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Enhancing the properties of poly(N-isopropylacrylamide) hydrogels through interpenetrating polymer networks with chitosan: a review

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Abstract. Poly(N-isopropylacrylamide) (PNIPAM) is a widely studied thermoresponsive hydrogel which has great potential in controlled drug delivery due to its volume-phase transition near physiological temperature. However, its application is limited by poor mechanical strength, slow response kinetics, and lack of multi-stimuli responsiveness. This review discusses the enhancement of PNIPAM properties through the formation of Interpenetrating Polymer Networks (IPNs) with chitosan, a biocompatible and pH-sensitive natural polymer. Integrating chitosan into PNIPAM-based hydrogels yields IPNs with improved structural stability, higher drug-loading capacity, and multi-responsive behavior. Chitosan introduces pH sensitivity and binding sites, while the interpenetrating architecture reinforces mechanical integrity and tunes diffusion. These systems enable sustained and controlled drug release over 8–12 h under simulated physiological conditions, with release profiles tunable via crosslinking density and environmental stimuli. Despite challenges in reproducibility, crosslinker toxicity, and long-term stability, chitosan–PNIPAM IPNs are promising for advanced drug delivery in multi-stimuli environments such as the gastrointestinal tract or tumor tissues.

Keywords: hydrogel, PNIPAM, chitosan, interpenetrating network

1. Introduction

Polymers are large molecules composed of repeating structural units (monomers) linked by covalent bonds. Synthetic polymers such as polyethylene and polypropylene are widely used in plastics, while natural polymers (e.g., proteins, DNA) are fundamental to biological structures and functions [1, 2].

In medicine, polymers play a transformative role owing to their biocompatibility, biodegradability, and functional flexibility. They are particularly valuable in drug delivery because they enable controlled release of therapeutics through stimuli-responsive mechanisms. One extensively studied polymer is poly(N-isopropylacrylamide) (PNIPAM), a temperature-responsive smart hydrogel with a Lower Critical Solution Temperature (LCST) around 32–34 °C. Below the LCST, PNIPAM chains adopt a hydrophilic, extended state, absorbing water to form a hydrogel; above the LCST, they collapse into a hydrophobic state, releasing encapsulated substances. This behavior makes PNIPAM promising for controlled drug delivery, especially in tumor treatments where localized temperature changes can trigger release [3].

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A smart material can sense and dynamically respond to environmental changes like temperature, pH, or light by changing their physical or chemical properties, and because of that, smart systems are increasingly employed in cutting-edge applications in areas such as drug delivery, soft robotics, and biosensing.

Below the LCST, PNIPAM chains exhibit a hydrophilic, extended state, absorbing a significant amount of water to form a hydrogel. When the temperature rises above the LCST, the molecular chains will rapidly transition to a hydrophobic, collapsed state, releasing encapsulated substances. This property makes PNIPAM highly promising for controlled drug delivery applications, particularly in tumor treatment strategies where localized temperature change can trigger drug release.

Furthermore, as a hydrogel, PNIPAM's hydrophilic, cross-linked polymer networks can swell in water without dissolving. Their high water content, soft mechanics, and permeable structure make them ideal for biomedical uses such as wound healing scaffolds and controlled-release carriers [1, 2].

However, pure PNIPAM hydrogels suffer from several limitations: relatively poor mechanical strength, slow response rates, and responsiveness limited to temperature alone. These drawbacks restrict their use in precision-controlled drug-delivery systems.

Chitosan is a natural cationic polysaccharide derived from the deacetylation of chitin, which is extracted from crustacean shells like crab and shrimp or fungal cell walls.

As a natural cationic polysaccharide, chitosan possesses excellent biocompatibility, biodegradability, and mucoadhesiveness (the property of materials to adhere to mucosal surfaces and remain attached for a long period), resulting in its wide application in drug delivery system. It can protonate and swell in acidic environments, while deprotonating and contracting in neutral conditions. Introducing chitosan into PNIPA to form an Interpenetrating Polymer Network (IPN) structure, which is a structure formed by two or more polymers physically entangled without covalent bonding, can enable the integration of dual temperature and pH responsiveness, thus significantly enhancing the overall performance of the hydrogel [4, 5].

Sodium Alginate (SA) is a natural anionic polysaccharide extracted from brown algae, whose molecular chains are rich in carboxyl groups (-COOH), endowing it with excellent pH responsiveness, good biocompatibility, biodegradability, and the ability to undergo ionic crosslinking under mild conditions, such as in the presence of Ca^{2+} [6]. Thus the sodium alginate-PNIPAM IPN can integrate dual temperature and pH responsiveness, rapid kinetics, and enhanced mechanical properties, significantly expanding the application potential of PNIPAM hydrogels in fields such as smart drug delivery [6, 7].

In this review, the role of chitosan in forming IPNs with PNIPA will be evaluated over three criteria: stability, controlled release, and multi-responsive system.

2. Evaluations

2.1. Stability

The integration of IPN architecture fundamentally enhances the physical strength and drug loading capacity of PNIPA hydrogels. The IPN structure creates a dual-network system where independent polymer networks interpenetrate without covalent bonding, enabling remarkable mechanical reinforcement, as described above. This architecture allows stress distribution through topological entanglements, significantly improving fracture resistance and compressive strength while maintaining the temperature-responsive behavior of PNIPA.

The crosslinking density of the secondary network serves as a critical tuning parameter, with higher degrees of crosslinking producing denser matrices that not only enhance mechanical robustness but also provide more controlled release profiles, which will be discussed later. This synergistic combination of mechanical reinforcement and enhanced drug-carrier interactions transforms PNIPA from a fragile, limited-

capacity material into a robust, high-performance drug delivery platform capable of sustaining structural integrity under physiological conditions while achieving drug loading capacities orders of magnitude greater than pure PNIPA hydrogels [2, 8].

According to the systematic study published in *Journal of Applied Polymer Science*, the incorporation of SA (4-13 wt%) into crosslinked PNIPAM networks creates a more robust architecture that maintains the fundamental temperature responsiveness (volume phase transition temperature ≈ 33°C) while substantially improving the hydrogel's stability under various environmental conditions. The SA chains function as both reinforcing agents and water channels within the network. Scanning Electron Microscopy (SEM) analysis, a high-resolution imaging technique that utilizes a focused beam of electrons to scan the surface of a sample and detects signals generated from interactions between electron and sample to obtain information about the sample's surface morphology and composition, revealed that semi-IPN hydrogels develop a porous microstructure with pore size increasing with SA content, which simultaneously enhances mechanical stability and prevents the formation of the dense skin layer that typically plagues pure PNIPAM hydrogels during collapse [7].

Critically, the hydrogen bonding between SA's carboxyl groups and PNIPAM's amide groups under acidic conditions (pH 1.2) creates additional crosslinking points that restrict excessive swelling and stabilize the network, while the electrostatic repulsion between ionized carboxylate groups at alkaline pH (7.4) prevents collapse and maintains swelling capacity. This dual stabilization mechanism - physical reinforcement through chain interpenetration and chemical stabilization through interpolymer interactions - enables the semi-IPN hydrogels to maintain their structural integrity and responsive properties through multiple stimulation cycles, significantly advancing their potential for practical applications in drug delivery systems where consistent performance under varying physiological conditions is essential [7].

In another case about loading diclofenac sodium, a Nonsteroidal Anti-Inflammatory Drug (NSAID) with typical anti-inflammatory, analgesic, antipyretic effects, and potential impacts on the development of the central nervous system [9, 10], the enhancement in physical integrity is achieved through a dual-network; and the incorporation of a second chitosan network, which is subsequently crosslinked with glutaraldehyde, creating an independent yet interpenetrating web that shares and dissipates mechanical stress. This structural innovation is evidenced by the formation of a much more robust hydrogel that maintains its architectural integrity during repeated swelling/deswelling cycles, a scenario where pure PNIPA tends to fracture or permanent deformation (changing its shape) due to its inherent brittleness [11]. Figure 1 shows the structure of diclofenac sodium, and Figure 2 shows the structure of glutaraldehyde.

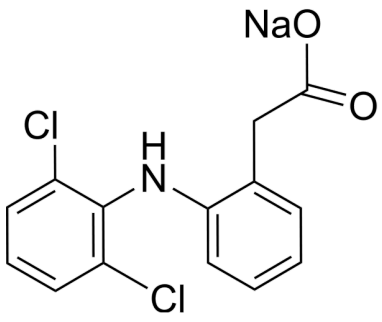


Figure 1. Structure of diclofenac sodium

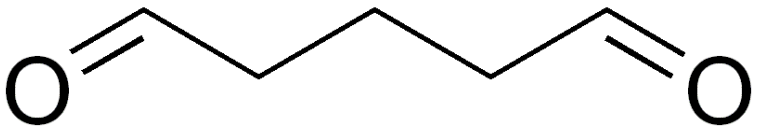


Figure 2. Structure of glutaraldehyde

The crosslinking density of the chitosan network serves as a critical tuning parameter--higher glutaraldehyde concentrations yield a denser and more rigid IPN matrix, dramatically increasing its resistance to compressive forces and thereby enabling practical handling and implantation. While pure PNIPA exhibited a nearly zero loading capacity for the anionic model drug diclofenac sodium, the chitosan-PNIPA IPN achieved a dramatic increase to 16–18 mg/g. This was directly attributed to the electrostatic interaction between the cationic amine groups of the incorporated chitosan network and the anionic drug molecules, creating efficient binding sites that pure PNIPA lacked [11].

In addition, an increase in glutaraldehyde concentration (0 → 0.7 vol%) can also increase the cross-linking density of chitosan, resulting in greater network compactness, extended drug diffusion pathways, and enhanced controlled-release capabilities.

Regarding drug loading capabilities, while the study showed rapid release (> 80% in 40 minutes) of positively charged pilocarpine HCl, a drug used to treat salivary gland hypofunction, dry mouth, etc., due to electrostatic repulsion with protonated chitosan amino groups, this very mechanism highlights the IPN's potential for enhanced loading of anionic therapeutic agents [8, 12].

2.2. Controlled release& multi-responding

The integration of chitosan via an Interpenetrating Network (IPN) architecture fundamentally overcame the critical limitations of pure PNIPA in controlled drug delivery.

One preparation method involves constructing an IPN structure using chemical cross-linking agents. Researchers employed glutaraldehyde as a cross-linker to conjugate Carboxymethyl Chitosan (CMCS) with PNIPAM, forming a semi-IPN hydrogel [13]. The CMCS component introduces pH sensitivity due to its anionic carboxymethyl groups, which exhibit enhanced swelling at high pH and contraction at low pH. Swelling ratio are calculated by immersing the hydrogel samples in buffer solutions of different pH values and equilibrated at a constant temperature for a specific duration before being weighed or measured for volume. Figure 3 shows the structure of Carboxymethyl Chitosan (CMCS).

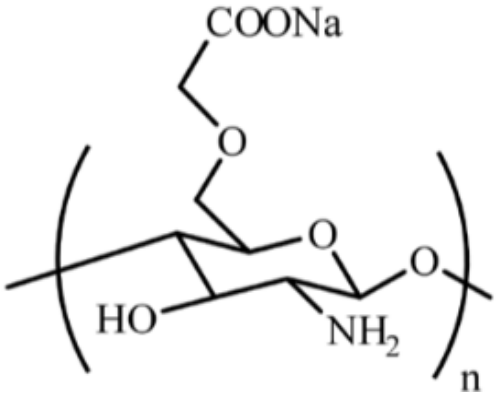


Figure 3. Structure of Carboxymethyl Chitosan (CMCS)

Thus, this system retains the LCST characteristics of PNIPAM (approximately 33°C) while introducing pH-responsive behavior—exhibiting minimal swelling near the isoelectric point and demonstrating polyanionic or polycationic properties when deviating from it.

Also, in the case of chitosan-PNIPAM, integrating PNIPAM into IPNs enabled precise control over release kinetics responding to complex physiological cues. The study revealed a dual-release trigger mechanism: in deionized water, the drug remained tightly bound and release was minimal, but in environments mimicking physiological conditions (0.9% NaCl or pH 8.0 buffer), ion exchange competitively disrupted the electrostatic bonds, initiating a sustained release that extended beyond 8 hours [11].

Figure 4 shows Diclofenac release profiles from PNIPA/chitosan IPNs in water and in NaCl 0.9% at 20 and 37°C. Figure 5 shows Diclofenac release profiles from PNIPA/chitosan IPNs in pH 8.0 phosphate buffer at 20 and 37°C.

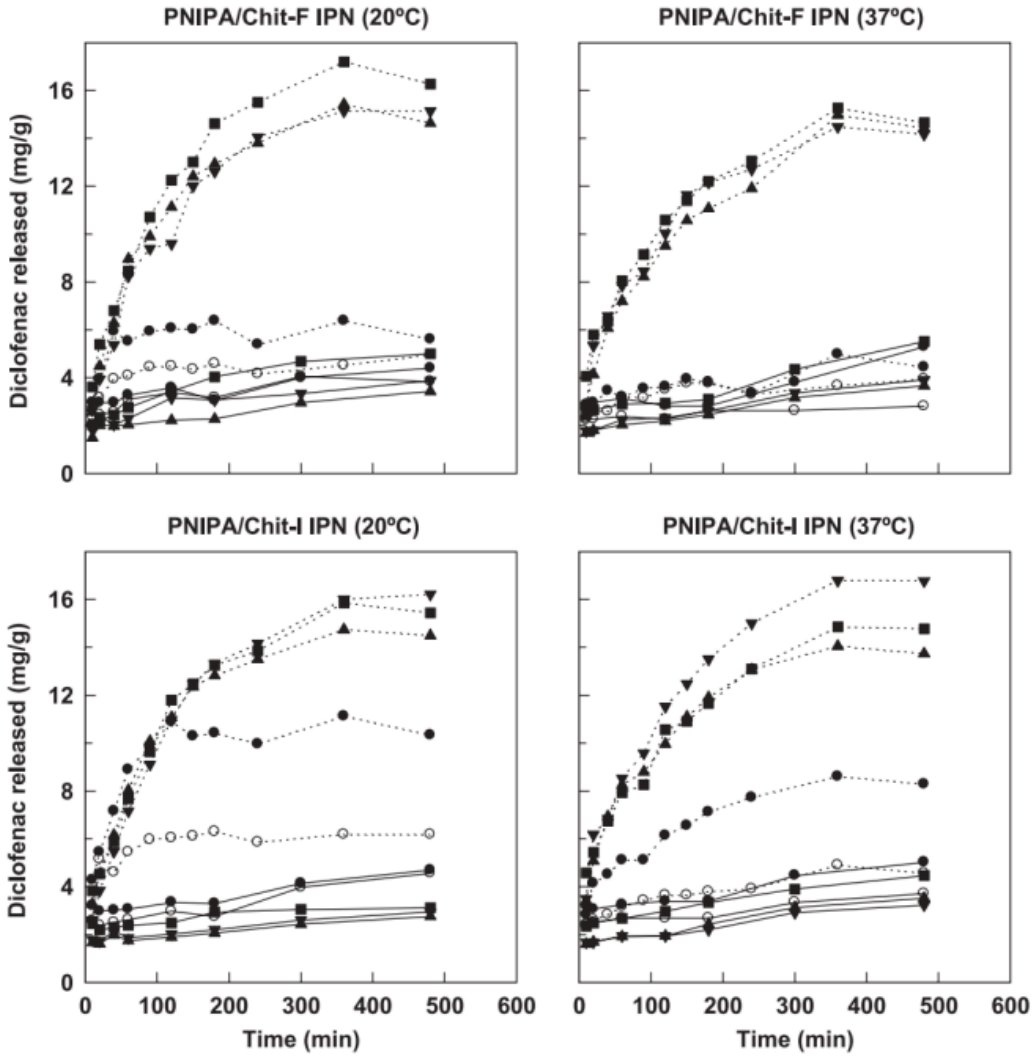


Figure 4. Diclofenac release profiles from PNIPA/chitosan IPNs in water (continuous line) and in NaCl 0.9% (dashed lines) at 20 and 37°C. IPN-0 (○), IPN-1 (●), IPN-3 (■), IPN-5 (▲) and IPN-7 (▼) [11]

Designation after IPN represents the volume percentage concentration of the glutaraldehyde solution used for cross-linking chitosan: for example, IPN-1 corresponds to a 0.1% glutaraldehyde concentration (vol%),

and so on.

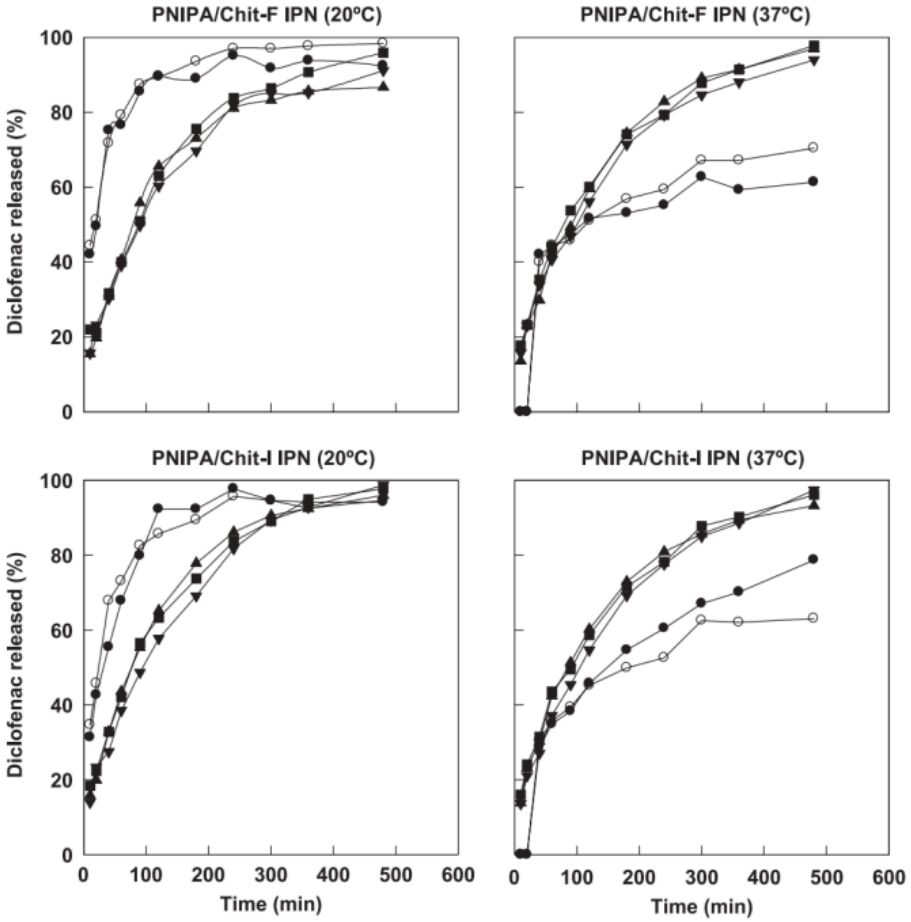


Figure 5. Diclofenac release profiles from PNIPA/chitosan IPNs in pH 8.0 phosphate buffer at 20 and 37°C. Keys same as Figure 4

Furthermore, the crosslinking density of the chitosan network is controlled by the glutaraldehyde concentration, which is really crucial. Higher crosslinking degrees created a denser network, as evidenced by High-Sensitivity Differential Scanning Calorimetry analysis (HS-DSC, an advanced analytical technique with high sensitivity, used to precisely measure the change in heat flow of a sample under a controlled temperature program) showing smaller PNIPA microdomains and reduced cooperativity of the phase transition, which modulated the release rate [11].

Thus, the chitosan-PNIPA IPN successfully evolved the functionality of PNIPA from a simple temperature-responsive material to a sophisticated drug delivery platform capable of high-capacity loading and finely tuned, multi-stimuli-controlled release.

The incorporation of chitosan into poly(N-isopropylacrylamide) (PNIPA) through Interpenetrating Polymer Network (IPN) technology can also significantly enhance multi-stimuli sensitivity compared to conventional PNIPA hydrogels.

A kind of chitosan-PNIPA IPN exhibits temperature responsiveness with a well-defined Lower Critical Solution Temperature (LCST) at approximately 34°C, while simultaneously gaining potent pH sensitivity that enables dramatic swelling variations across physiological pH ranges. The research demonstrated that these IPNs achieved an impressive equilibrium swelling ratio of 18 g/g at 25°C and pH 7.4, which dramatically

decreased to 4 g/g when the temperature increased to 40°C, representing a 4.5-fold reduction in swelling capacity.

The systems also displayed remarkable pH-dependent behavior, with swelling ratios increasing by 300-400% when pH decreased from 7.4 to 3.0 due to protonation of chitosan's amino groups. This dual responsiveness translated directly to enhanced drug loading capabilities, with the IPNs achieving up to 20% (w/w) loading of diclofenac sodium - a substantial improvement over pure PNIPA hydrogels. The controlled release profiles were equally impressive, showing near-zero release in acidic conditions (pH 1.2) while achieving sustained release over 8-12 hours at intestinal pH (7.4), with the release rate being further modulated by temperature changes. These sophisticated response mechanisms, coupled with the improved mechanical stability imparted by the IPN architecture, position chitosan-PNIPA IPNs as advanced platforms for gastrointestinal drug delivery and other applications requiring precise environmental responsiveness [11].

Also, as demonstrated by Verestiuc et al., the semi-IPN structure comprising PNIPA and chitosan enables exceptional pH-dependent swelling behavior, reaching a maximum equilibrium swelling degree of 2200% at 29°C and pH 2.0 – a value that surpasses conventional PNIPA hydrogels by more than 20 fold when compared to its performance at pH 10. This dramatic swelling enhancement directly correlates with improved mechanical durability, as the network maintains structural integrity even at extreme swelling ratios, attributable to the physical entanglement between PNIPA and chitosan chains coupled with tunable crosslinking density [8].

The cationic nature of chitosan ($-NH_3^+$ groups at acidic pH) provides numerous electrostatic binding sites that can dramatically increase drug payload for negatively charged molecules while simultaneously enabling pH-triggered release kinetics. Thus, the chitosan-PNIPA IPN system transforms conventional thermoresponsive hydrogels into versatile platforms with strengthened physical properties and customizable drug loading/release profiles based on electrochemical interactions [8].

3. Discussion

The development of chitosan-PNIPAM Interpenetrating Networks (IPNs) represents a significant advancement in smart drug delivery systems, successfully integrating temperature and pH responsiveness within a single polymeric matrix. As demonstrated by Alvarez-Lorenzo et al., these systems achieve remarkable improvements in drug loading capacity (up to 20% w/w for diclofenac sodium) and controlled release profiles, showing minimal release in acidic conditions while providing sustained release over 8-12 hours at intestinal pH. The 4.5-fold reduction in swelling capacity when temperature increases from 25°C to 40°C, coupled with 300-400% swelling increase when pH decreases from 7.4 to 3.0, provides compelling evidence of their dual-stimuli responsiveness [1].

Despite these promising results, several limitations persist in current IPN strategies. The inherent batch-to-batch variability of natural chitosan creates significant challenges in manufacturing reproducibility, particularly in achieving consistent molecular weight and degree of deacetylation across production scales. Furthermore, the crosslinking methods employed, typically using glutaraldehyde, raise concerns about residual crosslinker toxicity and potential immunogenic responses [1, 2].

Also, for chitosan, the relatively rapid enzymatic degradation (typically 2-4 weeks) often mismatches with the slower degradation timeline of synthetic PNIPAM components, potentially leading to unpredictable release kinetics over extended periods. These systems also face fundamental challenges in balancing mechanical stability with responsive sensitivity - higher crosslinking densities improve mechanical strength but typically reduce responsiveness and swelling capacity [4].

Looking forward, the field must address several critical obstacles for clinical translation. The primary challenges include: (1) achieving precise control over network architecture to ensure reproducible drug release profiles; (2) developing non-toxic, efficient crosslinking strategies that eliminate potential leachables; (3) optimizing the balance between chitosan's rapid degradation and PNIPAM's stability to achieve predictable long-term performance [5]; and (4) enhancing the specificity of stimulus recognition to prevent premature triggering in non-target environments.

For pharmaceutical implementation, additional hurdles must be overcome. The sterilization of these systems presents particular challenges, as conventional methods (autoclaving, gamma irradiation) may alter the delicate balance of network properties and affect drug stability. Scale-up manufacturing poses another significant obstacle, as maintaining homogeneity in network formation during large-scale production remains technically demanding. Regulatory concerns regarding the characterization of these complex systems - including precise quantification of the degree of interpenetration, network topology, and drug distribution within the matrix - present additional complications for pharmaceutical approval. Finally, the long-term stability of these systems under storage conditions, including potential changes in responsiveness and drug release profiles over time, requires thorough investigation before clinical application can be realized.

Future progress will likely depend on developing novel characterization techniques for better understanding network topology, creating more reproducible chitosan derivatives, and establishing standardized manufacturing protocols that can ensure consistent product quality across production scales [11].

4. Conclusion

Chitosan-PNIPAM IPN hydrogels represent a significant advance in smart biomaterials, overcoming inherent limitations of pure PNIPAM by integrating temperature and pH responsiveness. These systems exhibit enhanced mechanical stability, high drug-loading capacity (up to 20 wt% for anionic drugs), and sustained release over 8–12 h under physiological conditions. Future work should focus on developing non-toxic crosslinking strategies, standardizing chitosan derivatives, and optimizing network architecture for clinical-scale production. With further refinement, chitosan-PNIPAM IPNs hold strong potential for targeted drug delivery in complex biological environments such as the gastrointestinal tract or tumor tissues.

References

[1] Hoffman, A. S. (2002). Hydrogels for biomedical applications. *Advanced Drug Delivery Reviews, 54*(1), 3–12. https://doi.org/10.1016/S0169-409X(01)00239-3

[2] Dragan, E. S. (2014). Design and applications of interpenetrating polymer network hydrogels: A review. *Chemical Engineering Journal, 243*, 572–590. https://doi.org/10.1016/j.cej.2014.01.065

[3] Kawaguchi, H. (2020). On going to a new era of microgel exhibiting volume phase transition. *Gels, 6*(3), Article 26. https://doi.org/10.3390/gels6030026

[4] Peniche, C., Argüelles-Monal, W., Peniche, H., & Acosta, N. (2003). Chitosan: An attractive biocompatible polymer for microencapsulation. *Macromolecular Bioscience, 3*(10), 511–520. https://doi.org/10.1002/mabi.200300019

[5] Berger, J., Reist, M., Mayer, J. M., Felt, O., & Gurny, R. (2004). Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics, 57*(1), 35–52. https://doi.org/10.1016/S0939-6411(03)00160-7

[6] Lee, K. Y., & Mooney, D. J. (2012). Alginate: Properties and biomedical applications. *Progress in Polymer Science, 37*(1), 106–126. https://doi.org/10.1016/j.progpolymsci.2011.06.003

[7] Zhang, G., Zha, L., Zhou, M., Ma, J., & Liang, B. (2005). Preparation and characterization of pH- and temperature-responsive semi-interpenetrating polymer network hydrogels based on linear sodium alginate and crosslinked poly(N-isopropylacrylamide). *Journal of Applied Polymer Science, 97*(5), 1931–1940. https://doi.org/10.1002/app.21957

[8] Verestiuc, L., Ivanov, C., Barbu, E., & Tsibouklis, J. (2004). Dual-stimuli-responsive hydrogels based on poly(N-isopropylacrylamide)/chitosan semi-interpenetrating networks. *International Journal of Pharmaceutics, 269*(1), 185–194. https://doi.org/10.1016/j.ijpharm.2003.09.031

[9] Small, R. E. (1989). Diclofenac sodium. *Clinical Pharmacy, 8*(8), 545–558.

[10] Kudo, C., Kori, M., Matsuzaki, K., Yamai, K., Nakajima, A., Shibuya, A., Niwa, H., Kamisaki, Y., & Wada, K. (2003). Diclofenac inhibits proliferation and differentiation of neural stem cells. *Biochemical Pharmacology, 66*(2), 289–295. https://doi.org/10.1016/S0006-2952(03)00235-1

[11] Alvarez-Lorenzo, C., Concheiro, A., Dubovik, A. S., Grinberg, N. V., Burova, T. V., & Grinberg, V. Y. (2005). Temperature-sensitive chitosan-poly(N-isopropylacrylamide) interpenetrated networks with enhanced loading capacity and controlled release properties. *Journal of Controlled Release, 102*(3), 629–641. https://doi.org/10.1016/j.jconrel.2004.10.021

[12] Fox, P. C., Atkinson, J. C., Macynski, A. A., Wolff, A., Kung, D. S., Valdez, I. H., Jackson, W., Delapenha, R. A., Shiroky, J., & Baum, B. J. (1991). Pilocarpine treatment of salivary gland hypofunction and dry mouth (xerostomia). *Archives of Internal Medicine, 151*(6), 1149–1152. https://doi.org/10.1001/archinte.1991.00400060085014

[13] Ma, J., Xu, Y., Fan, B., & Liang, B. (2007). Preparation and characterization of sodium carboxymethylcellulose/poly(N-isopropylacrylamide)/clay semi-IPN nanocomposite hydrogels. *European Polymer Journal, 43*(6), 2221–2228. https://doi.org/10.1016/j.eurpolymj.2007.02.026