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Synthesis and Characterization of pH-Sensitive Poly (N-isopropylacrylamide-co-acrylic Acid) Hydrogels for Controlled Release of Doxorubicin

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Abstract

pH-responsive polymeric hydrogels have attracted significant attention as intelligent biomaterials for site-specific and controlled drug delivery in cancer therapy due to their ability to respond to the acidic tumor microenvironment. In the present study, poly (N-isopropylacrylamide-co-acrylic acid) [P(NIPAM-co-AAc)] hydrogels were synthesized via free radical copolymerization and systematically characterized to evaluate their suitability for controlled delivery of doxorubicin, a widely used chemotherapeutic agent. The copolymer hydrogels were prepared using N-isopropylacrylamide and acrylic acid as monomers, N,N′-methylenebisacrylamide as a crosslinking agent, and ammonium persulfate as a thermal initiator. The formation and structural integrity of the hydrogels were confirmed by Fourier transform infrared spectroscopy, while thermal behavior was assessed using differential scanning calorimetry. Surface morphology and internal network structure were examined by scanning electron microscopy, revealing a porous architecture favorable for drug loading and diffusion. Swelling studies demonstrated pronounced pH-dependent behavior, with significantly higher swelling ratios under mildly acidic conditions compared to physiological pH, confirming the successful incorporation of pH-responsive functional groups. Doxorubicin loading efficiency was determined using equilibrium swelling methods, and in vitro release studies were conducted at pH 7.4 and 5.5 to simulate normal physiological and tumor microenvironments, respectively. The release profiles indicated sustained and controlled drug release over an extended period, with accelerated release under acidic conditions due to enhanced network expansion. The release kinetics suggested diffusion-controlled and swelling-assisted mechanisms. Overall, the findings demonstrate that P(NIPAM-co-AAc) hydrogels exhibit desirable physicochemical properties, efficient drug encapsulation, and pH-triggered release behavior, highlighting their potential as promising carriers for targeted and controlled anticancer drug delivery applications.

Keywords: pH-sensitive hydrogel; poly (N-isopropylacrylamide-co-acrylic acid); controlled drug release; doxorubicin; smart polymer; cancer drug delivery.

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INTRODUCTION

A promising area within polymer and composite science for advanced biomedical applications is the development of stimuli-responsive polymeric hydrogels for controlled and targeted drug delivery. These smart hydrogels possess the ability to reversibly alter their physical and chemical properties in response to external environmental stimuli such as temperature, pH, ionic strength, and electric or magnetic fields [1, 2]. Such adaptive behavior enables precise modulation of drug release profiles, thereby enhancing therapeutic efficacy while minimizing adverse effects.

Among the various stimuli, pH responsiveness is particularly significant in cancer therapy, as the tumor microenvironment and intracellular compartments such as endosomes and lysosomes exhibit a distinctly acidic pH compared to normal physiological conditions [3, 4]. This intrinsic difference provides an opportunity to design polymeric systems capable of site-specific drug release.

Poly(N-isopropylacrylamide) (PNIPAM) is a widely studied thermoresponsive polymer with a lower critical solution temperature (LCST) close to physiological temperature (~32°C), making it attractive for biomedical applications. However, the lack of intrinsic pH sensitivity in pure PNIPAM hydrogels restricts their applicability in pH-triggered drug delivery systems [5]. To overcome this limitation, extensive research has focused on the copolymerization of PNIPAM with pH-sensitive monomers such as acrylic acid (AAc). The incorporation of ionizable carboxylic acid groups introduces pH-dependent swelling behavior driven by electrostatic repulsion and osmotic pressure within the polymer network, thereby enabling controlled drug release [6].

Doxorubicin, a potent anthracycline chemotherapeutic agent, is extensively used in the treatment of various malignancies including breast cancer, ovarian cancer, and hematological cancers. Despite its clinical effectiveness, doxorubicin suffers from rapid systemic distribution and severe dose-limiting toxicities, particularly cardiotoxicity. These drawbacks have spurred considerable interest in the development of polymer-based delivery systems that enhance tumor localization, extend circulation time, and enable controlled release in response to tumor-specific stimuli [7,8].

In this context, pH-sensitive P(N-isopropylacrylamide-co-acrylic acid) [P(NIPAM-co-AAc)] hydrogels represent a highly promising polymer composite platform for intelligent drug delivery. The synergistic combination of thermoresponsive PNIPAM segments and acid-responsive acrylic acid moieties results in a multifunctional hydrogel network capable of responding to both temperature and pH variations. These copolymer hydrogels exhibit minimal swelling and drug release under physiological conditions, while undergoing significant swelling and accelerated drug release in acidic environments characteristic of tumor tissues [8,9]. Such behavior enhances drug bioavailability at the target site while reducing systemic exposure and toxicity.

The present study aims to synthesize and comprehensively characterize P(NIPAM-co-AAc) hydrogels as pH-responsive carriers for the controlled delivery of doxorubicin. The effects of varying pH conditions on swelling behavior, drug loading efficiency, and in vitro drug release kinetics were systematically investigated in relation to copolymer composition and network structure. The outcomes of this work are expected to contribute to the development of a safe, efficient, and polymer-based smart drug delivery system for targeted cancer therapy.

MATERIAL AND METHODS

All study followed conventional procedures for labs. The Materials and Methods section gives a full list of the study's tools, materials, and experimental techniques. This is important for making sure that the results are reliable and can be repeated.

Materials

N-Isopropylacrylamide (NIPAM) was supplied by Sigma-Aldrich (USA), and acrylic acid (AAc) was purified using vacuum distillation. Ammonium persulfate (APS) was used as the free radical

initiator, while N,N′-Methylenebisacrylamide (MBA) was used as the crosslinking agent. We got doxorubicin hydrochloride from a drug store in its original form. All other analytical-grade reagents and solvents were used without any further purification. Throughout the studies, deionized water was used.

Synthesis of P(NIPAM-co-AAc) Hydrogels

We used water-based solutions to make pH-sensitive P(NIPAM-co-AAc) hydrogels by free radical copolymerization. Deionized water (10 mL) was used to dissolve N-isopropylacrylamide (1.0 g) and acrylic acid (0.2 g). Subsequently, N,N′-methylenebisacrylamide (0.02 g) and ammonium persulfate (0.01 g) were added as cross-linker and initiator, respectively. The polymerization process took 6 hours at 60°C. After being taken out of the molds, the hydrogels were cut into discs and rinsed with deionized water numerous times to get rid of any unreacted monomers or leftover initiators. The hydrogels were filtered and then dried in a vacuum at room temperature until they reached a constant weight [10]. Table 1 comprising of the formulation composition of P(NIPAM-co-AAc) hydrogel prepared by free-radical copolymerization

Table 1. Formulation composition of P(NIPAM-co-AAc) hydrogel prepared by free-radical copolymerization

Sr. No.	Component	Quantity
1	N-Isopropylacrylamide	1.00 g
2	Acrylic acid	0.20 g
3	N,N′-Methylenebisacrylamide	0.02 g
4	Ammonium persulfate	0.01 g
5	Deionized water	10 mL
6	Nitrogen gas	Purged for 15 min

Characterization Study

The Characterization Study section talks about the structural, thermal, and morphological tests that were done to make sure the hydrogels were made correctly and to see how their physicochemical properties could be used in controlled drug delivery systems.

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier transform infrared spectroscopy (FTIR, Bruker Tensor 27, Germany) was used to check the chemical structure of the hydrogels that were made. Potassium bromide was used to grind up dried hydrogel samples, which were then made into pellets. We got spectra from 4000 to 400 cm^{-1} with a resolution of 4 cm^{-1} [11].

Differential Scanning Calorimetry (DSC)

We used differential scanning calorimetry (DSC, TA Instruments, USA) to look at the hydrogels' thermal characteristics. The dried sample, which weighed around 5 to 10 mg, was heated in an aluminum pan in a nitrogen environment from 25 to 300°C at a rate of 10°C per minute [12].

Scanning Electron Microscopy (SEM)

We used scanning electron microscopy (SEM, JEOL JSM-6510LV, Japan) to look at the hydrogels' surface appearance and internal structure. The freeze-dried hydrogel samples were broken, stuck on aluminum stubs, coated with gold, and then looked at with an accelerating voltage of 15 kV [13].

Swelling Studies

We used gravimetry to measure how much hydrogels swelled as the pH of buffer solutions changed from 7.4 to 5.5 at 37°C. The hydrogel discs were weighed (W_d) and then put in the right buffer solutions. The samples were taken out, carefully cleaned to remove any moisture from the surface, and weighed (W_s) at set times. The outcomes of each experiment, conducted three times, were reported as

the mean with the standard deviation indicated [14]. This is the formula for finding the swelling ratio (SR):

$$SR = \frac{W_s - W_d}{W_d}$$

Drug Loading

We used the equilibrium swelling approach to add doxorubicin to the hydrogels. Dried hydrogel discs were put in an aqueous doxorubicin solution (1 mg mL^{-1}) and left to expand in the dark at 25°C for 24 hours. After loading, the samples were carefully cleaned with distilled water to get rid of any medications that were loosely attached, and then they were dried in a vacuum. We used a UV-visible spectrophotometer (Shimadzu UV-1800, Japan) to measure the absorbance of the leftover medicine solution at 480 nm [15]. We found out the drug loading efficiency (DLE) by:

$$DLE\ (\%) = \frac{\text{Amount of drug loaded}}{\text{Initial amount of drug}} \times 100$$

In -Vitro Drug Release Studies

In-vitro release studies were performed in phosphate buffer solutions at pH 7.4 and 5.5, sustained at a temperature of 37 ± 0.5°C, employing a shaking water bath. Twenty milliliters of release media were added to hydrogel discs with drugs, and the mixture was stirred at 100 rpm. We took out 2 mL of the releasing medium at regular intervals and added new buffer to it. We used spectrophotometry at 480 nm to measure how much doxorubicin was emitted. We figured it and showed the total percentage of medication release over time [16, 17].

Statistical Analysis

All data are expressed as mean ± standard deviation (SD) (n = 3). Statistical comparisons between groups were performed using OriginPro software, and differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The Results and Discussion section provides a thorough analysis of the experimental results using suitable tables and figures. It further examines these findings within the framework of the existing literature, emphasizing the importance and prospective uses of the current study.

Structural Characterization by FTIR

In the end, Fourier transform infrared spectroscopy proved that P(NIPAM-co-AAc) hydrogels had formed. Figure 1 shows the normal Fourier transform infrared spectra of PNIPAM, acrylic acid, and the hydrogel copolymer that was made. The N-H stretching vibrations of the amide group in NIPAM correspond to the particular absorption band about 3290 cm^{-1}. The amide I band, which is the big peak at about 1650 cm^{-1}, is caused by the C=O stretching of the amide. The amide II band, which is the band near 1540 cm^{-1}, is caused by the N-H bending. The copolymer spectra show an extra absorption band at about 1720 cm^{-1}, which shows that the carboxylic acid (-COOH) group comes from acrylic acid. The findings indicate that the crosslinked hydrogel network was successfully formed through the copolymerization of NIPAM and AAc [18].

Thermal Analysis by DSC

We used DSC to look at how the manufactured hydrogels reacted to heat. The thermogram of the P(NIPAM-co-AAc) hydrogel showed a big endothermic transition between 135 and 150°C, which is the same temperature as the glass transition temperature (Tg) of the copolymer network. The lack of noticeable melting peaks in the crosslinked hydrogel shows that it is amorphous. The addition of acrylic acid units and a higher crosslinking density likely improves intermolecular interactions and network stiffness, as seen by the much higher Tg compared to pure PNIPAM [19] (Figure 2).

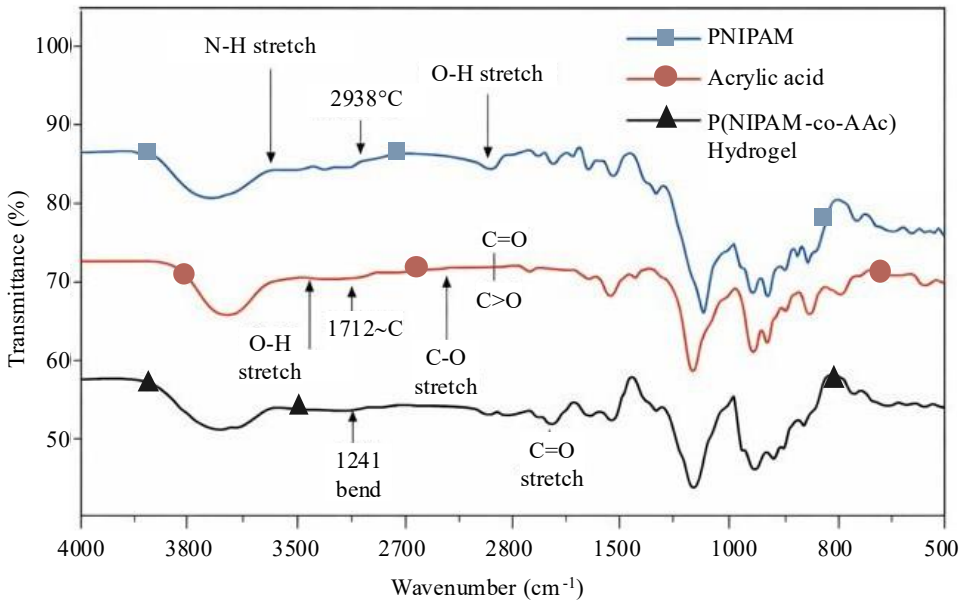

Figure 1. FTIR spectra of PNIPAM, acrylic acid, and P(NIPAM-co-AAc) hydrogel showing characteristic functional groups and confirmation of copolymer formation.

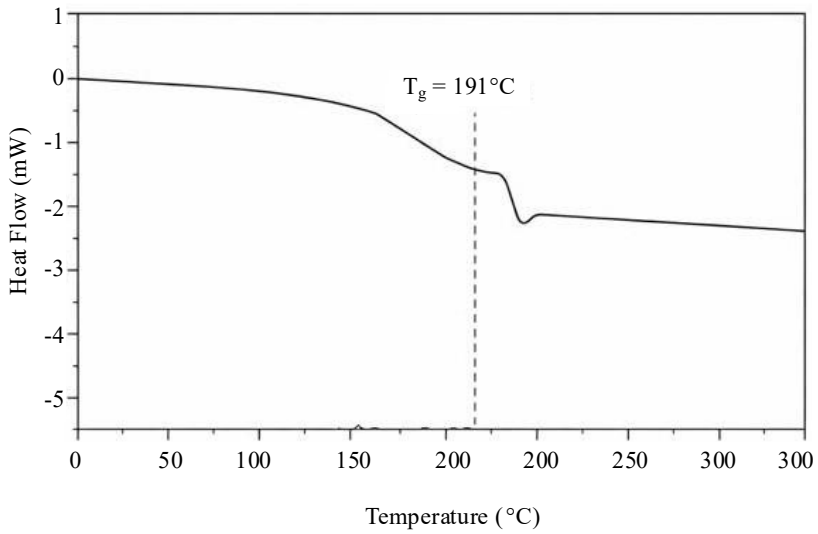

Figure 2. DSC thermogram of P(NIPAM-co-AAc) hydrogel indicating the glass transition temperature and amorphous character of the polymer network.

Morphological Analysis by SEM

We employed scanning electron microscopy to look at the surface and inside of the freeze-dried hydrogels. As seen in Figure 3, hydrogels had a three-dimensional network structure with interconnected pores. This porous structure makes it easier to load drugs, manage how they diffuse when they are released, and take up water. The rather even pore size distribution showed that the crosslinking was uniform across the hydrogel matrix [20].

pH-Dependent Swelling Behaviour

The swelling properties of P(NIPAM-co-AAc) hydrogels were assessed at pH 7.4 and pH 5.5 to replicate physiological conditions and tumor microenvironments, respectively. Table 2 shows the equilibrium swelling ratios, and Figure 4 shows the same information. The hydrogels swelled far more at acidic pH than at neutral pH. When the pH is lower, the ionization of carboxylic acid groups increases

the electrostatic attraction between polymer chains and raises the osmotic pressure inside the network. This is what causes this behavior. Hydrogels that are particularly sensitive to pH are the best for delivering drugs to cancer cells [21].

Table 2. Equilibrium swelling ratios of P(NIPAM-co-AAc) hydrogels at different pH values (37°C).

Sr. No.	pH	Swelling Ratio (SR)
1	7.4	6.8 ± 0.4
2	5.5	12.3 ± 0.6

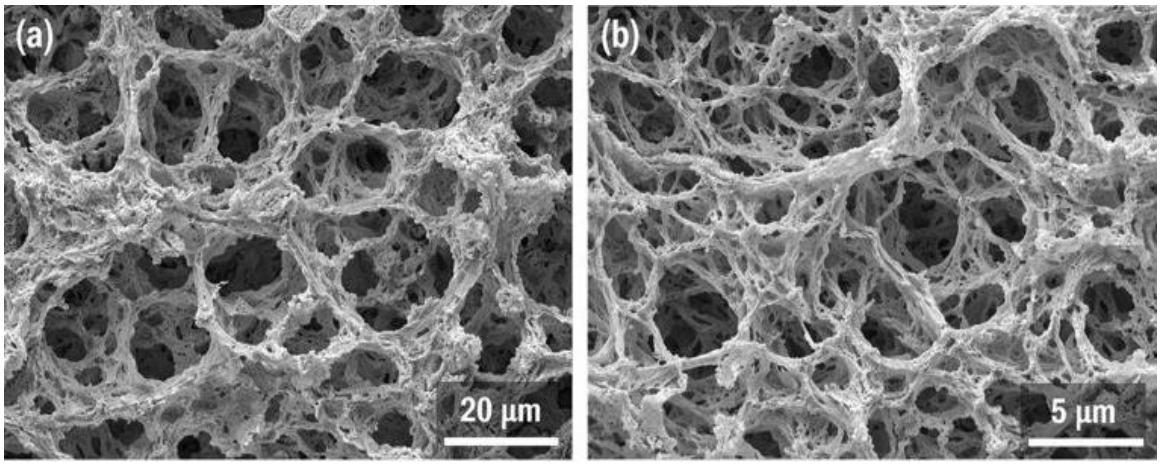

Figure 3. SEM micrographs of freeze-dried P(NIPAM-co-AAc) hydrogels showing a porous and interconnected network structure favourable for drug loading and release.

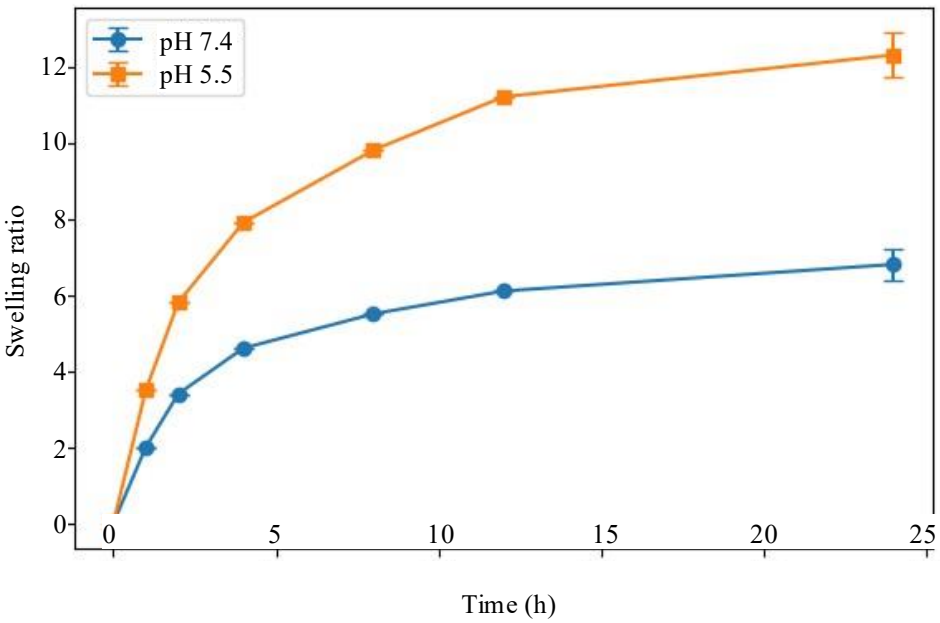

Figure 4. Swelling profiles of P(NIPAM-co-AAc) hydrogels at pH 7.4 and pH 5.5 (37°C). Data are presented as mean ± SD (n = 3).

Drug Loading Efficiency

Table 3 shows the results, which were obtained using UV-visible spectrophotometry to measure how well the hydrogels loaded doxorubicin. The high loading efficiency is due to the hydrogel network's porosity and the strong electrostatic interactions between the positively charged doxorubicin molecules and the negatively charged carboxyl groups of acrylic acid [22].

Table 3. Doxorubicin loading efficiency of P(NIPAM-co-AAc) hydrogels.

Sample	Drug Loading Efficiency (%)
P(NIPAM-co-AAc)	78.5 ± 3.2

In-Vitro Drug Release Studies

The releasing behavior was shown to be sustained and pH-dependent. A considerably higher release was achieved at an acidic pH (5.5), in contrast to the slower release at a physiological pH (7.4). More swelling of the hydrogel network and protonation of functional groups, which reduce interactions between doxorubicin and the polymer matrix, are the key reasons for this greater release under acidic circumstances. The ability to selectively deliver drugs to tumor tissues through pH-triggered release is extremely desirable. Oxytocin cumulative release patterns from P(NIPAM-co-AAc) hydrogels in vitro at pH 7.4 and pH 5.5 (37°C). In Figure 5, we can see the doxorubicin in vitro release profiles at pH 7.4 and pH 5.5 from the P(NIPAM-co-AAc) hydrogels. Tabulated in Table 4 are the results of the cumulative releases [23].

Table 4: Cumulative percentage of doxorubicin released at different pH values.

Time (h)	Release at pH 7.4 (%)	Release at pH 5.5 (%)
6	22.4 ± 1.8	38.7 ± 2.1
12	35.6 ± 2.3	58.9 ± 2.7
24	48.2 ± 2.9	74.5 ± 3.1
48	61.3 ± 3.4	89.2 ± 3.6

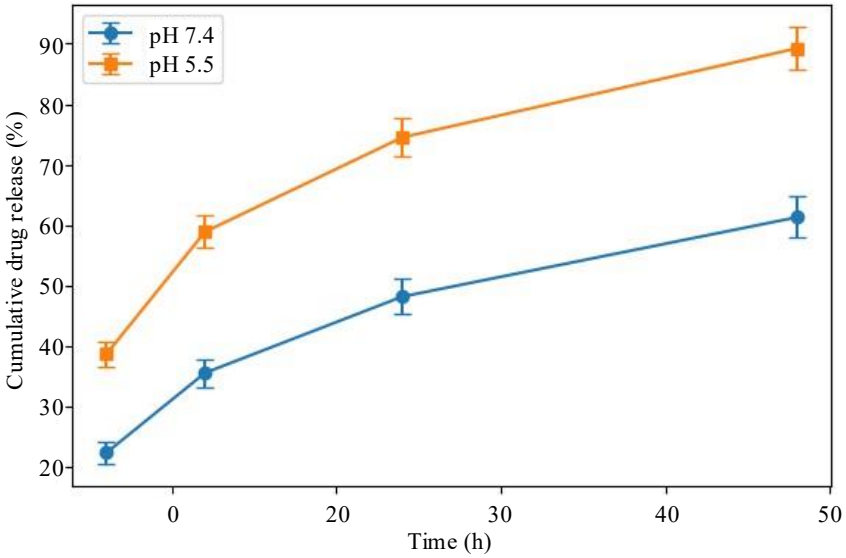

Figure 5. In-vitro cumulative release profiles of doxorubicin from P(NIPAM-co-AAc) hydrogels at pH 7.4 and pH 5.5 (37°C). Data are expressed as mean ± SD (n = 3).

Drug Release Kinetics

The Higuchi model produced the strongest correlation coefficients, which means that diffusion was what caused the release. Release exponent (n) values between 0.5 and 1.0 show that transport is not normal (non-Fickian) and includes diffusion and polymer relaxation modes. We used a number of kinetic models to fit the release data, such as the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The kinetic parameters are shown in Table 5.

The results show that adding acrylic acid to the PNIPAM network made the hydrogels respond to changes in pH. The porous structure showed a lot of swelling under acidic conditions and strong contacts between the drug and polymer, which made it possible to control the release and load the drug

effectively. The data shows that P(NIPAM-co-AAc) hydrogels can be smart carriers for getting doxorubicin to tumors, as seen by the much higher release at pH 5.5 compared to pH 7.4. The synthetic hydrogels have a lot of promise as regulated and site-specific delivery systems for anticancer drugs since they can release drugs when the pH changes and have good physical and chemical properties [24].

Table 5. Release kinetic parameters for doxorubicin from P(NIPAM-co-AAc) hydrogels.

Model	pH 7.4 (R^2)	pH 5.5 (R^2)
Zero-order	0.912	0.925
First-order	0.934	0.941
Higuchi	0.962	0.971
Korsmeyer–Peppas (n)	0.63	0.71

Comparison with other pH-responsive Hydrogel Systems

To place the performance of the developed P(NIPAM-co-AAc) hydrogels in context, a brief comparison with other reported pH-responsive hydrogel systems was made. In the present study, the synthesized P(NIPAM-co-AAc) hydrogels exhibited a pronounced pH-dependent swelling behaviour (SR 6.8 ± 0.4 at pH 7.4 and 12.3 ± 0.6 at pH 5.5) and a markedly higher cumulative doxorubicin release under acidic conditions (89.2 ± 3.6% at pH 5.5 after 48 h), confirming their suitability for tumour-mimicking environments. Several previously reported pH-responsive hydrogel systems—such as alginate/PNIPAM blends, chitosan-based semi-IPN hydrogels, magnetic composite hydrogels and multi-responsive nanogels—also demonstrate enhanced drug release at acidic pH. However, many of these systems rely on additional polymeric matrices, inorganic fillers or complex fabrication strategies to achieve pH sensitivity and structural stability. In contrast, the present work employs a simple and reproducible free-radical copolymerization of N-isopropylacrylamide and acrylic acid to generate a chemically cross-linked network with well-defined porosity and dual thermo-/pH-responsive behaviour. Notably, compared with composite and semi-IPN systems, the P(NIPAM-co-AAc) hydrogels developed in this study exhibit a favourable balance between structural simplicity, high drug-loading efficiency (78.5 ± 3.2%) and strong pH-triggered release performance. This highlights the advantage of directly incorporating ionisable acrylic acid units into the PNIPAM backbone, enabling effective pH-regulated swelling and diffusion-controlled release without the need for additional functional components.

Considerations for Clinical Translation

Although the present P(NIPAM-co-AAc) hydrogel system demonstrated promising pH-responsive swelling behaviour and enhanced doxorubicin release under tumour-mimicking conditions, several challenges must be considered for potential clinical translation. The current investigation is limited to physicochemical characterization and in-vitro drug release studies, and no biological performance data have yet been generated. First, comprehensive biocompatibility and cytotoxicity evaluations are required to confirm the safety of the copolymer network and any residual components originating from the polymerization process, such as unreacted monomers or initiator fragments. In particular, the long-term fate of poly(N-isopropylacrylamide)-based materials in biological environments and their potential accumulation or degradation behaviour must be systematically examined. Secondly, although doxorubicin loading and release were efficient in vitro, the interaction of the hydrogel matrix with proteins, enzymes and physiological fluids may significantly influence swelling behaviour, drug diffusion and structural integrity in vivo. Overall, while the present study establishes the pH-responsive P(NIPAM-co-AAc) hydrogels as a promising controlled delivery platform, further biocompatibility studies and in-vivo investigations are necessary to validate their safety and therapeutic potential prior to clinical application.

CONCLUSION

We were able to make P(HN-isopropylacrylamide-co-acrylic acid) hydrogels and test them to see whether they could change how doxorubicin spreads based on pH sensitivity. The copolymer network

showed clear swelling behavior that changed with pH, had a porous structure, and was good at holding drugs. Studies on in vitro drug release have shown that acidic conditions, which mimic the tumor microenvironment, lead to better and longer-lasting drug release. According to this study, P(NIPAM-co-AAc) hydrogels may be able to safely and effectively deliver cancer-fighting drugs to specific areas while also lowering systemic toxicity and increasing therapeutic efficacy.

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Conflict of Interest
None

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