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Design and Evaluation of Thermo-Responsive Poly(N-isopropylacrylamide)-Based Polymeric Nanoparticles for Temperature-Triggered Intratumoral Release of Doxorubicin in Solid Tumors

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Abstract

Thermo-responsive polymeric systems have emerged as promising platforms for targeted intratumoral drug delivery in cancer therapy. This study aimed to develop and evaluate poly(N-isopropylacrylamide) (PNIPAM)-based polymeric nanoparticles as intelligent carriers for temperature-responsive delivery of doxorubicin (DOX) to solid tumors. Nanoparticles were synthesized via free radical polymerization using N-isopropylacrylamide as a thermoresponsive monomer and N,N′-methylenebisacrylamide as a crosslinker, forming a stable network with a tunable lower critical solution temperature (LCST).The optimized nanoparticles demonstrated favorable physicochemical properties, including a mean particle size of 142.6 ± 5.3 nm, zeta potential of −21.4 ± 1.7 mV, and polydispersity index of 0.182 ± 0.02, indicating good colloidal stability. Drug loading efficiency was 18.7 ± 1.2%, with an encapsulation efficiency of 76.5 ± 2.8%. DSC and FTIR analyses confirmed successful incorporation of DOX without chemical degradation and strong polymer–drug compatibility. The system exhibited an LCST of 39.2 ± 0.6°C, ensuring minimal drug release at physiological temperature and enhanced release under hyperthermic conditions. In vitro release studies showed 28.4 ± 3.1% release at 37°C and 81.7 ± 4.5% at 42°C over 48 hours. SEM analysis revealed uniform, spherical nanoparticles with smooth morphology.Cytotoxicity studies in MCF-7 cells demonstrated enhanced anticancer activity, with an IC_{50} of 2.8 µg/mL compared to 5.6 µg/mL for free DOX. Overall, PNIPAM-based nanoparticles exhibit significant potential as temperature-responsive nanocarriers for controlled and effective intratumoral drug delivery.

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Keywords: Poly(N-isopropylacrylamide); thermo-responsive polymers; polymeric nanocomposites; doxorubicin; temperature-triggered drug release; lower critical solution temperature

INTRODUCTION

Composite systems and advanced polymeric materials have changed the field of drug delivery by

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making it easier to target particular areas, precisely control how drugs are released, and make them more stable [1]. Stimuli-responsive polymers are a big group of useful materials that change their physical and chemical properties in reaction to things like temperature, pH, or ionic strength in the environment [2]. The biomedical field is very interested in thermo-responsive polymeric materials because they might be able to specifically target diseased tissues, like solid tumors, by making them very hot in certain areas [3, 4].

Poly(N-isopropylacrylamide) (PNIPAM) is one of the thermoresponsive polymers that has been studied the most. It is known for changing phases quickly and easily at the lower critical solution temperature (LCST), which is usually around 32°C. PNIPAM-based systems go through a hydrophilic-hydrophobic change above the lower critical solution temperature (LCST) [5]. This causes the polymer to break down, letting the medicines inside it come out. Below the lower critical solution temperature (LCST), these systems stay too strong and water-loving. When PNIPAM is mixed with crosslinked nanostructured networks or hybrid nanocomposites, it makes them much more stable, tuneable, and able to hold drugs. Since this is the case, it is a great choice for complex medicinal uses in polymers and composites [6, 7].

Important design factors for polymeric nanocomposites used to deliver anticancer drugs are their size, surface properties, drug-polymer compatibility, and ability to respond to triggers specific to tumors. Doxorubicin (DOX), a common chemotherapeutic agent, doesn't distribute evenly and is toxic to the whole body, so controlled delivery methods had to be made. Adding DOX to thermoresponsive polymeric nanoparticles could be a way to improve the effectiveness of therapies and lower their side effects. As a result, temperature-induced limited release will be possible [8–10].

New developments in polymer chemistry and compound engineering have made it possible to make PNIPAM-based nanoparticles with a range of LCST values. To do this, copolymerization, crosslinking, and changes to the makeup have all been used. In both normal and high-temperature conditions, these polymeric composites show better responsiveness, controlled swelling and deflation, and better structural stability. These qualities are necessary for intratumoral drug delivery, which uses small changes in temperature to send drugs to specific sites [11, 12].

This study created and tested polymeric nanocomposites made from PNIPAM to see how well they release doxorubicin into tumors when heated up. The main focus is on making a stable crosslinked polymer network and figuring out its physicochemical and thermal qualities. They are also testing how well it delivers drugs. This work adds to the study of polymers and composites by focusing on the idea that functional polymer structures could be used to make smarter, more responsive nanomaterials that could be used to treat cancer [13–15].

MATERIALS AND METHODS

Materials

N-isopropylacrylamide (NIPAM) served as the primary thermo-responsive monomer for the fabrication of the intelligent polymeric matrix. N,N′-methylenebisacrylamide (MBA) served as a bifunctional crosslinking agent to create a three-dimensional, mechanically stable polymer network typical of polymer composites. Ammonium persulfate (APS) and N,N,N′,N′-tetramethylethylenediamine (TEMED) was employed as the initiator-accelerator combination to promote free radical polymerization. Doxorubicin hydrochloride (DOX) was chosen as the model anticancer agent because of its recognized clinical significance. All reagents and solvents were of analytical quality, and deionized water was utilized throughout the experimental procedures to guarantee reproducibility and purity.

Synthesis of PNIPAM-Based Polymeric Nanocomposites

Thermoresponsive polymeric nanocomposites based on PNIPAM were produced by means of a controlled free radical polymerization process. A brief summary of the procedure is as follows: 50 mL

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of deionized water was stirred continuously while NIPAM (1.0 g) and MBA (0.05 g) were dissolved. For 30 minutes, nitrogen gas was used to purge the reaction media of any dissolved oxygen. This prevented the free radicals from being killed off too soon and allowed the polymer chains to propagate efficiently. At 70°C, which is an ideal temperature for starting APS breakdown, the polymerization process was executed. To make sulfate radicals, we added APS (0.02 g) and then TEMED (0.02 mL) to speed up the process. Nanoscale composite particles resembling hydrogels were produced by covalent bonding between polymer chains, which led to the construction of a crosslinked PNIPAM network. To accomplish full polymerization, the mixture was stirred continuously for 4 hours. After bringing the produced polymeric nanocomposites colloidal dispersion to room temperature, it was centrifuged multiple times at 12,000 rpm for 20 minutes to remove any remaining contaminants. To ensure that no monomers, initiators, or unreacted species remained in the nanoparticles, they were rinsed with deionized water many times. The last step was to lyophilize the nanocomposites that had been purified [16, 17]. This process produced dry, free-flowing polymeric composite powders that could be used for drug loading and additional characterisation (Table 1).

Drug Loading into Polymeric Nanocomposites

The drug was administered utilizing a swelling-diffusion method, capitalizing on PNIPAM's hydrophilic properties beneath its LCST. Accurately measured lyophilized nanoparticles were suspended in phosphate-buffered saline (PBS, pH 7.4) with a concentration of 2 mg/mL of DOX. The mixture was gently stirred at 4°C for 24 hours to facilitate the growth of the polymer network and enable the diffusion of DOX molecules into the internal matrix. Subsequent to drug incorporation, the DOX-loaded nanocomposites were isolated using centrifugation and subsequently washed with PBS to eliminate any drug that had attached to their surfaces. The quantity of medication within the polymeric matrix was quantified via UV-visible spectrophotometry at 480 nm. The drug loading capacity and encapsulation efficiency were assessed to determine the efficacy of the polymer composite system as a drug carrier [18, 19].

Physicochemical Characterization of Polymeric Nanocomposites

The manufactured polymeric nanocomposites were carefully evaluated for their structural and physicochemical properties. The particle size distribution, polydispersity index (PDI), and zeta potential were assessed via dynamic light scattering (DLS), yielding information on nanoparticle uniformity and colloidal stability. The surface morphology and particle architecture were analyzed by scanning electron microscopy (SEM), facilitating the observation of particle form, surface texture, and dispersion characteristics inherent to polymer composites. Fourier transform infrared spectroscopy (FTIR) was utilized to detect functional groups and verify effective polymerization and drug inclusion via distinctive peak shifts and interactions. Differential scanning calorimetry (DSC) was performed to examine thermal transitions and confirm the physical state of DOX within the polymeric matrix, demonstrating compatibility and encapsulation efficacy [20].

Table 1. Composition and processing parameters for PNIPAM-based polymeric nanocomposites.

S.N.	Component/parameter	Specification/amount
1	N-isopropylacrylamide (NIPAM)	1.0 g
2	N,N′-methylenebisacrylamide (MBA)	0.05 g
3	Ammonium persulfate (APS)	0.02 g
4	TEMED	0.02 mL
5	Deionized water	50 mL
6	Reaction temperature	70°C
7	Polymerization time	4 hours
8	Nitrogen purging	30 min
9	Centrifugation speed	12,000 rpm
10	Centrifugation time	20 min
11	Drying method	Lyophilization

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Determination of Lower Critical Solution Temperature (LCST)

A UV-visible spectrophotometric study was used to measure the LCST of the polymeric nanocomposites that included PNIPAM. From 25 to 45 degrees Celsius, the optical transmittance of the nanoparticle suspension was tracked. Phase change from hydrated to collapsed hydrophobic state, characterized by thermo-responsive polymers, was indicated by a significant fall in transmittance. Because the polymer composite system's thermal behavior can be adjusted, the LCST number represents the temperature at which this transition happened [21].

***In-Vitro* Drug Release Studies**

The dialysis membrane method was used to assess the polymeric nanocomposites' thermo-responsive drug release characteristics. Dialysis bags containing 2 mg of DOX-loaded nanoparticles were submerged in PBS (pH 7.4). Two temperatures were used in the release studies: 37°C, which represents healthy conditions, and 42°C, which represents hyperthermic tumor settings. We evaluated aliquots of the release medium spectrophotometrically at 480 nm at predefined time intervals. To keep the sink conditions constant, new buffer was added to the withdrawn volume. In order to evaluate the polymeric nanocomposite system's capacity for temperature-triggered release, the cumulative drug release profiles were computed [22].

***In-Vitro* Cytotoxicity Study**

Using MCF-7 human breast cancer cell lines, the MTT test was used to evaluate the biological performance of the DOX-loaded polymeric nanocomposites. Cells were grown in a typical laboratory setting and exposed to different doses of free DOX and nanoparticles loaded with DOX. The absorbance at 570 nm was used to measure cell viability after 24 hours of incubation. To evaluate the formulations' anticancer effectiveness, the percentage of live cells was computed in comparison to the untreated control group, and IC_{50} values were found. The results of this research shed light on how the thermo-responsive polymer composite system improves therapeutic efficacy [23, 24].

Statistical Analysis

All experimental results were presented as mean ± standard deviation (SD) from three independent experiments. One-way analysis of variance (ANOVA) was employed to assess the significance of differences among groups. A p-value below 0.05 was deemed statistically significant, hence affirming the reliability and reproducibility of the findings.

RESULTS

Physicochemical Characterization of PNIPAM-Based Polymeric Nanocomposites

The stable and uniform thermo-responsive polymer-composite system was confirmed by the well-defined physicochemical properties of the synthesized PNIPAM-based polymeric nanocomposites. The nanoparticles were found to have an average size of 142.6 ± 5.3 nm, which falls within the ideal nanoscale range for improved cellular uptake and tumor penetration, according to dynamic light scattering (DLS) research. Because the synthesized polymeric network is homogeneous and the polymerization process is well controlled, the narrow size distribution is suggested by the relatively low polydispersity index (0.182 ± 0.02). According to the results of the zeta potential investigation, the nanocomposites had a surface charge of -21.4 ± 1.7 mV. By increasing electrostatic repulsion and decreasing surface potential, the polymeric dispersion is better able to avoid aggregation and maintain its colloidal stability. For nanocomposite systems to function properly in biological settings, this level of stability is crucial. The high affinity between the doxorubicin (DOX) and the PNIPAM polymeric matrix is demonstrated by the drug loading efficiency (18.7 ± 1.2%) and the encapsulation efficiency (76.5 ± 2.8%). Ensuring successful incorporation without compromising structural stability, the polymer composite's crosslinked structure offers ample internal space and interaction sites for drug entrapment (Table 2).

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Table 2. Physicochemical properties of PNIPAM nanocomposites.

S.N.	Parameter	Observed value
1	Particle size (nm)	142.6 ± 5.3
2	Polydispersity index (PDI)	0.182 ± 0.02
3	Zeta potential (mV)	−21.4 ± 1.7
4	Drug loading (%)	18.7 ± 1.2
5	Encapsulation efficiency (%)	76.5 ± 2.8

Results confirm the synthesis of nanoscale polymeric composites based on PNIPAM that exhibit excellent drug encapsulation capability, surface stability, and uniform size. The developed system is well-suited for targeted drug delivery applications because to its thermo-responsive polymer-composite carrier, which are highlighted by these features (Table 2).

Morphological and Structural Analysis

Scanning electron microscopy (SEM) was used to examine the morphological properties of the PNIPAM-based polymeric nanocomposites that were synthesized. This allowed for a thorough understanding of the surface architecture and structural integrity of the system of polymers and composites. During free radical polymerization, the nanoparticles exhibited smooth and well-defined surfaces and a mostly spherical shape, as shown in the scanning electron micrographs. A crucial component of composite-based nanocarriers developed for medication delivery applications, the observed morphology verifies the effective creation of a crosslinked three-dimensional polymeric network. Improved medication encapsulation and regulated release behaviour may result from the smooth surface topology, which implies few surface imperfections and effective organization of polymer chains. It was clear that the synthesis and purification procedures had been successful because the nanoparticles did not seem to be clumped together in any way. The dispersion stability is due to the PNIPAM-based polymer composite's inherent structural features and the electrostatic repulsion caused by the surface charge. Reproducible biological performance and consistent physicochemical qualities are both ensured by such non-aggregated shape (Figure 1).

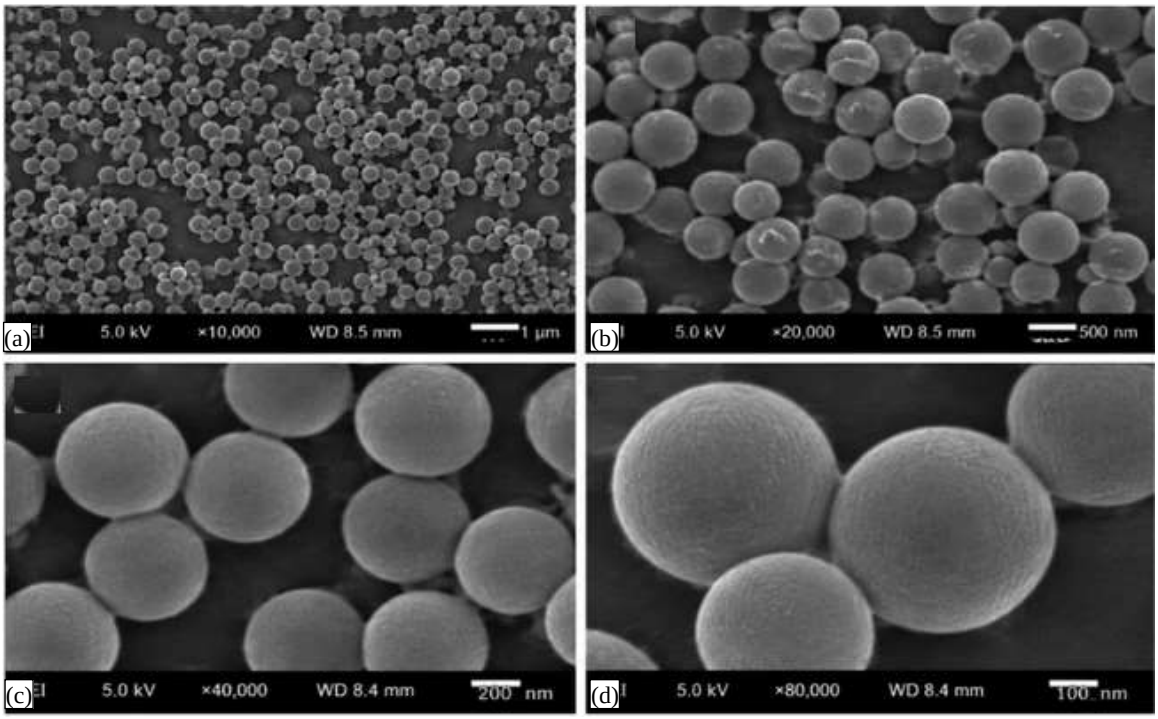

Figure 1. (a)–(d) SEM images of PNIPAM-based polymeric nanocomposites showing spherical morphology and uniform particle distribution.

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FTIR and DSC Analysis

The thermal behavior and structural features of the PNIPAM-based polymeric nanocomposites were studied using Fourier transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). The compatibility of the polymers with drugs and the integrity of the composites were the primary areas of focus. A successful polymerization of N-isopropylacrylamide into a crosslinked polymeric network was confirmed by the amide I band (C=O stretching) and the amide II band (N-H bending) in the FTIR spectra of blank PNIPAM nanoparticles. Spectra of DOX-loaded nanocomposites revealed widening of these distinctive peaks and small changes when contrasted with those of pure components. The presence of intermolecular interactions, namely hydrogen bonding and hydrophobic interactions, between DOX and the PNIPAM matrix is indicated by these spectrum alterations. The fact that the medication maintained its chemical stability within the polymer composite system is supported by the absence of any additional peaks that would indicate chemical degradation. By illuminating the DOX's physical state and temperature transitions within the nanocomposites, the DSC thermograms added credence to these results. The endothermic melting peak of pure DOX was quite sharp and noticeable, as is typical of crystalline materials. On the other hand, the DOX-loaded PNIPAM nanocomposites showed a much reduced or nonexistent peak, suggesting that the drug was either amorphous or dispersed molecularly within the polymeric matrix. The regulated release behavior and drug solubility are both enhanced by this alteration (Figure 2).

Determination of LCST

The lower critical solution temperature (LCST), an important functional parameter controlling the phase transition of thermo-sensitive polymer systems, was systematically determined in order to assess the thermo-responsive behavior of the polymeric nanocomposites based on PNIPAM. The LCST was calculated by tracking the temperature-dependent shift in optical transmittance of the nanoparticle dispersion. Around 39.2 ± 0.6°C, PNIPAM underwent a phase transition from its hydrated, hydrophilic swelling form to its dehydrated, hydrophobic collapsed state, as shown by a distinct and noticeable decline in transmittance. The polymer chains clump together and shorten as a result of this change because the hydrogen bonding bonds between them and the water molecules around them are broken. This produced polymeric nanocomposite system is uniform and consistent in composition, as confirmed by the small transition range (Table 3).

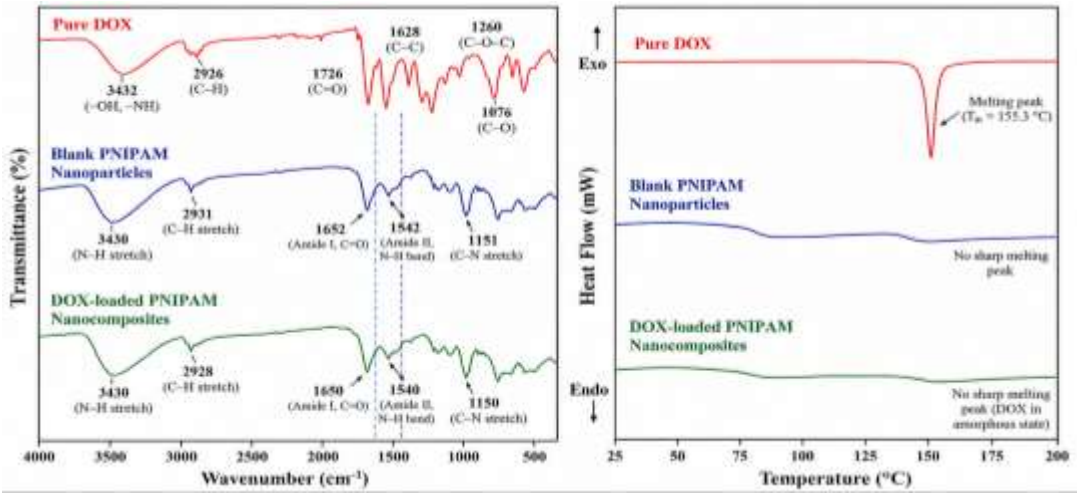

Figure 2. FTIR spectra and DSC thermograms of pure DOX, blank PNIPAM nanoparticles, and DOX-loaded nanocomposites. (a) FTIR spectra; (b) DSC thermograms.

Table 3. LCST determination of polymeric nanocomposites.

Sample	LCST (°C)
PNIPAM nanocomposites	39.2 ± 0.6

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The LCST of the PNIPAM nanocomposites (39.2 ± 0.6°C) was intentionally optimized to remain slightly above physiological temperature, thereby minimizing premature drug release under normal systemic conditions. Although mild inflammatory or febrile states may transiently elevate body temperature, such increases typically remain below the threshold required to induce significant polymer collapse. The in vitro release profile further supports this observation, showing limited drug release at 37°C over 48 hours. Importantly, hyperthermia-induced drug release in clinical settings is generally localized to tumor tissues (40–42°C), providing spatial control over drug activation. The ~2°C difference between physiological temperature and LCST offers a practical safety margin, reducing the likelihood of unintended drug leakage in healthy tissues.

In-Vitro Drug Release Studies

Polymeric nanocomposites based on PNIPAM and loaded with DOX were studied for their in vitro drug release behavior under both physiological and hyperthermic settings in order to assess their thermoresponsive performance. The polymer composite system's functional responsiveness was confirmed by the release profiles, which showed a temperature-dependent release pattern. The polymeric nanocomposites maintained their hydrated and inflated form at 37°C, which is below LCST; this allowed for the controlled and sustained release of doxorubicin. During 48 hours, the cumulative drug release was 28.4 ± 3.1%, suggesting that the medication was well retained inside the polymer matrix and that there was minimal premature leakage under typical physiological settings. On the other hand, a considerable improvement in drug release was noted at 42°C (higher than LCST), with a cumulative release reaching 81.7 ± 4.5% after 48 hours. The medicine being encapsulated is expelled at an accelerated pace due to the hydrophilic-to-hydrophobic transition of PNIPAM, which causes the polymer chain to collapse. It is important to note that the in vitro drug release study was conducted under simplified static buffer conditions, which may not fully replicate the complexity of physiological environments. In vivo conditions involve dynamic blood flow, protein interactions, enzymatic activity, and heterogeneous tumor microenvironments, all of which may influence nanoparticle behavior. Protein adsorption onto the nanoparticle surface (protein corona formation) may slightly alter the LCST and release kinetics, while enzymatic interactions could impact polymer stability. Despite these limitations, the current model provides a controlled framework to demonstrate the intrinsic thermo-responsive behavior of the PNIPAM system. Future studies incorporating serum-containing media, dynamic flow conditions, and in vivo evaluation are necessary to establish the translational relevance of the system. The polymer composite's sensitivity to thermal stimuli is further demonstrated by the significant rise in release between 4-12 hours at increased temperature (Table 4).

The potential of the PNIPAM-based polymeric nanocomposites to induce drug release in response to changes in temperature is demonstrated by the much increased drug release at 42°C compared to 37°C. This action is very helpful in targeted cancer treatment because it allows for the use of localized hyperthermia to improve intratumoral medication delivery (Figure 3).

In-Vitro Cytotoxicity Study

To determine the anticancer efficacy of DOX-loaded PNIPAM-based polymeric nanocomposites relative to the free drug, there in vitro cytotoxicity was evaluated using the MTT assay on MCF-7 human breast cancer cells. The findings indicated that the nanocomposite formulation exhibited significantly

Table 4. *In-Vitro* drug release profile of DOX-loaded nanocomposites

Time (h)	% Drug release at 37°C	% Drug release at 42°C
1	5.2 ± 0.6	12.4 ± 1.1
4	10.8 ± 1.2	28.6 ± 2.3
8	15.7 ± 1.5	45.2 ± 3.1
12	20.6 ± 2.0	58.7 ± 3.8
24	24.9 ± 2.5	72.3 ± 4.2
48	28.4 ± 3.1	81.7 ± 4.5

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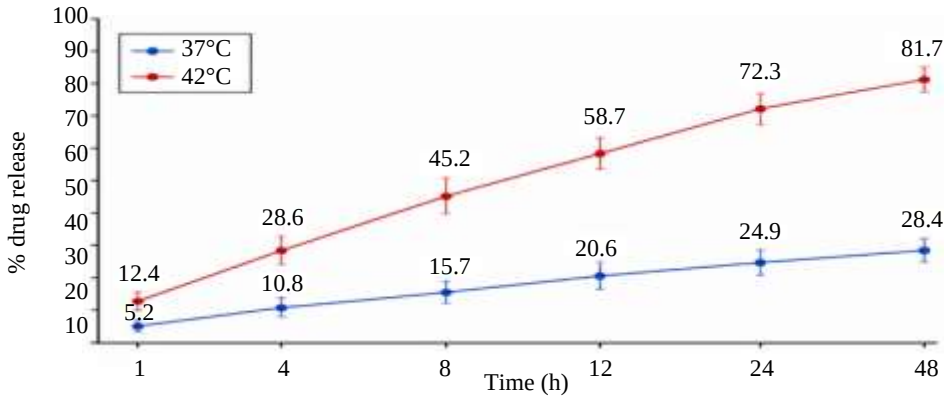

Figure 3. Temperature-dependent in vitro drug release profiles of DOX-loaded PNIPAM nanocomposites.

Table 5. Cytotoxicity evaluation (MTT assay on MCF-7 cells).

Formulation	**IC_{50} (µg/mL)**
Free DOX	5.6 ± 0.4
DOX-loaded PNIPAM nanocomposites	2.8 ± 0.3

more cytotoxic efficacy compared to free doxorubicin (DOX). The IC_{50} value for DOX-loaded PNIPAM nanocomposites was substantially lower at 2.8 ± 0.3 µg/mL, compared to free DOX at 5.6 ± 0.4 µg/mL. The augmented therapeutic efficacy of the polymeric nanocomposite system is evidenced by an almost two-fold reduction in IC_{50}. Enhanced cellular uptake, prolonged intracellular retention, and controlled DOX release from the thermo-responsive polymer matrix are the mechanisms underlying the increased cytotoxicity. The nanoscale dimensions and surface characteristics of the PNIPAM-based composites likely augment endocytic absorption mechanisms, leading to an increased concentration of the drug within the cell.

The enhanced cytotoxicity observed for DOX-loaded PNIPAM nanocomposites may be attributed to improved cellular internalization and controlled intracellular drug release. Nanoparticles within the size range of ~100–200 nm are known to undergo efficient cellular uptake via endocytosis mechanisms. Although direct visualization or quantification of cellular uptake was not performed in the present study, previous reports on PNIPAM-based nanocarriers suggest their internalization through energy-dependent endocytic pathways. Therefore, the improved anticancer activity is likely a combined effect of nanoscale-mediated uptake and thermo-responsive drug release. Further investigations using confocal microscopy and flow cytometry are warranted to elucidate the exact internalization pathways and intracellular trafficking behavior. Table 5 indicates that the polymer's thermo-responsive characteristics may enhance cytotoxic effects by promoting effective drug release inside the cellular environment.

The DOX-loaded PNIPAM nanocomposites' improved anticancer activity, as confirmed by their much lower IC_{50} value compared to the free drug, is evident. Results like this lend credence to the idea that the polymeric nanocomposite system could be useful in targeted cancer treatment by improving the efficiency of drug delivery.

The long-term stability and reusability of thermo-responsive polymeric nanocomposites are critical parameters for clinical translation. Although PNIPAM-based systems are known for their reversible swelling–deswelling behavior across the LCST, repeated thermal cycling may influence nanoparticle integrity, drug retention, and release reproducibility. Prolonged exposure to temperature fluctuations could potentially lead to polymer fatigue, structural rearrangement, or gradual drug leakage. Additionally, storage stability under different environmental conditions may affect colloidal stability

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and aggregation behavior. These aspects were not investigated in the present study and represent an important limitation. Future studies should focus on evaluating long-term storage stability, colloidal behavior in biological media, and the effects of repeated thermal cycling on drug release performance.

CONCLUSION

This study produced successfully polymeric nanocomposites based on thermo-responsive poly(N-isopropylacrylamide) (PNIPAM) to release doxorubicin intratumorally when the temperature is triggered. With nanoscale particle size, narrow polydispersity, and an appropriate surface charge, the produced nanocomposites demonstrated favourable physicochemical features that guaranteed good colloidal stability and systemic uniformity in the polymer-composite. The capacity of the crosslinked polymer network to successfully absorb and hold the medicine was validated by its high encapsulation efficiency and drug loading. Chemical degradation-free drug integration was shown by FTIR and DSC tests, suggesting a durable composite matrix and high polymer-drug compatibility. With an LCST of 39.2°C—just over physiological temperature—the device allowed for almost no drug leakage under typical settings and increased release under hyperthermic ones. Additional in vitro drug release tests corroborated the temperature dependence, with the polymer collapsing at 42°C leading to substantially increased release. The IC_{50} value was lower in DOX-loaded nanocomposites compared to free drug, indicating increased cellular uptake and regulated intracellular drug release, which led to improved anticancer activity in cytotoxicity experiments. Polymeric nanocomposites based on PNIPAM show remarkable thermo-responsive properties and efficacy in drug administration. The significance of sophisticated polymer and composite design in creating next-generation drug delivery platforms is underscored by these findings, which also demonstrate their potential as smart polymer-composite systems for targeted cancer therapy.

Declarations

- *Consent for publication:* All the authors approved the manuscript for publication.
- *Availability of data and material:* All required data is available.
- *Competing interests:* All authors declare no competing interests.
- *Funding:* Not applicable.
- *Authors' contributions:* All authors have equal contributions.
- *Conflict of interest:* The authors declare that they have no conflict of interest.

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