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Thermosensitive in Situ Gels: Mechanisms, Properties, and Applications in Drug Delivery

Ms. B. Pooja

Department of Pharmaceutics, Annamacharya College of Pharmacy (autonomous), Rajampet, Andhra Pradesh, India.
bandipooja936@gmail.com

ABSTRACT

Thermosensitive hydrogels are polymeric networks that undergo sol-gel transitions in response to temperature changes, offering advantages such as biocompatibility, tunable gelation, and sustained drug release. This review explores the classification, properties, and applications of thermosensitive hydrogels in drug delivery. These hydrogels are categorized as either positive (upper critical solution temperature, UCST) or negative (lower critical solution temperature, LCST) based on their gelation behavior. Their mechanical properties, adhesion, and drug release mechanisms are influenced by factors such as polymer composition, crosslinking density, and environmental conditions. Thermosensitive hydrogels provide targeted, prolonged release, and are applicable across various administration routes, including transdermal, rectal, and cancer therapy. Novel formulations, such as chitosan/pluronic/β-glycerophosphate (CS/PF/BGP) and poly(alanine)-poly(ethylene glycol)-poly(alanine) (PAla-PEG-PAla), combined with micro/nanocarriers, have demonstrated enhanced retention, controlled burst release, and significant potential for advanced biomedical applications. This review highlights the versatility and promise of thermosensitive hydrogels as intelligent biocompatible materials for drug delivery, and offers insights into their properties, mechanisms, and recent advancements in the field.

Keywords: Thermosensitive hydrogels, In situ gelling, Drug delivery, Sustained release, Chitosan/Pluronic, Upper critical solution temperature (UCST), Lower critical solution temperature (LCST)

INTRODUCTION

When used as a drug delivery system, intra-articular (IA) hydrogels confer prolonged therapeutic effects, sustained drug release, and reduced systemic toxicity. Their high-water content imparts properties akin to tissue cushioning and lubrication.1 By facilitating precise dosage, enhancing joint retention, and enabling depot-based controlled drug release, in situ forming hydrogels—administered as liquids that undergo gelation under physiological conditions—augment bioavailability and therapeutic efficacy.[2]

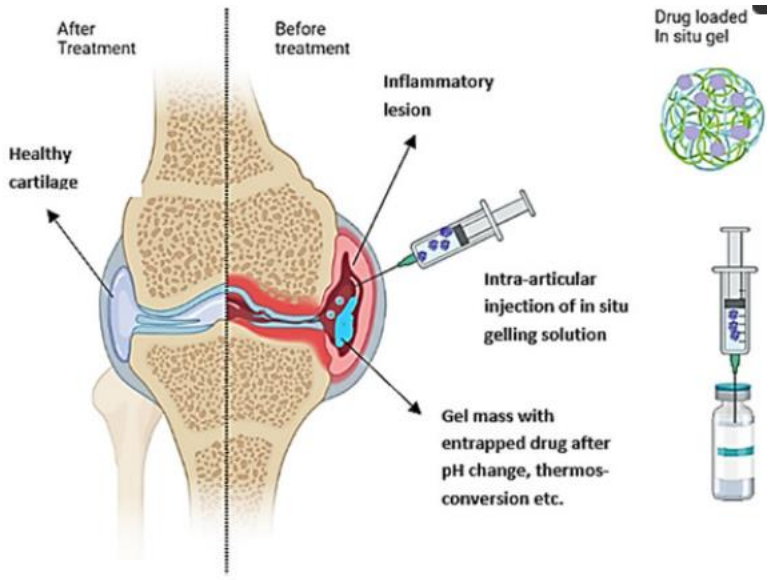
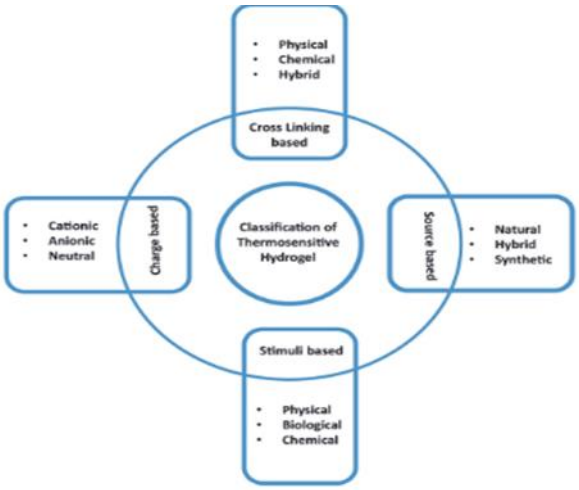


FIGURE:1 Diagrammatic illustration of the in-situ gelling drug formulation IA delivery into healthy tissue and inflammatory osteoarthritis (OA) joints following therapy.

Thermosensitive hydrogels, characterized by their thermosensitive groups, exhibit diverse gelation temperatures, depending on their composition and nature. These polymers are categorized into two types: those with an upper critical solution temperature (UCST), which respond favorably to temperature changes, and those with a lower critical solution temperature (LCST), which respond unfavorably.3 In the domain of drug delivery, oral and intravascular administration methods are prevalent because of their efficiency and practicality. However, these routes have several limitations, including suboptimal targeted drug delivery, restricted sustained release, and potential adverse effects. Literature indicates that thermosensitive hydrogels are environmentally benign materials with minimal adverse effects and suitable drug administration properties. Consequently, researchers have explored the application of thermosensitive hydrogels for drug delivery to address these challenges.[4]

Thermosensitive hydrogels are applicable in the human body because of their sol-gel transition properties, allowing for the encapsulation of various hydrophilic and hydrophobic drugs within the matrix for prolonged release at physiological temperatures. Traditional drug administration routes encounter challenges; however, the targeted and sustained release capabilities of thermosensitive hydrogels render them promising alternatives for drug delivery. The exceptional properties and biocompatibility of thermosensitive hydrogels have attracted global interest. This review primarily focuses on the background, characteristics, and applications of thermosensitive hydrogels in intravaginal, transdermal, oral, ophthalmic, cancer therapy, and cell-loaded drug delivery systems. Additionally, recent advancements in the application of thermosensitive hydrogels for drug delivery are also discussed. The initial section of this review elucidates the materials, classification, and potential properties of thermosensitive hydrogels, and the subsequent section highlights recent findings in their applications. Finally, we present observations based on the research discussed above. We believe this review will provide researchers with a comprehensive understanding of thermosensitive hydrogels for drug delivery applications.[5]

Classification of the thermosensitive hydrogel



Thermosensitive hydrogels are classified into physical, chemical, and hybrid bonding-based categories based on the process of crosslinking. Furthermore, these hydrogels are categorized and characterized according to their fundamental material composition, which is essential for selecting an appropriate thermosensitive hydrogel for specific drug delivery applications.[6]

MATERIAL AND METHODOLOGY

Material	**Notes**
Chitosan (from shrimp shells, low viscosity)	Polymer for gel formation
Pluronic F127 (M.W. 12,600)	Thermosensitive polymer
Sodium β-glycerol phosphate (glycerol 2-phosphate disodium salt hydrate)	Crosslinker / gelling agent
Etanercept (Embrel)	Therapeutic protein
Dulbecco's Modified Eagle's Medium (DMEM, high glucose, with GlutaMAX	Cell culture medium
Fetal Bovine Serum (FBS)	Cell culture supplement
Penicillin/Streptomycin	Antibiotics for cell culture
MTS reagent (3-(4,5-Dimethylthiazol-2-yl)-5-	Cell viability assay

(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium)	
Calcein-AM/Ethidium homodimer-1 LIVE/DEAD	Cytotoxicity/live-dead assay

METHODOLOGY

Preparinghydrogel

Chitosan/pluronic (CS/PF) hydrogels were synthesized by dissolving 1.2% (w/v) chitosan in 1% (v/v) acetic acid, after which the pH was approximately 6.4 using 0.1 M NaOH, followed by cooling. Pluronic F127 was incorporated to form a 20% (w/v) solution, and the mixture was agitated overnight at 4 °C until a transparent solution was achieved. The CS/PF solution was stirred at 4 °C, and β-glycerophosphate (BGP, 10% w/v) was added incrementally to facilitate the formation of CS/PF/BGP hydrogels for crosslinking.

Properties of thermosensitive hydrogel's physicochemical makeup

Mechanical property

The swelling ratio of polymeric hydrogel materials is a critical determinant of their dual mechanical properties, namely, viscoelasticity and rubber-like elasticity. A high swelling ratio imparts viscoelastic characteristics, whereas a low ratio imparts rubber-like elasticity. Given the inherent limitations of the mechanical strength of polymers, researchers are focusing on modifying the matrix and reinforcement to enhance thermosensitive hydrogels for drug delivery applications. Noteworthy advancements have been made in studies such as that by Imran et al., who developed a thermosensitive, stretchable hydrogel exhibiting exceptional mechanical properties, with promising applications in the biomedical field. Engineered hydrogels are promising candidates for advanced therapeutic systems owing to their balanced strength and flexibility.[7]

Adhesion

Adhesion, which relies on internal structure and chemical bonding, is crucial for the compatibility of materials with living tissues. Conventional hydrogels, characterized by a high-water content, exhibit poor adhesion owing to weak hydrogen bonds and reduced interfacial contact with the substrates. Excessive water absorption leads to gaps between the hydrogel and target surfaces, complicating biomedical applications involving moist and delicate tissues. To address this issue, researchers have developed hydrogels that account for target textures. Thermosensitive hydrogels demonstrate superior adherence to conventional hydrogels because thermopolymers inherently possess greater stickiness. Consequently, thermosensitive hydrogels present viable alternatives for biomedical applications that require robust surface interactions.[8]

Thermosensitive Gels and Their Comparison to Other Stimuli-Sensitive Gels

Triblock copolymers, characterized by both hydrophilic and hydrophobic segments, are frequently employed for the formation of thermo-responsive in situ hydrogels. These polymers exhibit a sol-to-gel transition at physiological temperature (37 °C), facilitating the delivery of both hydrophilic and hydrophobic pharmaceuticals. Notably, these hydrogels are biocompatible and biodegradable, rendering them suitable for various administration routes, including mucosal, transdermal, ocular, oral, buccal, and injectable routes. They offer a sustained drug release for several days. Furthermore, these hydrogels are applicable in tissue engineering, such as wound healing and cartilage regeneration, owing to their ability to mimic the cellular microenvironment. The mechanical strength of these materials can be enhanced by ultraviolet (UV) radiation. In intra-articular (IA) applications, gel materials can preserve the cartilage. For cartilage 3D printing, a hydrogel composed of methacrylate chondroitin sulfate combined with a glycol triblock copolymer has demonstrated potential.[9,10,11]

Materials Sensitive to Temperature and the Gelation Mechanism

Thermosensitive hydrogels are particularly well suited for drug delivery applications because of their ability to form insoluble, hydrophilic, three-dimensional networks that swell in aqueous environments and exhibit both solid-like and fluid characteristics. The thermal responsiveness of these polymers is governed by the equilibrium between their hydrophilic and hydrophobic segments. Temperature variations influence the interaction of these segments with water molecules, altering their solubility and inducing sol–gel phase transitions. The versatility of these hydrogels is attributed to their capacity for reversible gelation in response to temperature fluctuations, often comprising of both hydrophobic and hydrophilic components. This dynamic response to physiological conditions facilitates a controlled drug release, which enhances patient compliance and therapeutic efficacy. Thermosensitive hydrogels can be categorized as either positive or negative based on their gelation behavior.[12]

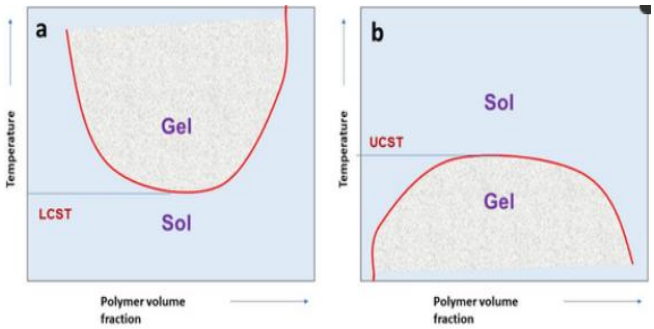


FIGURE: Sol-gel phase transition behavior of thermosensitive polymers (**a**) at lower critical solution temperature (LCST) and (**b**) at upper critical solution temperature

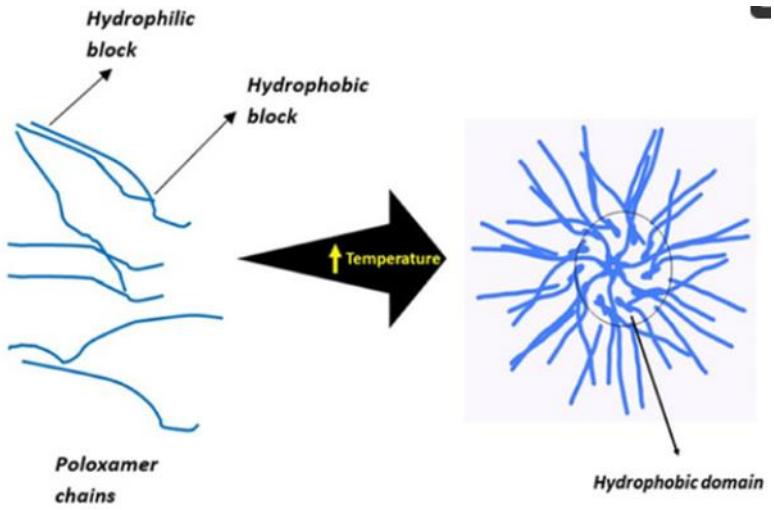
Positive thermosensitive hydrogels

The upper critical solution temperature (UCST) characterizes positive-thermosensitive hydrogels. Below this temperature, the hydrogels underwent a gel-to-sol transition driven by enthalpic changes,

contraction, and solubility. Despite this property, natural polymers such as agarose, gelatin, and amylose have limited applications in drug delivery.[13]

Negative thermosensitive hydrogels

Owing to their hydrophobic interactions and increased entropy of water molecules, negative thermosensitive hydrogels exhibit a lower critical solution temperature (LCST) and undergo a sol-to-gel transition above this temperature. This characteristic renders them suitable for in situ gelling drug delivery systems, particularly for intra-articular applications. Poly (N-isopropyl acrylamide) (PNIPAAm), with an LCST near 32 °C, remains in solution during storage, but transitions to a gel at physiological temperature (37 °C), facilitating sustained drug release. The volume phase transition temperature can be modulated by incorporating charged monomers or adjusting the hydrophilic-to-hydrophobic ratio. Monomers, such as vinyl pyridine, acrylic acid, and acrylamide, have been employed



to synthesize PNIPAAm copolymers. [14,15,16]

FIGURE: Mechanism of a temperature-sensitive system

The intra-articular (IA) injection of micro- and nanoparticles has been explored to enhance drug retention in the joint cavity. Examples of such carriers include liposomes, microspheres, nanoparticles (NPS), and microcrystals. Notably, synovial macrophages phagocytose microparticles, and nanoparticles are rapidly cleared. To address this, in situ-forming thermosensitive hydrogels have been utilized as vehicles to improve joint retention. Beyond extending drug residence, micro/nanoparticles facilitate continuous release and mitigate the initial burst effect, which is often associated with in situ gels. Furthermore, they enhance the permeability of the synovial membrane and increase the solubility of the lipophilic compounds. Several studies have investigated the use of thermosensitive gels in conjunction with micro- and nanocarriers. [17,18]

Mechanism of Drug Release from Thermoreversible In Situ Gels

Similar to other hydrogels, thermoreversible in situ gels primarily facilitate drug release through passive diffusion, which may occur with or without accompanying erosion or chemical reactions. The release rate is influenced by factors such as the degree of crosslinking, gel mesh size, polymer structure, additives, and environmental conditions. Molecules traverse the expanded gel matrix at rates that are dependent on their size. Larger molecules are released more slowly, enabling sustained delivery, whereas smaller molecules disperse more readily. This phenomenon is exemplified in PCLA–PEG–PCLA triblock copolymer gels, where hybrid covalent crosslinks provide enhanced viscoelasticity and delayed release compared to noncovalent gels, with stronger crosslinking further impeding diffusion. In such systems, drug release is governed by both gel erosion and diffusion through the gel, with the dominant process determined by the physicochemical properties of the drug and the gel composition.[19]

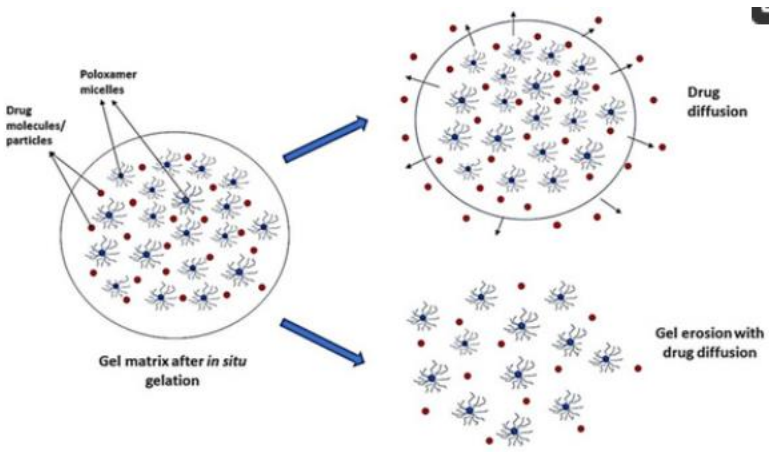


FIGURE: Drug release mechanisms from thermosensitive in situ gels

APPLICATIONS

System for transdermal medication delivery

The prolonged release and biocompatibility of thermosensitive hydrogels facilitate efficient transdermal drug delivery. Qiao et al. employed chitosan and genipin to create a silk dressing infused with paracetamol, achieving a sol–gel transition, enhanced permeability, and sustained release for up to 12h. Nirmayanti et al. developed a poloxamer-based valsartan hydrogel with an increased bioavailability. Thermosensitive hydrogels have also been combined with microneedle technology to improve the transdermal delivery. Khan et al. formulated poloxamer (PF127, P87)-based in situ depots within microneedle-induced skin micropores, and demonstrated phase conversion at approximately 32 °C. The characterization confirmed the stability, crosslinking, and controlled solid dispersion. In vitro studies

revealed sustained curcumin permeation and deeper epidermal deposition compared to untreated skin, underscoring the effectiveness of microneedle-assisted hydrogels for prolonged drug release.[20,21]

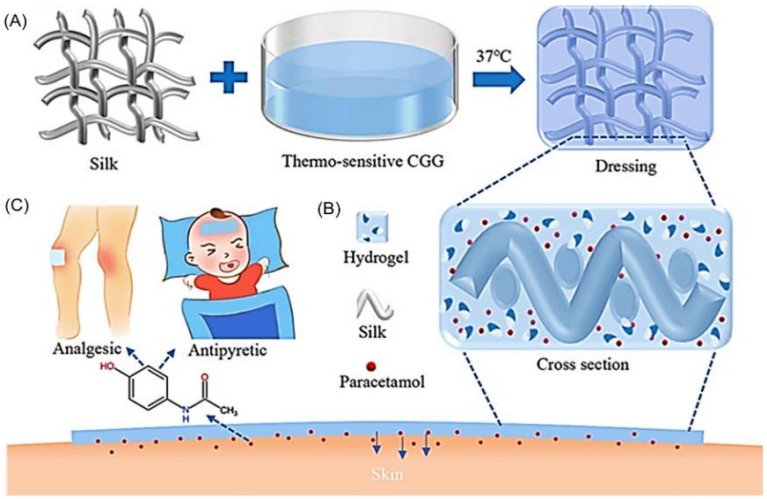


FIGURE: An illustration of a medical dressing made of thermosensitive hydrogels. (A) Synthesis of CGG hydrogel medicinal dressing based on silk fabric. (B) Image of a medical dressing made of silk fabric pierced with CGG hydrogel. (C) Transdermal application of a thermoresponsive medicinal dressing for analgesic and antipyretic purposes. reprinted with permission under the copyright from Qiao et al..

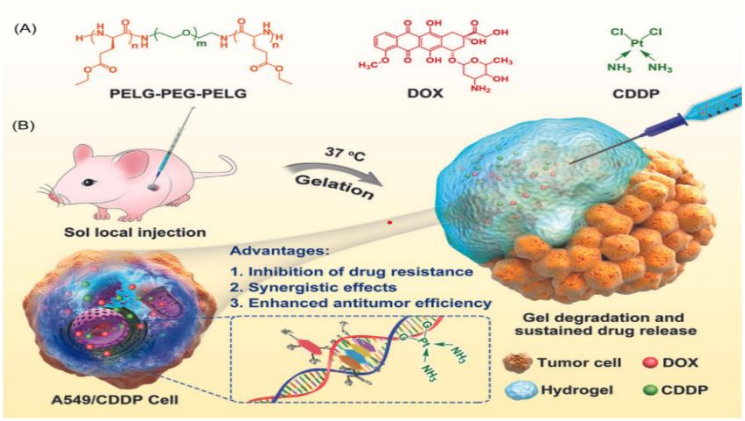
Rectal drug delivery

Despite being often associated with discomfort and limited compatibility with conventional formulations, rectal drug delivery serves as a viable alternative to oral and parenteral administration, offering both local and systemic therapeutic effects. Recent advancements have been achieved through the application of intelligent biocompatible thermosensitive technologies. To facilitate continuous irinotecan release with a more straightforward rectal administration compared with traditional hydrogels, Din et al. developed a reversible nanocarrier system by dispersing solid nanoparticles within a poloxamer solution. Xue et al. formulated an in situ poloxamer 407-based thermosensitive hydrogel incorporating Kangfuxin liquid, which is a traditional Chinese medicine derived from Periplaneta americana. The therapeutic efficacy of this hydrogel in rectal drug delivery was demonstrated by its successful repair of colonic mucosal membranes in animal models of ulcerative colitis, following optimization of gelation and mechanical strength.[22,23,24]

System for delivering drugs for cancer treatment

Conventional chemotherapy is often associated with significant adverse events. Cancer remains a major global health challenge. Therefore, researchers are exploring the use of thermosensitive hydrogels to provide safer, more targeted, and sustained cancer treatment. Zhang et al. developed an injectable hydrogel composed of ferrimagnetic chitosan and iron oxide nanotubes, designed for the controlled release of doxorubicin and near-infrared (NIR)-induced hyperthermia, which exhibited strong anticancer efficacy. Lu et al. enhanced drug release duration and inhibited tumor growth in mice by 72.5% by

integrating paclitaxel with honokiol nanosuspension-loaded thermogels (HK-NS-Gel). Khan et al. engineered poloxamer 407–CMCS thermogels crosslinked with glutaraldehyde for the delivery of 5-fluorouracil (5FU), demonstrating cytotoxic effects against HeLa and MCF7 cells and achieving zero-order release kinetics. Further innovations include hybrid drug-loaded systems (doxorubicin + cisplatin) to overcome multidrug resistance, and nanocomposite hydrogels with bioimaging capabilities for



HER2-positive breast cancer.[25]

FIGURE: Overview of thermosensitive hydrogels for dual drugs. (A) Chemical structures of doxorubicin, cisplatin, and PELG-PEG-PELG. The benefits of the PELG-PEG-PELG thermosensitive hydrogel filled with doxorubicin and cisplatin for local combination therapy in a naked MDR tumor mouse model are shown schematically in (B), which was reproduced by Lv et al.

Challenges and Future Perspectives of Thermosensitive InSitu Gels in Drug Delivery

Thermosensitive in situ gels represent a promising platform for localized and controlled drug delivery, offering the advantages of minimally invasive administration, improved patient compliance, and potential for sustained therapeutic effects. Despite these benefits, several critical challenges have hindered their widespread clinical use. One of the primary limitations of these materials is their mechanical and structural instability under physiological conditions. Many current formulations cannot withstand the complex biological environment, which includes enzymatic degradation, dynamic shear forces, and fluctuations in pH. This instability frequently results in premature drug leakage, inadequate retention at the target site, and ultimately suboptimal therapeutic outcomes. Another significant drawback is the burst release phenomenon, which is characterized by initial rapid drug discharge. Such uncontrolled release can compromise the therapeutic efficacy, increase the risk of systemic side effects, and limit the overall duration of drug action. Achieving reproducible and predictable release kinetics is a major formulation challenge.

In addition to these technical hurdles, long-term safety concerns persist, particularly with respect to polymer degradation products, potential irritation of local tissues, and risk of immunogenic reactions. From industrial and translational perspectives, issues related to scalability, sterility assurance, and batch-to-batch reproducibility pose significant barriers to commercial production. Moreover, the regulatory complexities and variability in patient responses further complicate the clinical translation of these systems.

Future research directions will focus on advanced material engineering to develop multifunctional hydrogels that are responsive to multiple physiological stimuli, including pH and enzymatic activity, thereby enabling site-specific and temporally controlled drug release. The incorporation of nanotechnologies, such as nanoparticles or liposomes, holds promise for mitigating burst release and enhancing targeted therapeutic delivery. Furthermore, the development of personalized formulations tailored to individual patient needs may optimize the clinical outcomes. Collaborative efforts among researchers, clinicians, and regulatory agencies are essential to bridge the gap between preclinical success and routine clinical application.

Summary And Conclusion

Hydrogels, particularly thermosensitive "smart" variants, have emerged as highly promising platforms for advanced drug delivery owing to their unique physicochemical properties and versatility for drug delivery applications. These three-dimensional polymeric networks possess a remarkable capacity to absorb and retain large volumes of water while maintaining their structural integrity, rendering them ideal matrices to encapsulate, protect, and control the release of therapeutic agents. A distinctive feature of thermosensitive hydrogels is their ability to undergo reversible sol–gel transitions in response to temperature changes, thereby enabling site-specific and sustained drug release. Temperature responsiveness is typically categorized based on whether the system exhibits a lower critical solution temperature (LCST) or upper critical solution temperature (UCST). Among these, poly(N-isopropylacrylamide) (PNIPAAm) is the most extensively studied LCST-type hydrogel and is widely recognized for its sharp and reversible phase-transition behavior. The biomedical potential of thermosensitive hydrogels is evident from their applicability across diverse routes of administration, including injectable, oral, ocular, and intratumoral delivery systems. Their ability to provide localized, sustained, and minimally invasive therapeutic release offers substantial advantages over conventional drug formulations. Recent advances in hydrogel design, such as the chitosan/pluronic/β-glycerophosphate (CS/PF/BGP) and poly(L-alanine)-poly (ethylene glycol)-poly(L-alanine) (PAla-PEG-PAla) systems, have demonstrated superior biocompatibility, enhanced residence time at the target site, and more controlled release kinetics than previous systems. Furthermore, the incorporation of nanocarriers or microparticles into hydrogel matrices has been shown to mitigate burst release, thereby improving therapeutic efficacy and safety. Importantly, the versatility of hydrogel crosslinking strategies, ranging from physical to chemical or hybrid approaches, allows for the precise modulation of mechanical, swelling, and degradation properties, thus tailoring these systems to meet specific clinical requirements.

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