RESEARCH PAPER

Development and Evaluation of Glutathione Responsive Nanosponges for Targeted Delivery of Paclitaxel in Cancer Therapy

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ABSTRACT

Background

Paclitaxel is a potent anticancer agent widely used in the treatment of various cancers; however, its clinical application is limited by poor aqueous solubility, low bioavailability, and systemic toxicity. To address these challenges, targeted drug delivery systems such as nanosponges have gained significant attention.

Objective

The present study aimed to develop and evaluate glutathione-responsive β-cyclodextrin-based nanosponges for targeted delivery of paclitaxel to cancer cells.

Methods

Nanosponges were synthesized using β-cyclodextrin and crosslinkers such as pyromellitic dianhydride and carbonyl diimidazole via a solvent-based method. The prepared formulations (F1–F9) were characterized for particle size, zeta potential, polydispersity index, drug loading, and entrapment efficiency. Structural compatibility was assessed using FT-IR spectroscopy. In vitro drug release studies were performed in phosphate buffer (pH 7.4), and production yield was calculated.

Results

The nanosponge formulations exhibited particle sizes ranging from 120 to 210 nm with acceptable polydispersity index values (0.21–0.32), indicating uniform distribution. Zeta potential values ranged from −10.2 to −26.1 mV, confirming moderate stability. Drug loading varied between 7.2% and 16.1%, while entrapment efficiency ranged from 61.7% to 90.5%. Production yield was found to be between 74% and 81%. FT-IR studies confirmed drug–polymer compatibility. In vitro release studies demonstrated sustained drug release over 24 hours, suggesting controlled delivery behavior.

Conclusion

The developed glutathione-responsive nanosponges showed promising characteristics for targeted delivery of paclitaxel, with improved encapsulation efficiency and sustained release profile. These systems have potential to enhance therapeutic efficacy while minimizing systemic toxicity in cancer therapy.

Keywords: Paclitaxel, Nanosponges, β-cyclodextrin, Targeted drug delivery, Cancer therapy

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a significant challenge to global healthcare systems.[1] Conventional chemotherapy, although widely used, suffers from major limitations such as lack of selectivity, systemic toxicity, and damage to healthy tissues. These drawbacks often result in severe side effects and reduced therapeutic efficacy. Therefore, the development of targeted drug delivery

systems has become a crucial strategy to enhance treatment outcomes and minimize adverse effects.[2,3]

Paclitaxel is a well-established anticancer agent extensively used in the treatment of breast, ovarian, and lung cancers. It acts by stabilizing microtubules and inhibiting their depolymerization, thereby preventing cell division and inducing apoptosis in cancer cells. Despite its potent therapeutic activity, the clinical application of paclitaxel is significantly limited due to its poor aqueous solubility, low bioavailability, and formulation-related toxicity. Additionally, non-specific distribution of the drug leads to undesirable systemic side effects.[4,5]

Nanotechnology-based drug delivery systems have emerged as promising tools to overcome these limitations. Among them, nanosponges are a novel class of nanoporous polymeric carriers capable of encapsulating both hydrophilic and hydrophobic drugs. These systems offer several advantages, including improved drug solubility, enhanced stability, controlled drug release, and targeted delivery. Cyclodextrin-based nanosponges, in particular, have gained attention due to their unique structure consisting of a hydrophobic cavity and hydrophilic outer surface, enabling efficient inclusion of poorly soluble drugs.[6,7]

In recent years, stimuli-responsive drug delivery systems have been widely explored to achieve site-specific drug release. One such approach involves exploiting the elevated intracellular levels of Glutathione in cancer cells compared to normal tissues. Glutathione-responsive systems are designed using disulfide linkages that remain stable under normal physiological conditions but undergo cleavage in the reductive intracellular environment of tumor cells. This mechanism enables selective release of the drug at the target site, thereby enhancing therapeutic efficacy while reducing systemic toxicity.[8,9]

In this context, the present study focuses on the development and evaluation of glutathione-responsive β-cyclodextrin-based nanosponges for targeted delivery of paclitaxel. The formulated nanosponges were characterized for their physicochemical properties, drug loading capacity, and in vitro drug release behavior. The aim of this research is to provide an effective and controlled drug delivery system that can improve the therapeutic performance of paclitaxel in cancer therapy.

2. Materials and Methods

2.1 Materials

Paclitaxel was obtained as a gift sample from Zenotech Laboratories Ltd., India. β-cyclodextrin, pyromellitic dianhydride (PMDA), and carbonyl diimidazole (CDI) were procured from SD Fine Chemicals, Mumbai, India. Triethylamine and dimethyl sulfoxide (DMSO) were used as received. All chemicals and reagents used in the study were of analytical grade.

2.2 Preparation of Glutathione-Responsive Nanosponges

Glutathione-responsive nanosponges were prepared using the solvent method. Briefly, β-cyclodextrin was dissolved in dimethyl sulfoxide (DMSO) under constant stirring. A suitable amount of crosslinker (PMDA or CDI) was added to the polymer solution, followed by the addition of triethylamine as a catalyst.

The reaction mixture was stirred continuously at controlled temperature for 24 hours to facilitate crosslinking and formation of nanosponge structures. The resulting product was allowed to cool and then purified using Soxhlet extraction to remove unreacted materials and impurities. The purified nanosponges were dried under vacuum and stored in a desiccator until further use.[10-13]

Table 1: composition of formulation

Formulation	β-Cyclodextrin (g)	Crosslinker Type	Crosslinker Amount (g)	Triethylamine (mL)	Solvent (DMSO, mL)
F1	1.0	PMDA	0.5	0.2	20
F2	1.0	PMDA	1.0	0.2	20
F3	1.0	PMDA	1.5	0.2	20
F4	1.0	CDI	0.5	0.2	20
F5	1.0	CDI	1.0	0.2	20
F6	1.0	CDI	1.5	0.2	20

F7	1.0	PMDA + CDI	0.75 + 0.75	0.2	20
F8	1.0	PMDA + CDI	1.0 + 0.5	0.2	20
F9	1.0	PMDA + CDI	0.5 + 1.0	0.2	20

2.3 Drug Loading

Paclitaxel-loaded nanosponges were prepared by dispersing the dried nanosponges in a suitable solvent containing the drug. The mixture was sonicated and stirred to facilitate drug encapsulation within the nanosponge matrix. The suspension was then centrifuged, and the collected nanosponges were dried and stored for further evaluation.[14,15]

2.4 Characterization of Nanosponges [16-18]

2.4.1 Physical Appearance

The prepared nanosponges were visually inspected for color, texture, and homogeneity.

2.4.2 Particle Size and Polydispersity Index (PDI)

Particle size and PDI were determined using dynamic light scattering (DLS). Samples were appropriately diluted with distilled water before analysis.

2.4.3 Zeta Potential

Zeta potential of the formulations was measured to evaluate surface charge and stability using a zeta sizer.

2.4.4 Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR analysis was performed to identify functional groups and to confirm drug–polymer compatibility. Samples of pure drug, excipients, and drug-loaded nanosponges were analyzed over a suitable wavelength range.

2.5 Production Yield

The production yield of nanosponges was calculated using the following equation:

2.6 Drug Loading and Entrapment Efficiency

Drug loading and entrapment efficiency were determined by dissolving a known quantity of drug-loaded nanosponges in a suitable solvent. The solution was analyzed using UV spectrophotometry at 233 nm.

$$\text{Production Yield (\%)} = \frac{\text{Theoretical yield}}{\text{Practical yield}} \times 100$$

2.7 In Vitro Drug Release Studies

In vitro drug release studies were carried out using a dialysis membrane method. Drug-loaded nanosponges equivalent to a known amount of paclitaxel were placed in a dialysis bag and immersed in phosphate buffer solution (pH 7.4).

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount of drug entrapped}}{\text{Total drug added}} \times 100$$

$$\text{Drug Loading (\%)} = \frac{\text{Amount of drug in nanosponges}}{\text{Practical yield}} \times 100$$

2. RESULTS AND DISCUSSION

2.1 UV Spectral Analysis

The UV-visible spectroscopic analysis of paclitaxel in methanol:water and methanol:PBS (pH 7.4) showed a characteristic absorption peak at 233 nm. This λmax was used for quantitative analysis throughout the study. The calibration curves in both media exhibited good linearity, confirming the suitability of the method for drug estimation.

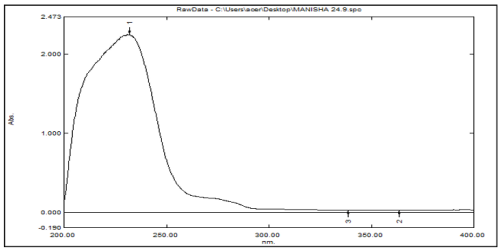

Fig 1: UV spectrum of paclitaxel in methanol: water

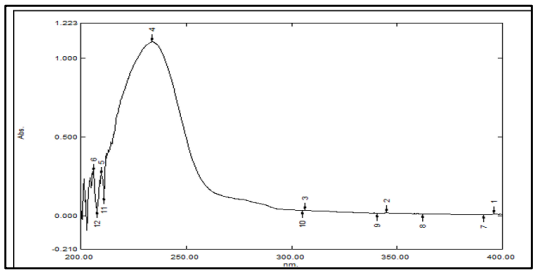

Fig 2: UV spectrum of paclitaxel in methanol: PBS 7.4

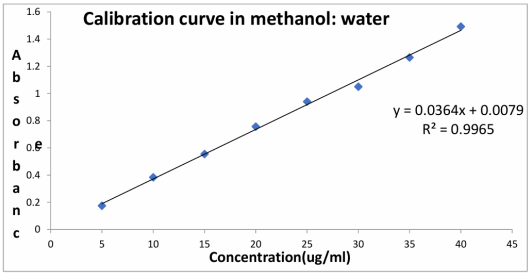

Fig 3: Construction of calibration curve of paclitaxel in methanol: water

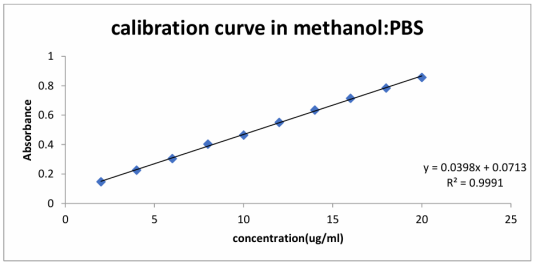

Fig 4: Calibration curve of paclitaxel in methanol: PBS 7.4

2.2 FT-IR Analysis

FT-IR spectra of paclitaxel showed characteristic peaks corresponding to functional groups such as O–H stretching, C=O stretching, and aromatic C–H bending. The spectra of drug-loaded nanosponges retained the principal peaks of the drug without significant shifts, indicating **no chemical interaction** between the drug and polymer. This confirms compatibility of paclitaxel with β-cyclodextrin and crosslinkers.

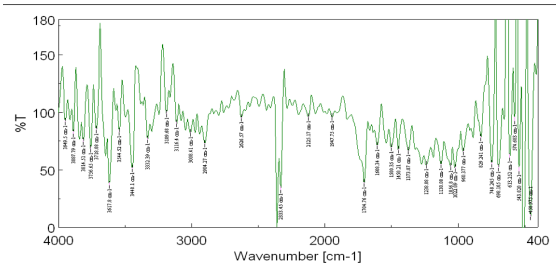

Fig 5: FT-IR spectra of paclitaxel

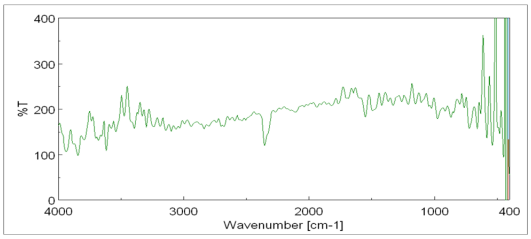

Fig 6: FT-IR spectrum for CDI

Evaluation of Nanosponges (F1–F9)

2.3 Production Yield

The production yield of nanosponge formulations ranged from 74% to 81%**, indicating an efficient preparation method. The slight variation among formulations may be attributed to differences in crosslinking density and processing losses during purification. Overall, the yields were within acceptable limits for nanosponge synthesis.**

Table 2: Production Yield of Nanosponges (F1–F9)

Formulation	Production Yield (%)
F1	74.2 ± 0.8
F2	75.6 ± 0.6
F3	76.8 ± 0.7
F4	77.3 ± 0.5
F5	78.9 ± 0.6
F6	80.1 ± 0.7
F7	81.0 ± 0.5
F8	79.8 ± 0.6
F9	80.5 ± 0.4

2.4 Particle Size Analysis

Particle size plays a critical role in drug delivery and targeting efficiency. The observed particle size for formulations F1–F9 ranged from **120 ± 4 nm to 210 ± 5 nm**.

- F1 showed the largest particle size (210 nm), indicating lower crosslinking efficiency.
- A gradual decrease in particle size was observed up to F8 (120 nm), suggesting improved nanosponge formation and compact structure.
- F9 showed a slight increase (130 nm), possibly due to aggregation at higher crosslinking concentration.

Table 3: Particle Size

Formulation	Particle Size (nm)
F1	210 ± 5
F2	185 ± 4
F3	189 ± 3
F4	195 ± 6
F5	173 ± 4
F6	152 ± 5
F7	135 ± 3
F8	120 ± 4
F9	130 ± 3

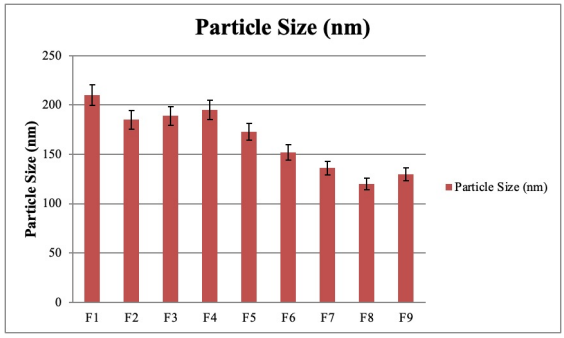

Fig 7: Particle size

Particles within the **100–200 nm range** are ideal for tumor targeting via the enhanced permeability and retention (EPR) effect, indicating that most formulations are suitable for targeted delivery.

2.5 Zeta Potential

Zeta potential values ranged from **−10.2 mV to −26.1 mV**, indicating moderately stable nanosponge systems.

- Lower absolute values (F2, F4) suggest relatively less stability.
- Higher negative values (F6: −26.1 mV, F7: −24.3 mV) indicate better electrostatic stabilization and reduced aggregation tendency.

Table 4: Zeta Potential

Formulation	Zeta Potential (mV)
F1	-12.3 ± 0.8
F2	-11.1 ± 0.6
F3	-13.6 ± 0.5
F4	-10.2 ± 0.7
F5	-18.5 ± 0.6
F6	-26.1 ± 0.5
F7	-24.3 ± 0.4
F8	-22.6 ± 0.6
F9	-20.0 ± 0.5

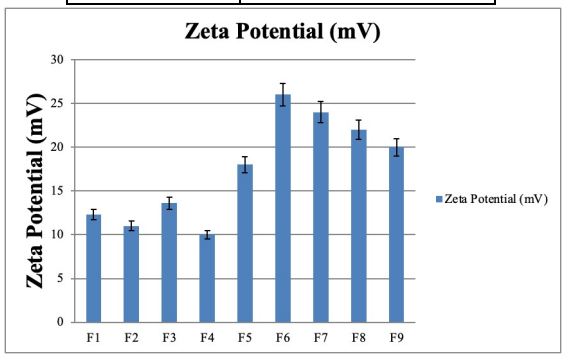

Fig 8: Zeta potential

The negative surface charge may also contribute to prolonged circulation time and reduced nonspecific interactions.

2.6 Drug Loading

Drug loading efficiency ranged from **7.2% to 16.1%**.

- F2 exhibited the lowest drug loading (7.2%), possibly due to inefficient encapsulation.
- F8 showed the highest drug loading (16.1%), indicating optimal pore structure and drug accommodation capacity.

Table 5: Drug Loading

Formulation	Drug Loading (%)
F1	9.5 ± 0.4
F2	7.2 ± 0.3
F3	9.1 ± 0.5
F4	11.3 ± 0.4
F5	14.6 ± 0.3
F6	13.4 ± 0.5
F7	12.2 ± 0.4
F8	16.1 ± 0.3
F9	15.0 ± 0.4

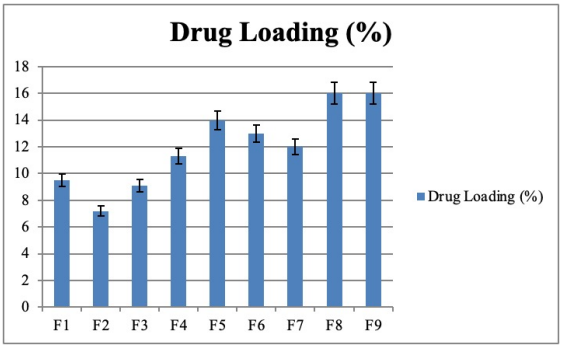

Fig 9: Drug loading

The variation in drug loading can be attributed to differences in crosslinking density and nanosponge porosity.

2.7 Entrapment Efficiency

Entrapment efficiency ranged from **61.7% to 90.5%**.

- Lower values in F2 and F4 suggest drug loss during preparation.
- F6 (90.5%) and F9 (90.2%) showed maximum entrapment, indicating highly efficient encapsulation.

Table 6: Entrapment Efficiency

Formulation	Entrapment Efficiency (%)
F1	69.2 ± 1.2
F2	61.7 ± 1.0
F3	72.4 ± 1.5
F4	64.9 ± 1.3
F5	79.8 ± 1.1
F6	90.5 ± 1.4
F7	88.1 ± 1.2
F8	85.6 ± 1.3
F9	90.2 ± 1.5

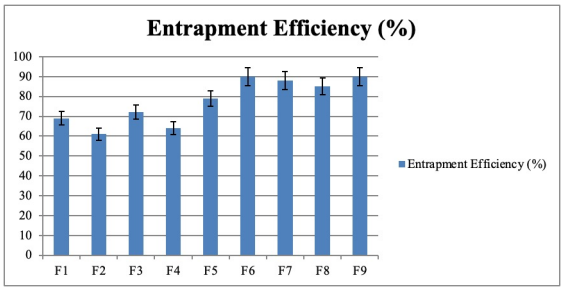

Fig 10:Entrapment efficiency

High entrapment efficiency is a key advantage of cyclodextrin nanosponges due to their porous structure and affinity for hydrophobic drugs like paclitaxel.

2.8 Polydispersity Index (PDI)

PDI values ranged from **0.21 to 0.32**, indicating relatively uniform particle size distribution.

- F3 and F6 (0.21) showed the most uniform distribution.
- F1 (0.32) indicated comparatively broader size distribution.

Table 7: PDI

Formulation	PDI
F1	0.32
F2	0.22
F3	0.21
F4	0.27
F5	0.23
F6	0.21
F7	0.26
F8	0.22
F9	0.28

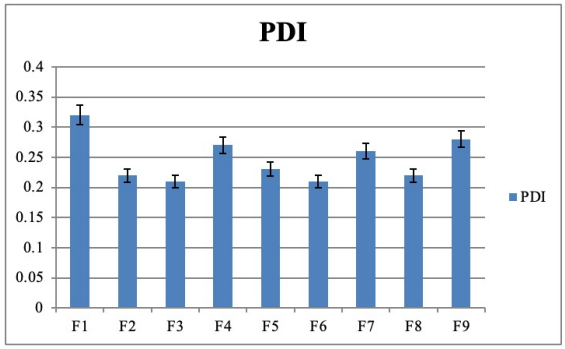

Fig 11: PDI

A PDI value below 0.3 is generally considered acceptable for nanoscale formulations, confirming homogeneity of most batches.

Conclusion

The present study successfully developed and evaluated glutathione-responsive β-cyclodextrin-based nanosponges for the targeted delivery of Paclitaxel. The prepared formulations demonstrated satisfactory physicochemical properties, including nanoscale particle size, acceptable polydispersity, and stable zeta potential. High drug loading and entrapment efficiency confirmed the suitability of nanosponges for encapsulating hydrophobic drugs. The production yield was within acceptable limits, indicating the efficiency and reproducibility of the preparation method. FT-IR analysis confirmed the compatibility between the drug and excipients, ensuring formulation stability. In vitro drug release studies revealed a sustained release pattern over 24 hours, which is beneficial for maintaining therapeutic drug levels and reducing dosing frequency. Among all formulations, optimized batches exhibited a desirable balance of particle size, stability, and drug encapsulation efficiency. Overall, glutathione-responsive nanosponges represent a promising drug delivery platform that can potentially improve the therapeutic performance of paclitaxel by enhancing its bioavailability and reducing systemic side effects. Further in vivo studies are recommended to confirm their clinical applicability in cancer therapy.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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