



Development of a Green-synthesized GNP/CQD-reinforced TSP–GG Hydrogel Bead System for pH-sensitive and Sustained Doxorubicin Release in Colorectal Cancer Therapy

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ABSTRACT

Colorectal cancer (CRC) therapy using doxorubicin (DOX) is often limited by systemic toxicity and non-specific drug release in the gastrointestinal tract. To address this challenge, a novel pH-responsive bio-nanocomposite hydrogel bead system was developed using tamarind seed polysaccharide (TSP) and gellan gum (GG) as the polymer matrix, reinforced with green-synthesized graphene nanoparticles (GNPs) reduced using cinnamon extract and coconut shell-derived carbon quantum dots (CQDs). The hydrogel beads were fabricated through ionic crosslinking with 4 wt.% CaCl₂ and characterized using FTIR, XRD, SEM–EDX, UV–Vis, and photoluminescence analyses. Swelling and *in vitro* drug release studies performed at pH 1.0, 6.6, and 7.2 demonstrated strong pH-responsive behavior, with a maximum swelling ratio of 1580% at pH 7.2. The nanocomposite exhibited 99% encapsulation efficiency and achieved 99% cumulative DOX release after 128 h under colonic conditions, while only 0.67% release occurred at pH 1.0, confirming effective protection in gastric environments. Additionally, the hydrogel showed notable antibacterial activity against *E. coli* and *S. aureus*, along with antioxidant activity (IC₅₀ = 5 mg/mL). Cytotoxicity studies on HT-29 colorectal cancer cells revealed controlled drug delivery, with IC₅₀ values of 48 µg/mL for free DOX and 96 µg/mL for DOX-loaded hydrogel, confirming sustained-release behavior. These results highlight the potential of the TSP–GG/GNP/CQD bio-nanocomposite hydrogel as a multifunctional and environmentally sustainable platform for colon-targeted drug delivery in colorectal cancer therapy.

Keywords: Antibacterial activity; Polymer matrix; Biocomposites; UV–Vis spectroscopy; Photoluminescence.

1. INTRODUCTION

Colorectal cancer is the third most common malignancy and remains a major contributor to cancer mortality. Conventional therapeutic strategies, including surgery, radiotherapy, and chemotherapy, are often associated with systemic toxicity, non-specific drug distribution, and severe side effects, thereby limiting treatment efficiency. These challenges necessitate the development of advanced drug delivery capable of targeted, sustained, and controlled release within the colonic environment.

Natural polysaccharides have emerged as promising candidates for biomedical drug delivery due to their biocompatibility, biodegradability, and functional versatility. Tamarind seed polysaccharide (TSP), a galactoxyloglucan-based biopolymer, contains abundant hydroxyl and carboxyl groups that facilitate hydrogen bonding, ionic interactions, and efficient drug encapsulation. Green synthesis of TSP-based nanoparticles has demonstrated effective therapeutic drug loading and controlled release behavior (Javaid *et*

al. 2024b). Structural investigations of TSP-based polymer electrolytes using XRD, FTIR, UV–Vis, and impedance spectroscopy revealed optimized amorphous characteristics with enhanced ionic transport and antioxidant potential, indicating suitability for drug delivery platforms incorporating graphene nanoparticles and carbon quantum dots (Keerthi *et al.* 2025; Maithilee *et al.* 2022). Furthermore, physicochemical characterization of extracted TSP confirmed its amorphous morphology and demonstrated notable antibacterial activity against *Escherichia coli*, along with significant antioxidant properties, reinforcing its biomedical relevance (Ren *et al.* 2022). Reinforcement of TSP matrices with cellulose nanofibers derived from waste materials improved interfacial bonding and mechanical stability, further supporting its application in sustainable nanocomposite drug carriers (Lal and Mhaske, 2021).

Gellan gum (GG) is an anionic microbial polysaccharide widely used in biomedical applications for its ability to form stable three-dimensional hydrogel networks via ionic crosslinking with divalent cations. Its

excellent biocompatibility, structural stability, and water-retention capability make it a promising material for controlled drug delivery systems (Al Rawahi *et al.* 2025; Atasoyu *et al.* 2025). ZnO-loaded GG sponges have demonstrated strong antibacterial activity and cytocompatibility for biomedical applications. Beyond drug delivery, GG-based materials have been widely explored for catalytic systems (Hjazi, 2024), heritage material conservation (Rushdy *et al.* 2024), dye adsorption with high removal efficiency and regeneration stability (Abbasi *et al.* 2025), and enzyme immobilization with enhanced thermal stability and reusability (Wahba *et al.* 2024). Advanced GG-acacia gum nanocomposite hydrogels reinforced with inorganic nanoparticles have demonstrated excellent cytocompatibility, biofilm inhibition, and high water-uptake capacity, confirming their potential for biomedical applications (Abdullaev *et al.* 2023). Although significant progress has been made in polysaccharide-based hydrogels and nanocarbon materials for drug delivery applications, the development of hydrogel systems integrating dual polysaccharides (TSP-GG) with dual nanocarbon fillers (GNPs and CQDs) for pH-responsive colon-targeted drug delivery remains largely unexplored.

Coconut shell biomass has attracted significant attention as a sustainable carbon precursor due to its high fixed-carbon content, structural stability, and aromatic composition. Chitosan-based edible coatings incorporating young coconut shell liquid smoke exhibited strong antibacterial activity, with inhibition zones ranging from 7.23 to 8.30 mm against common pathogenic bacteria (Faisal *et al.* 2024). Ultrasound-treated ginger starch films containing coconut shell liquid smoke reduced *E. coli* O157:H7 by 1.33 log CFU/g (colony-forming units per gram) during refrigerated storage while improving barrier properties (Rahmasari and Polat, 2022). Coconut shell-derived pyrolytic oil was formulated into topical pharmaceutical preparations, demonstrating antimicrobial potential and formulation stability (James *et al.* 2022). Nickel-modified coconut shell biomass achieved a maximum hydrogen yield of 87.8 mmol g⁻¹ during catalytic pyrolysis, highlighting its high carbon conversion efficiency (Zhang *et al.* 2026). Coconut shell liquid smoke treatment enhanced fiber tensile strength by 33% and improved crystallinity and thermal stability in natural fiber composites (Suyuti *et al.* 2026). Coconut shell-derived hard carbon exhibited structural stability and favorable electrochemical performance as an anode material for sodium-ion batteries (Chen *et al.* 2026).

Moreover, coconut shell-derived reduced graphene oxide (rGO)-like carbon integrated with Fe₃O₄ nanoparticles has demonstrated tunable electromagnetic absorption and structural adaptability (Fitriani *et al.* 2026), while green-synthesized Fe₃O₄/rGO nanocomposites derived from coconut biomass exhibited

adjustable magnetic and microwave absorption properties (Husain *et al.* 2026). Thermogravimetric and calorific analyses further confirmed the high thermal stability and energy potential of coconut shell-based biomass blends for sustainable waste-to-energy applications (Anis *et al.* 2026). Collectively, these studies demonstrate the structural richness and high carbon yield of coconut shell biomass, supporting its utilization as a precursor for advanced nanocarbon materials such as graphene derivatives and carbon quantum dots. The combined incorporation of GNPs and CQDs provides synergistic benefits, including enhanced mechanical stability, improved drug-matrix interactions, higher drug loading efficiency, and additional antibacterial and antioxidant functionality.

Despite extensive research on individual polysaccharide matrices and single nanofiller systems, limited studies have integrated dual natural polysaccharides with dual biomass-derived carbon nanomaterials within a single multifunctional hydrogel platform. The strategic combination of tamarind seed polysaccharide and gellan gum, reinforced with green-synthesized graphene nanoparticles and coconut shell-derived carbon quantum dots, offers the potential to achieve enhanced pH-responsive swelling, controlled drug release, antibacterial protection, antioxidant functionality, and structural reinforcement simultaneously. Therefore, the present work focuses on the development of a sustainable, pH-sensitive bio-nanocomposite hydrogel system designed for colon-targeted drug delivery in colorectal cancer therapy. By integrating natural biopolymers with environmentally derived nanocarbon fillers, this approach advances beyond conventional mono-functional carriers toward multifunctional, green-engineered theranostic platforms.

2. MATERIALS AND METHODOLOGY

2.1 Materials

Tamarind seeds, cloves, and coconut shells were obtained from the local market at Erode, Tamil Nadu, India. Gellan gum was acquired from Kovai Cheenu Enterprises, Coimbatore, Tamil Nadu, India. Graphene (purity ≥ 99%) was obtained from Matrics Enterprises, Nagercoil, Tamil Nadu, India.

2.2 Extraction of Cinnamon (CM) Extract

The CM extract was acquired by the maceration technique. The CM samples were thoroughly cleaned with distilled water and air-dried to remove any residual contaminants. Approximately 3 g of CM fragments was submerged in 50 mL of a DI water-ethanol solvent mixture and incubated at 60 °C for 24 h with continuous magnetic agitation. Subsequent to extraction, the liquid was filtered using Whatman filter paper and then centrifuged to eliminate residual particles. The purified

extract was lyophilized and preserved at -4°C . The acquired CM extract was subsequently utilized as a natural reducing and stabilizing agent for the eco-friendly synthesis and functionalization of graphene nanoparticles (GNPs).

2.3 Extraction of TSP

The tamarind seeds were meticulously washed to eliminate residual pulp and extraneous substances, and then dried. The desiccated seeds were dehusked, and the kernels were segregated and milled into a fine powder. The powdered tamarind kernel was suspended in distilled water and heated at $60\text{--}70^{\circ}\text{C}$ with continuous agitation for 2–3 h to promote polysaccharide extraction. The resultant viscous slurry was filtered using muslin cloth to eliminate insoluble remnants. The tamarind seed polysaccharide (TSP) was precipitated from the filtrate using an excess of isopropyl alcohol (IPA) or ethanol and permitted to stand at room temperature for complete precipitation. The precipitated polysaccharide was gathered and thoroughly washed multiple times with the identical alcohol solvent to eliminate contaminants. The purified TSP was subsequently dried in a hot air oven at 50°C and stored for future use. TSP is a galactoxyloglucan mostly consisting of glucose, xylose, and galactose units. The backbone comprises β -(1 $\rightarrow$ 4)-linked D-glucan residues, with α -D-xylopyranosyl side chains connected at the O-6 position, partially substituted by β -D-galactopyranosyl residues.

2.4 Characterization Techniques

FTIR spectra were obtained in the $400\text{--}4000\text{ cm}^{-1}$ range using a Shimadzu IRSpirit. UV–Vis spectra were acquired using a JASCO V-630 spectrophotometer. The surface morphology was examined using a Gemini Zeiss SEM at 15 kV. EDX spectroscopy was employed to determine the elemental composition. X-ray diffraction patterns were obtained using a Shimadzu XRD-7000. Photoluminescence spectra were recorded using a Shimadzu RF-6000 spectrofluorometer. The pH was measured using a Metrohm 913 pH meter.

2.5 Synthesis of GNPs

Graphene nanoparticles (GNPs) were manufactured by a green reduction method. Graphene oxide (GO) was synthesized from graphite powder and suspended in distilled water (1 mg/mL) using ultrasonication for 60 min (Yan, 2018). A specified amount of CM was subsequently included in the GO solution, and the amalgam was heated to 70°C for 3 h with continuous stirring. The progressive color transition from brown to black signified the effective reduction of graphene oxide into graphene nanoparticles. The resultant GNPs were isolated by centrifugation at 8000 rpm for 20 min, rinsed three times with deionized water, and subsequently dried in an oven at 50°C (Fig. 1).

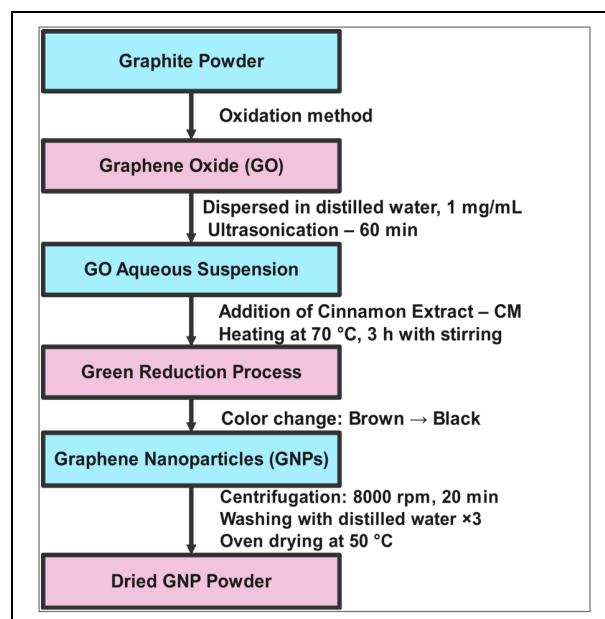


Fig. 1: Green synthesis of GNPs via cinnamon extract-mediated reduction of GO

2.6 Preparation of CQD

Carbon quantum dots (CQDs) were prepared by a pyrolysis–hydrothermal method using coconut shells (CS) as the carbon precursor. The collected carbon sources were meticulously rinsed with deionized water to remove surface contaminants, dried at 80°C , and subsequently carbonized in a muffle furnace at 400°C for 2 h. The procured carbonized substance was pulverized into a fine powder. To prepare CQDs, 1 g of powder was dispersed in 50 mL of distilled water for 30 min to attain a homogeneous suspension. The suspension underwent hydrothermal treatment at 180°C for 6 h in a Teflon-lined autoclave. Upon reaching room temperature, the materials were filtered to remove coarse particles, followed by centrifugation at 10,000 rpm for 20 min. The resultant CQD solution was lyophilized and preserved at 4°C for subsequent characterization.

2.7 Synthesis of TSP–GG/GNP/CQD Hydrogel Beads

TSP was isolated according to the method depicted in Fig. 2. The hydrogel beads were prepared using 0.3 g TSP, 0.3 g GG, 0.03 g GNPs, and 0.03 g CQDs dissolved in 10 mL deionized water, followed by ionic crosslinking in 4 wt.% CaCl_2 solution. The 0.03 g of GNPs and 0.03 g of CQDs were incorporated into the polymer matrix and continuously mixed for 1 h at room temperature to achieve uniform dispersion of the nanofillers. The composite solution was subsequently injected dropwise into a 4 wt.% CaCl_2 aqueous solution by syringe, resulting in the immediate production of spherical hydrogel beads through ionic crosslinking. The beads were further toughened using magnetic stirring for

30 min, followed by extensive washing with DI water to eliminate surplus Ca^{2+} ions. Then the beads were dried

under ambient circumstances or at 40–50 °C in a hot air oven.

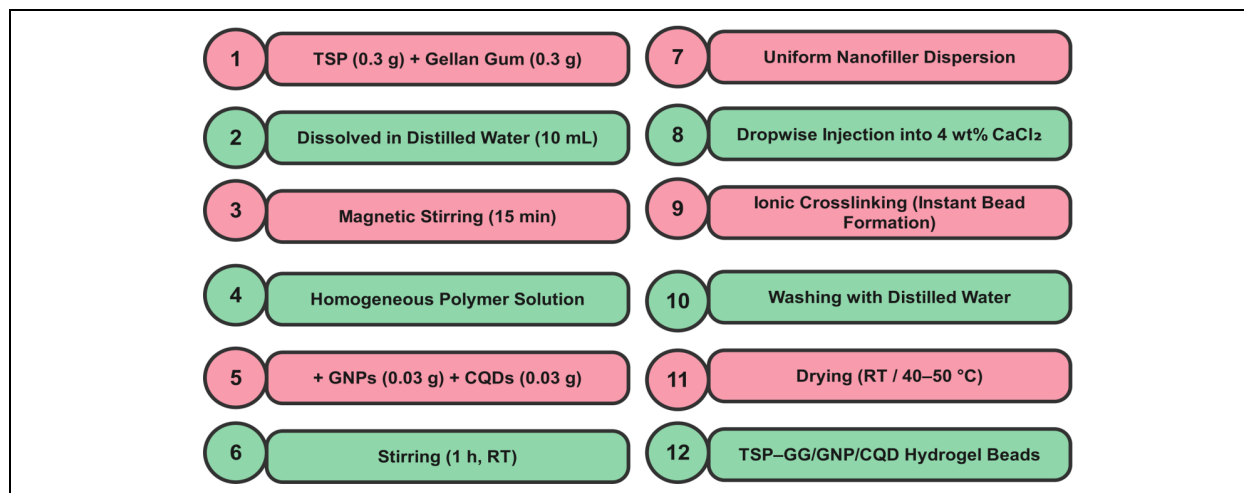


Fig. 2: Schematic illustration of the fabrication process for TSP–GG/GNP/CQD bio-nanocomposite hydrogel beads by the ionic crosslinking method

Table 1. Composition and concentration of materials used in the preparation of TSP–GG/GNP/CQD hydrogel beads

Sample	Water	Ca^{2+}	CQDs	GNPs	TSP	GG
TSP–GG/GN P/CQD	10 mL	4 wt. %	0.03 g	0.03 g	0.3 g	0.3 g

examined by a UV spectrophotometer at the peak absorption wavelength of 422 nm.

$$\text{Loading capacity} = \frac{\text{Weight of drug}}{\text{weight of beads without drug}} \times 100 \dots (2)$$

$$\text{Encapsulation Efficiency} = \frac{\text{Actual drug loaded}}{\text{Theoretical drug loaded}} \times 100 \dots (3)$$

2.8 Swelling Analysis

Swelling characteristics were assessed at buffer by pH levels of 1.0, 6.6, and 7.2 at ambient temperature. The 10 mg of desiccated carrier was submerged in 20 mL of buffer solution. Distended carriers were gathered at specified intervals, and surplus liquid was carefully eliminated with filter paper. Swelling ratios were determined by,

$$\text{Swelling ratio (SR\%)} = \frac{W_1 - W_2}{W_2} \times 100 \dots (1)$$

where, W_1 represents the weight of the hydrated carrier, while W_2 denotes the weight of the desiccated carrier.

2.9 DOX Study

To ascertain the loading capacity (LC) and encapsulation efficiency (EE) of DOX within the carrier, 100 mg of carrier was combined with 10 mL of 100 ppm DOX. The amalgam was agitated in the dark at ambient temperature for 72 h. The TSP–GG/GNP/CQD–DOX was isolated from the solution and rinsed with distilled water to eliminate remaining medication. The DOX carrier was ultimately desiccated at ambient temperature and shielded from light exposure (Tahmasebi and Mohammadi, 2025a). The remaining solutions were

2.10 Release of Drugs

DOX at the carrier was assessed in the dark at 37 °C for a duration of 72 h. At specified intervals, 2 mL of buffer was replaced and by equivalent volume of new buffer. A DOX carrier was submerged at specified time intervals in a buffer with pH levels of 1.0, 6.6, and 7.2 to replicate three phases of the gastrointestinal tract. Concentration of DOX emitted was measured by a UV–Vis spectrophotometer at the peak wavelength of 422 nm.

$$\text{Cumulative release} = \frac{\text{Amount of released DOX}}{\text{Amount of loaded DOX}} \times 100 \dots (4)$$

2.11 Kinetic Studies of *in-vitro* Drug

DOX from the carrier was assessed using multiple mathematical models, including Weibull models, Peppas, first-order, Higuchi, and zero-order, to ascertain drug release mechanism and kinetics.

2.12 Antibacterial Activity

The efficacy of TSP–GG/GNP/CQD was evaluated against Gram-negative *E. coli* and Gram-positive *S. aureus* using the colony-forming unit (CFU) method. Graphene nanoparticles, CM, and TSP–GG/GNP/CQD were dissolved in water using ultrasonication. The 1 mL sample was combined with 1

mL bacterial suspension at a concentration of 10^5 CFU/mL. Following a 2-hour incubation at 36 °C, 100 μ L of the solution was diluted in phosphate saline and subsequently plated on nutritional agar. The bacterial suspension devoid of samples served as the control group. The plates and materials, excluding membranes, were sterilized by UV light and autoclave.

2.13 Antioxidant Analysis

Antioxidant efficacy of TSP-GG/GNP/CQD was assessed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay, which measures antioxidants to diminish DPPH radicals. The 0.2 M DPPH was formulated at 96% ethanol to function as a working solution. Different carrier concentrations (2.5, 5, 10, 20, and 40 mg/L) were introduced to 3 mL of the DPPH solution. The mixture was meticulously incubated in the dark at ambient temperature for 1 h. Following incubation, absorbance at 522 nm was measured using a UV-Vis spectrophotometer with an ethanol blank. Inhibition percentages were determined by,

$$\text{Inhibition \%} = \frac{A_B - A_A}{A_B} \times 100 \quad \dots (5)$$

A_A and A_B represent absorbance values for test and control carriers.

2.14 Cytotoxicity Analysis

The biocompatibility and cytotoxicity of TSP-GG/GNP/CQD and TSP-GG/GNP/CQD-DOX were assessed in HT-29 cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. HT-29 cells were cultured in 96-well plates using Dulbecco's Modified Eagle Medium (DMEM) supplemented with 1% streptomycin and 10% fetal bovine serum (FBS) at 36 °C in a 5% CO₂ atmosphere for 2 days. Subsequent to incubation, MTT solution was introduced to all wells, followed by a 4-hour incubation at 37 °C. Dimethyl sulfoxide (DMSO) was included, and the mixture was agitated at an ambient temperature for 15 min. Cell viability was evaluated with ELISA by measuring optical density (OD) at 490 nm (Javaid *et al.* 2024a).

$$\text{Cell viability (\%)} = \frac{OD_{\text{treated}}}{OD_{\text{control}}} \times 100 \quad \dots (6)$$

Absorbance of sample cells was designated as treated optical density, while absorbance of controls was referred to as control optical density. Untreated cells were treated with DMSO and culture media.

All experiments were conducted under controlled laboratory conditions at an ambient temperature of 25 ± 2 °C and a relative humidity of 50–

60%. Hydrogel preparation and synthesis procedures were performed using analytical-grade reagents and deionized water, and all glassware was thoroughly cleaned and dried prior to use to avoid contamination. The pH measurements were carried out using a calibrated Metrohm 913 pH meter, and experimental parameters such as stirring speed, temperature, and reaction time were carefully maintained to ensure reproducibility of the results. All experiments were performed under identical experimental conditions. Each measurement, including swelling analysis, drug loading, drug release, antibacterial activity, antioxidant analysis, and cytotoxicity studies, was conducted in triplicate ($n = 3$), and the results were expressed as the mean $\pm$ standard deviation (SD) to ensure the repeatability and reliability of the experimental data.

3. RESULTS AND DISCUSSION

3.1 FTIR and XRD Analysis

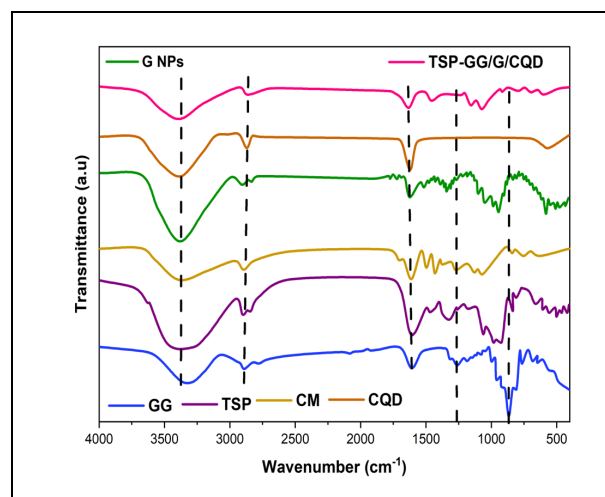


Fig. 3: FTIR spectra for GG, TSP, CM, GNPs, CQDs, TSP-GG/GNP/CQD, TSP-GG/GNP/CQD-DOX-loaded hydrogel, confirming functional group interactions and successful formation of the bio-nanocomposite structure

The FTIR spectra of GG, TSP, CM, GNPs, and CQDs (Fig. 3) display characteristic peaks at approximately 867.59, 1272.28, 1607.57, 2892.36, and 3379.36 cm^{-1} , corresponding to O–H, aliphatic C–H, carbonyl (C=O), and C–O/COO bonds. Peak at 937.63 cm^{-1} was ascribed to C=C stretching vibrations at CQD. A significant reduction at minor shifts and peak intensity at characteristic bands found at final TSP-GG/GNP/CQD suggest interactions among components, hence verifying successful synthesis of bio-nanocomposite hydrogel beads. As reported in previous analysis, FTIR analysis confirmed strong coordination between TSP functional groups (–OH, –COO). FTIR spectra of GG, TSP, CM, GNPs, CQDs, and TSP-GG/GNP/CQD were examined to elucidate the chemical composition. Interactions between functional groups and

CH₃COONa were evidenced by peak shifts and intensity changes, indicating successful salt-polymer complexation and enhanced ionic transport pathways (Saha *et al.* 2023).

Structural properties of the synthesized TSP-GG/GNP/CQD were examined by X-ray diffraction analysis. Fig. 4 illustrates significant diffraction peaks at 11.48°, 16.31°, and 25.23°, affirming semi-crystalline characteristics of GG, which were ascribed to intermolecular hydrogen bonding in their matrix. Peaks at 28.16° and 29° (110) and (200) planes indicate the level of ordering within the network. Peak at 35.40°, distinguished as an amorphous halo, suggests the existence of amorphous regions inside the GG matrix. The XRD pattern of TSP shows diffraction peaks at $2\theta = 39.55^\circ$, underscoring the crystalline characteristics of TSP. An XRD of biosynthesized graphene nanoparticles of CM extract displays significant distinctive peaks at $2\theta = 26.9^\circ$, 36.9° , and 44.3° . A d-spacing of CQDs on $2\theta = 31.5^\circ$, 45.6° , 56.5° , and 66.5° corresponds to the planes of carbon, indicating a polycrystalline structure. In prior research, XRD patterns revealed a significant reduction in crystalline peaks with increasing NaNO₃ content, indicating enhanced amorphous phase formation in the TSP-based polymer electrolyte films. The 30 wt.% NaNO₃ composition exhibited the lowest crystallinity, correlating with improved ionic mobility and higher electrical conductivity (Nandini *et al.* 2025).

3.2 FE-SEM and EDX

FE-SEM and EDX investigations were performed to evaluate the elemental composition and surface morphology of TSP-GG/GNP/CQD nanocomposites. The SEM image (Fig. 5a) of TSP-GG/GNP/CQD demonstrated a uniform and smooth surface morphology. Conversely, TSP-GG/GNP/CQD-DOX (Fig. 5b) showed enhanced porosity and a comparatively rougher, more textured surface than the unloaded hydrogel, showing effective drug incorporation within the matrix. Furthermore, elemental composition was corroborated by EDX evaluation, which confirmed inclusion of G, N, C, O, and Ca, thereby validating integration of nanoparticles into the polymeric network. Elemental mapping (MAP) analysis revealed a consistent

and homogeneous distribution of elements across the carrier surface, ensuring uniform nanoparticle dispersion throughout the nanocomposite structure. In previous studies, SEM micrographs revealed a highly porous, interconnected network with uniform lignin dispersion within the gelatin matrix. The intact pore walls and absence of cracks confirm good structural integrity suitable for sustained drug delivery and wound healing (Kumar *et al.* 2025).

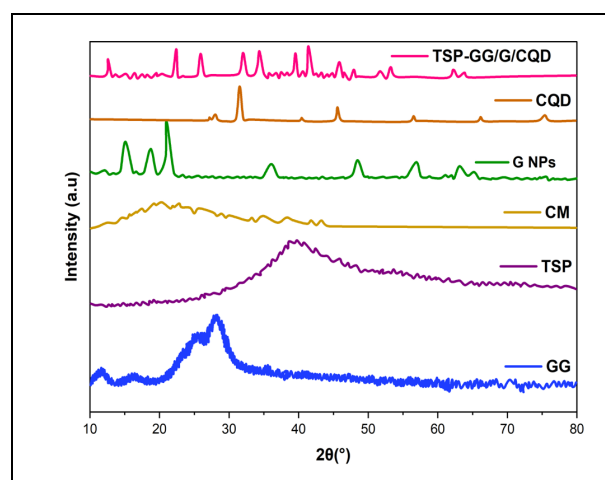


Fig. 4: XRD patterns GG, TSP, CM, GNPs, CQDs, TSP-GG/GNP/CQDs hydrogel, indicating the semi-crystalline structure and successful incorporation of nanocarbon materials within the polymer matrix

3.3 Optical Analysis

Fig. 6 depicts the optical characteristics of CQDs obtained from chitosan. The UV-Vis spectra of CQD solution display 2 peaks at 261 and 300 nm, indicative of $n-\pi^*$ at sp^3 hybridized areas and $\pi-\pi^*$ at sp^2 hybridized domains. The fluorescence spectra of blue CQDs exhibit pronounced emission at 485 nm, signifying a substantial Stokes shift. The incorporation of CQDs at the hydrogel nanocomposite results in a shift of the emission peak to 497 nm, accompanied by a significant increase in intensity. The fluorescence shift was ascribed to the hydrogel's environmental impact on the electronic structure of CQDs and the establishment of intermolecular contacts inside the composite matrix.

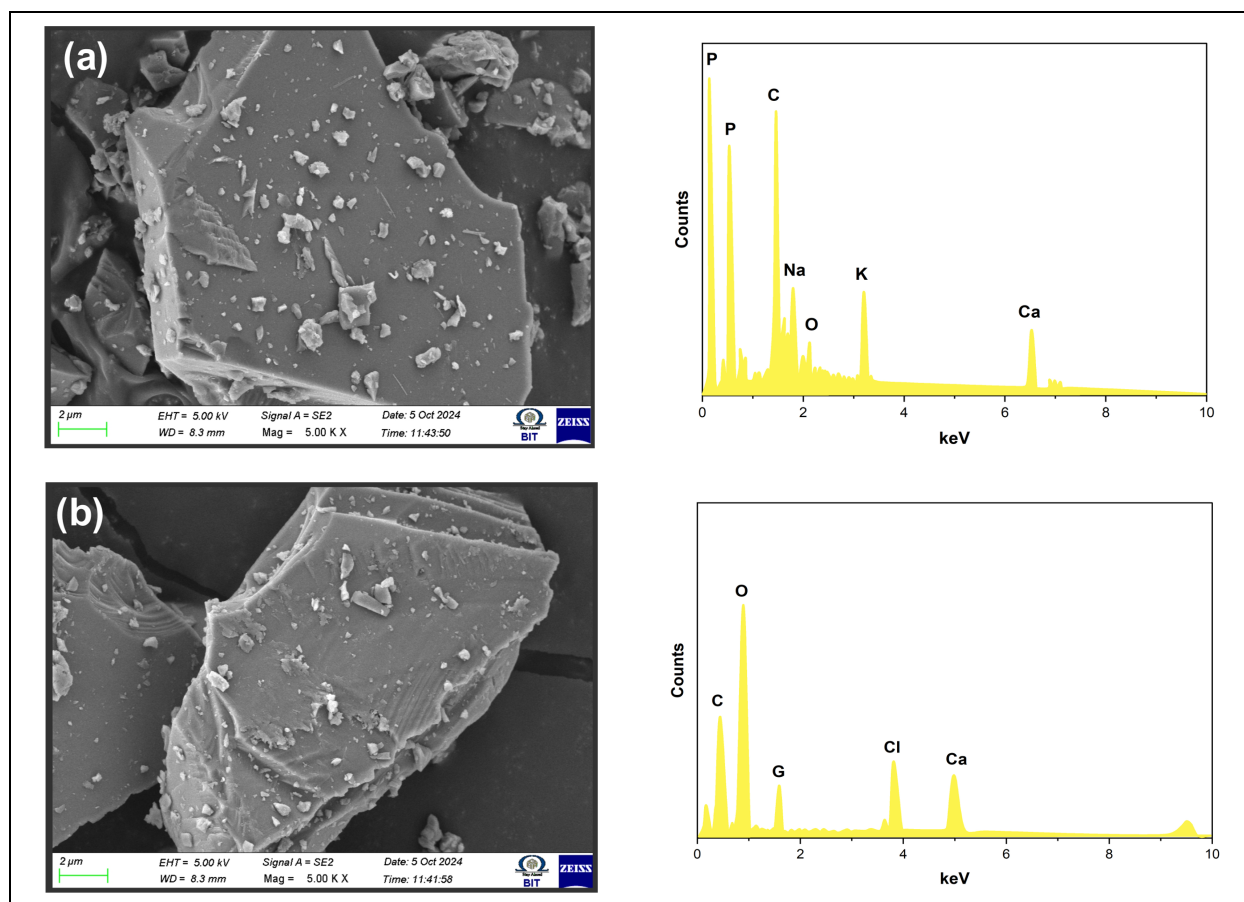


Fig. 5: (a) SEM–EDX mapping of TSP–GG/GNP/CQD nanocomposite and (b) Drug-loaded nanocomposite morphology and elemental distribution

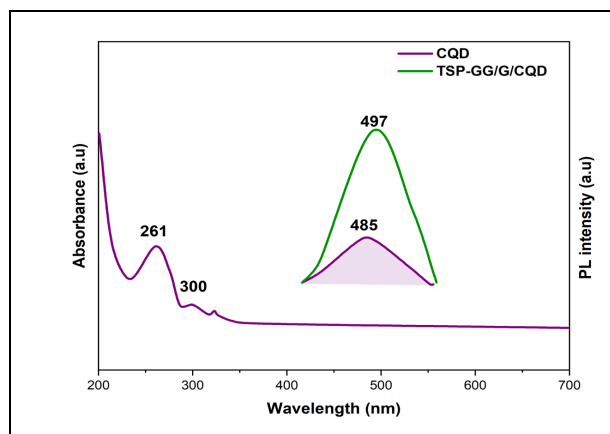


Fig. 6: UV–Vis absorption and fluorescence emission spectra of CQDs

3.4 DOX and Swelling Studies

Hydrogels absorb solvents or physiological fluids that permeate the internal network architecture. Critical elements include crosslinking density, polymer content, and mesh size, which directly affect the network's chemical and physical characteristics. The crosslinking, properties of the swelling environment, and

polymer type substantially influence swelling behavior. Regulating drug release is essential in transdermal drug delivery, and the degree of swelling of hydrogels is a critical determinant in this process. Fig. 7 illustrates the swelling properties of the carrier over 128 h in three solutions at pH values of 1.0, 6.6, and 7.2. At pH 1.0, the swelling ratio (SR) demonstrated a modest, consistent rise, indicating carrier stability at acidic stomach environments. Conversely, at pH 7.2, SR exhibited a substantial and sustained rise, attaining 1580%. Following 128 h at pH 7.2, the carrier showed mass loss because of reduction at SR, which signifies progressive breakdown of the carrier and degradation of the polymer network. The outcomes underscore pH sensitivity of the hydrogel, which can markedly affect the stability and effectiveness of controlled drug delivery systems, hence augmenting their applicability for targeted therapeutic interventions, especially at pH-variable settings like the gastrointestinal tract.

Encapsulation efficiency of DOX at TSP–GG/GNP/CQD attained 99%, indicating substantial drug-loading capacity. This exceptional efficiency was ascribed to the prevalence of functional groups within the nanocomposite matrix, notably carboxyl (–COOH) and hydroxyl (–OH) groups. The groups engage DOX by van

der Waals forces, hydrogen bonding, electrostatic interactions, and π - π stacking. At pH 7.2, carboxyl groups acquire a negative charge, thereby enhancing the encapsulation and adsorption of positively charged DOX. Drug release profiles were assessed at pH levels of 1.0, 6.6, and 7.2, showing the stomach, colonic fluid, and small intestinal simulations. Fig. 8 depicts the results of sustained and regulated release properties of doxorubicin at DOX-loaded TSP-GG/GNP/CQD. In the first 2 h, the total release rate of pH 1.0 was negligible, around 0.6745 %, consistent with swelling characteristics. Gellan gum experiences protonation in acidic environments, resulting in the formation of alginic acid. After 2 h, TSP-GG/GNP/CQD-DOX was transferred to small intestinal fluid for 4 h, resulting in a cumulative release of 1.02%. The DOX-loaded TSP-GG/GNP/CQD was subjected to *in vitro* release studies, and colonic fluid was used for the remaining duration. Discharge rate demonstrated steady progression over the following 4 h. Subsequently, release of DOX began to intensify, likely due to the deprotonation of gellan gum, resulting in the structural degradation of the TSP-GG/GNP/CQD. As reported in previous studies, an amino-acid-functionalized gellan gum nanocomposite incorporating CeO₂ nanoparticles was developed. The nanocomposite showed excellent antibacterial performance and adsorption efficiency, highlighting its relevance in drug delivery and water purification systems (Abbasi *et al.* 2024). The determined DOX release rate is 99% after 128 h. The release profile of doxorubicin exhibits a clear link with the swelling properties of TSP-GG/GNP/CQD. As a result, pH-responsive characteristics of TSP-GG/G/CQD were observed.

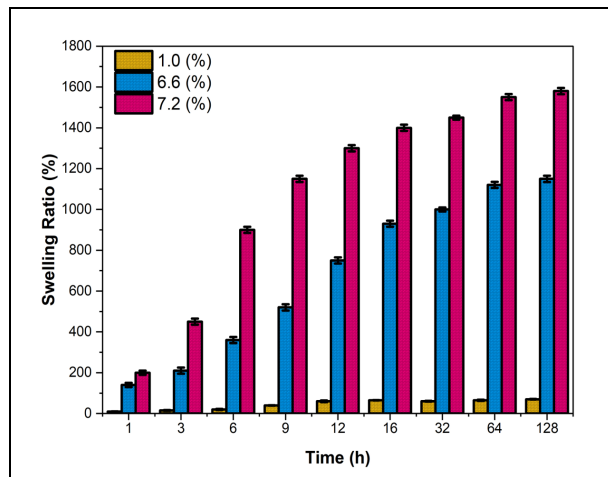


Fig. 7: Swelling behavior of TSP-GG/GNP/CQD hydrogel at different pH conditions, demonstrating strong pH-responsive swelling with maximum expansion under colonic pH conditions

The obtained drug release performance of the TSP-GG/GNP/CQD hydrogel system shows improved behavior compared with previously reported polysaccharide-based hydrogel drug delivery systems.

For example, in a previous study, approximately 84% DOX release was observed at pH 7.4 in an okra polysaccharide-alginate hydrogel system (Tahmasebi and Mohammadi, 2025b), whereas the present system achieved 99% cumulative drug release under colonic conditions (pH 7.2). This enhanced performance can be attributed to the synergistic effect of dual polysaccharide networks and dual nanocarbon reinforcement, which improves swelling behavior and drug diffusion pathways.

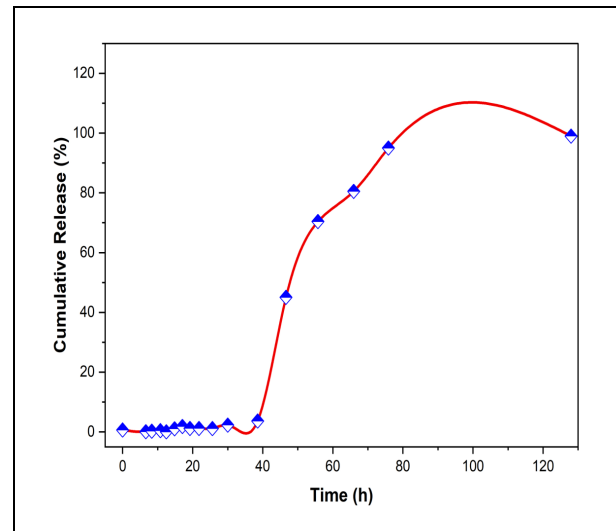


Fig. 8: pH-dependent DOX release profile of TSP-GG/GNP/CQD hydrogel beads, showing minimal release under acidic conditions and sustained drug release at colonic pH

Kinetic parameters for models were derived by linear regression, utilizing the coefficient of determination (R^2) to evaluate model fit. Among the models analyzed, the Higuchi model yielded the greatest R^2 value, indicating it most accurately characterizes the elimination profile of DOX. The theoretical framework was based on the assumption that the size of drug particles was significantly smaller than the thickness of the system. Thus, the elimination model yielded a kinetic equation that helps describe drug dissolution across diverse pharmaceutical formulations, including matrix tablets and transdermal delivery systems containing hydrophilic drugs.

Table 2. Kinetic model fitting results showing coefficient of determination (R^2) values for DOX release from TSP-GG/GNP/CQD hydrogel beads at different pH conditions

Model Kinetics	Coefficient of Determination		
	pH 1.0 (R^2)	pH 6.6 (R^2)	pH 7.2 (R^2)
Zero	0.88	0.89	0.91
Korsmeyer-Peppas	0.90	0.91	0.95
Weibull	0.93	0.94	0.98
Higuchi	0.92	0.93	0.97
First-order	0.93	0.93	0.98

The drug release behavior of the hydrogel is strongly influenced by its pH-responsive swelling characteristics and polymer network structure. At acidic pH (1.0), protonation of functional groups reduces polymer chain expansion, resulting in minimal swelling and limited drug release (Table 2). In contrast, at alkaline conditions (pH 7.2), deprotonation of carboxyl groups increases electrostatic repulsion within the polymer network, leading to significant swelling and enhanced drug diffusion. The kinetic modeling results indicate that the Higuchi and Weibull models show high correlation coefficients (R^2), suggesting that drug release is primarily governed by diffusion-controlled mechanisms coupled with polymer matrix swelling.

3.5 Antibacterial and Antioxidant Evaluation

The antibacterial activities of CM, graphene nanoparticles, and TSP-GG/GNP/CQD were comprehensively analyzed against Gram-positive and Gram-negative *S. aureus* and *E. coli* (Fig. 9a). Gram-negative bacteria generally demonstrate greater resistance to bioactive chemicals and plant extracts owing to more intricate cell wall architecture. Gram-negative bacteria's cell walls, reinforced by proteins functioning as hydrophilic channels, provide a barrier that restricts the ingress of hydrophobic substances, thus enhancing resistance. Conversely, cell wall architecture facilitates the entry of hydrophobic compounds, hence augmenting the efficacy of antimicrobial medicines within the bacterial category. Antimicrobial efficacy of CM extract was ascribed to constituents, including alkaloids, cinnamaldehyde, eugenol, flavonoids, steroids, coumarin, tannins, saponins, and phenols, while GNPs are integral to the antibacterial properties of this system. These nanoparticles can adhere to bacterial cell walls, provoke cytoplasmic contraction, compromise membrane integrity, and finally induce cell death. Moreover, graphene nanoparticles produce free radicals and ROS, provoke oxidative stress, resulting in bacterial cell mortality and DNA damage. The TSP-GG/GNP/CQD demonstrated substantial antibacterial efficacy against Gram-negative and Gram-positive microorganisms. Nonetheless, owing to structural disparities in bacterial cell walls, nanocomposites demonstrated greater efficacy against Gram-positive bacteria. The integration of graphene nanoparticles into a hydrogel matrix significantly improved antibacterial efficacy, underscoring its potential as a carrier for infection control, especially in treatments and devices that combine antimicrobial and anticancer capabilities.

Antioxidant efficacy of the carrier was assessed by DPPH assay, wherein the color transition of DPPH from purple to yellow signified robust antioxidant characteristics of the used materials. An IC₅₀ of the carrier was around 5 mg/mL. Polysaccharides at the carrier, including GG and TSP, demonstrate antioxidant action owing to carboxylate groups. Furthermore, GNP-

derived CM extract augmented the antioxidant activity of TSP-GG/GNP/CQD. Hydroxyl at the surface of graphene nanoparticles promotes electron transport, thereby defusing free radicals. The CM, abundant in bioactive substances such as phenols and flavonoids, augments the antioxidant activity of the carrier. These chemicals and graphene nanoparticles collaborate to enhance antioxidant activity, rendering TSP-GG/GNP/CQD appropriate for CRC.

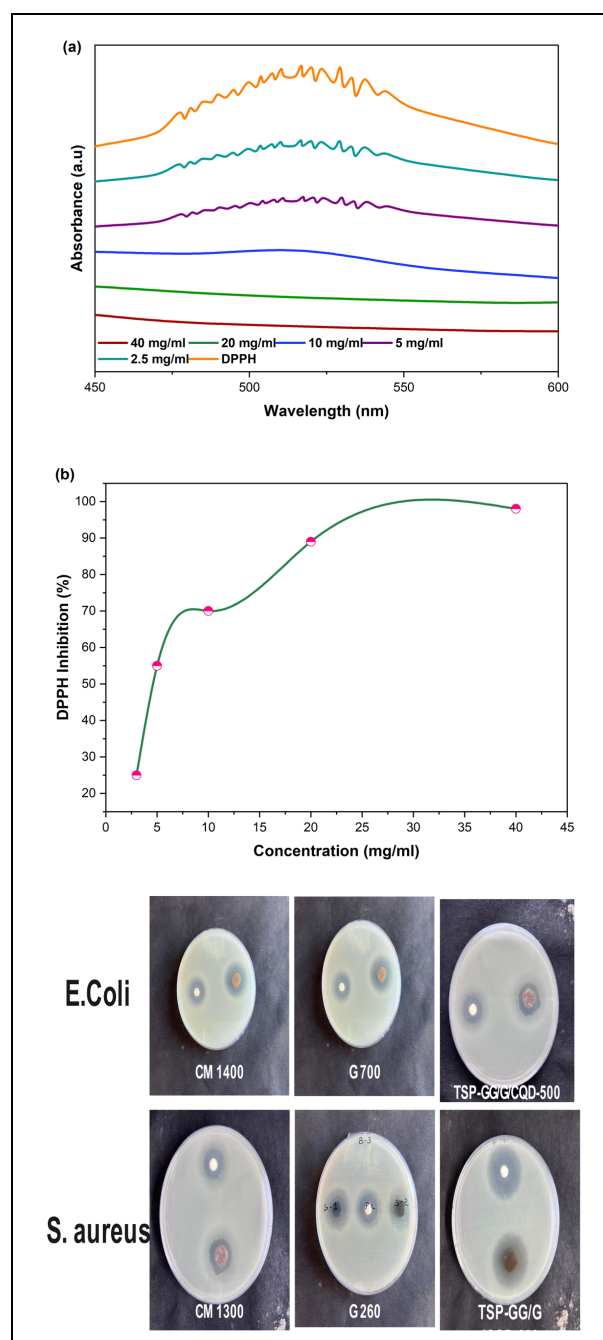


Fig. 9: (a) Antibacterial activity against *S. aureus* and *E. coli*, (b) DPPH radical scavenging activity at 520 nm, and (c) concentration-dependent DPPH inhibition and IC₅₀ values, demonstrating the antioxidant potential of the nanocomposite system

The antibacterial activity observed in the TSP–GG/GNP/CQD hydrogel system can be attributed to the presence of graphene nanoparticles and bioactive compounds derived from the cinnamon extract used during green synthesis. These components can disrupt bacterial cell membranes, generate reactive oxygen species (ROS), and induce oxidative stress, leading to bacterial cell death.

3.6 Cytotoxicity Analysis

An MTT assay was performed to assess the therapeutic efficacy and cytotoxicity of DOX, TSP–GG/GNP/CQD, and TSP–GG/GNP/CQD–DOX on HT-29 CRC cells. The IC₅₀ for free DOX was 48 µg/mL, whereas that for TSP–GG/GNP/CQD–DOX was 96 µg/mL, indicating a controlled and slower release of DOX from TSP–GG/GNP/CQD–DOX. This regulated release diminishes the systemic toxicity of DOX, hence reducing its adverse effects. Furthermore, TSP–GG/GNP/CQD demonstrated less toxicity at elevated concentrations, affirming their biocompatibility. Integrating graphene nanoparticles into a carrier significantly improves medication amplification and delivery of anticancer efficacy, producing ROS, which triggers oxidative stress. Prior research indicates that the tamarind seed polysaccharide–chitosan scaffold was developed. Cytotoxicity analysis confirmed its biocompatibility, indicating suitability for advanced drug delivery and wound-healing platforms (Sri *et al.* 2025). GNPs can initiate apoptotic pathways through the induction of oxidative stress, thereby facilitating cell death and DNA damage in cancer cells. The synergistic interaction between TSP–GG/GNP/CQD and DOX facilitates extended drug retention on the tumor, minimizes off-target effects, and enhances the therapeutic efficacy of CRC at HT-29. The outcomes underscore the bifunctional capabilities of TSP–GG/GNP/CQD, facilitating both effective drug transport and augmented anticancer efficacy.

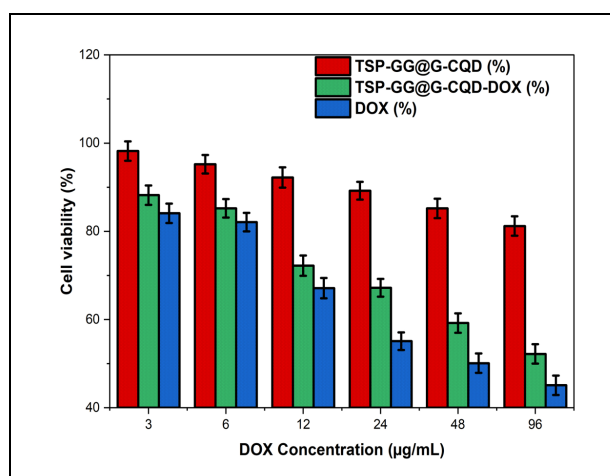


Fig. 10: Cytotoxicity of nanocomposites and DOX in HT-29 cells

The cytotoxicity studies demonstrated that the DOX-loaded hydrogel exhibited a higher IC₅₀ value compared to free DOX, indicating a slower and controlled drug release behavior (Fig. 10). This sustained release reduces the immediate cytotoxic impact while maintaining therapeutic efficacy against HT-29 colorectal cancer cells.

4. CONCLUSION

Colorectal cancer therapy using conventional doxorubicin (DOX) suffers from systemic toxicity, premature drug release in the upper gastrointestinal tract, and limited site-specific targeting, necessitating the development of an intelligent colon-responsive delivery system. In this research, a pH-sensitive hydrogel composed of tamarind seed polysaccharide (TSP) and gellan gum (GG), reinforced with green-synthesized graphene nanoparticles (GNPs) reduced using cinnamon extract and carbon quantum dots (CQDs) derived from coconut shells, was successfully developed for controlled DOX delivery. The hydrogel beads were fabricated by ionic crosslinking using 4 wt.% CaCl₂, followed by structural, morphological, and optical characterization using FTIR, XRD, SEM–EDX, UV–Vis, and photoluminescence techniques, along with swelling, drug loading, *in-vitro* release, antibacterial, antioxidant, and cytotoxicity evaluations. The optimized system exhibited a maximum swelling ratio of 1580% at pH 7.2, high encapsulation efficiency of 99%, and cumulative DOX release of 99% after 128 h under colonic conditions, while showing minimal release at pH 1.0 (0.67%). Strong antibacterial activity was observed against *E. coli* and *S. aureus*, with notable antioxidant activity (IC₅₀ = 5 mg/mL). Cytotoxicity studies on HT-29 cells demonstrated controlled release behavior, with IC₅₀ values of 48 µg/mL for free DOX and 96 µg/mL for DOX-loaded hydrogel. Therefore, the developed TSP–GG/GNP/CQD hydrogel represents a multifunctional, colon-targeted drug delivery platform with significant potential for CRC treatment and other biomedical uses requiring pH-responsive controlled release. Compared with conventional drug delivery systems, the developed TSP–GG/GNP/CQD hydrogel offers several advantages, including pH-responsive drug release, high encapsulation efficiency (99%), improved swelling behavior, and multifunctional biological activity such as antibacterial and antioxidant properties, which collectively enhance the effectiveness of colon-targeted chemotherapy while reducing premature drug release. Future studies could focus on *in vivo* evaluation, long-term biocompatibility assessment, and pharmacokinetic analysis to further validate the therapeutic potential of the developed hydrogel system. Additionally, exploring clinical translation and scalable fabrication methods could facilitate its application in advanced colorectal cancer treatment.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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