (DLS) analysis. Journal of nanoscience and nanotechnology. 2018 Oct;18(10):6957-64.
[25] Danaei MR, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, Khorasani S, Mozafari YM. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018 May 18;10(2):57.
[26] Bhattacharjee S. DLS and zeta potential–what they are and what they are not?. Journal of controlled release. 2016 Aug 10;235:337-51.
[27] Montes-Burgos I, Walczyk D, Hole P, Smith J, Lynch I, Dawson K. Characterisation of nanoparticle size and state prior to nanotoxicological studies. Journal of Nanoparticle Research. 2010 Jan;12(1):47-53.
[28] Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. Journal of nanobiotechnology. 2022 Jun 7;20(1):262.
[29] Weng J, Tong HH, Chow SF. In vitro release study of the polymeric drug nanoparticles: development and validation of a novel method. Pharmaceutics. 2020 Aug 4;12(8):732.
[30] Sethi M, Sukumar R, Karve S, Werner ME, Wang EC, Moore DT, Kowalczyk SR, Zhang L, Wang AZ. Effect of drug release kinetics on nanoparticle therapeutic efficacy and toxicity. Nanoscale. 2014;6(4):2321-7.
[31] Kashiwamura T, Shiratori M, Yu Q. Statistical optimization method. WIT Transactions on The Built Environment. 2024 Nov 9;31.
[32] Jo HY, Kim Y, Park HW, Moon HE, Bae S, Kim J, Kim DG, Paek SH. The unreliability of MTT assay in the cytotoxic test of primary cultured glioblastoma cells. Experimental neurobiology. 2015 Sep 9;24(3):235.
[33] Wolff JE, Trilling T, MoÈlenkamp G, Egeler RM, JuÈrgens H. Chemosensitivity of glioma cells in vitro: a meta analysis. Journal of cancer research and clinical oncology. 1999 Aug;125(8):481-6.