Applications of Thermoresponsive Hydrogels in Tissue Engineering: A Comprehensive Review

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Abstract

Thermoresponsive hydrogels have gained considerable attention in tissue engineering due to their unique sol–gel transition behaviour near physiological temperatures, enabling minimally invasive administration in situ scaffold formation, controlled release of therapeutic agents and enhanced integration with host tissues. Their ability to mimic the extracellular matrix (ECM) and encapsulate cells, growth factors or bioactive molecules makes them promising candidates for regeneration of structurally diverse tissues including cartilage, bone, neural, cardiac, skin, corneal and vascular systems (Hoffman, 1995; Li & Mooney, 2016). Recent advances in polymer chemistry, nanotechnology and bio-fabrication, particularly 3D and 4D bioprinting have significantly expanded the versatility and functionality of thermoresponsive hydrogels (Ramanathan, 2024; Wang et al., 2025). This review provides a comprehensive analysis of the fundamental mechanisms of thermoresponsive behaviour, major polymer systems and the most significant applications in tissue engineering. It also outlines cutting-edge innovations such as hybrid nanocomposite hydrogels, stimuli-responsive multifunctional scaffolds and their integration with cell therapies. Finally, the article discusses current limitations—such as mechanical weaknesses, biodegradation challenges and clinical translation barriers—and highlights future research directions needed to fully exploit the potential of thermoresponsive hydrogels in regenerative medicine (Liu et al., 2023; Kim et al., 2024).

Keywords: Thermoresponsive Hydrogels, Scaffold, Cartilage, Encapsulation, Tissue Engineering.

1. Introduction

Tissue engineering is a rapidly evolving field focused on repairing or regenerating damaged tissues using a combination of biomaterials, cells and bioactive molecules to promote cellular behaviour and tissue formation. Among various biomaterials hydrogels have emerged as one of the most promising classes due to their high water content which closely mimics the native extracellular matrix (ECM). Hydrogels maintain a hydrated environment conducive to cell survival, growth and differentiation. Specifically, thermoresponsive hydrogels—also known as thermosensitive hydrogels or thermogels—have garnered significant attention for their unique ability to undergo reversible sol-gel transitions in response to temperature changes, typically around physiological temperatures. This temperature sensitivity makes them particularly advantageous for a variety of biomedical applications especially in tissue engineering (Hoffman, 1995; Peppas et al., 2006a; Liu et al., 2023)

Thermoresponsive hydrogels are characterized by their ability to remain in a sol (liquid-like) state at lower temperatures and transition into a gel (solid-like) state when the temperature increases beyond a specific threshold referred to as the lower critical solution temperature (LCST). This thermally triggered phase change offers several advantages in tissue engineering. Notably, the ability to inject the hydrogel in its liquid form at room temperature for minimally invasive delivery, which subsequently undergoes gelation in situ at body temperature, is particularly beneficial. The gel matrix formed provides a stable environment for cell encapsulation, drug release and tissue formation, making thermoresponsive hydrogels an excellent tool for targeted therapy and tissue regeneration (Hoffman, 1995; Chen et al., 2024; Li and Mooney, 2016; Yang et al., 2024).

In tissue engineering, thermoresponsive hydrogels play an essential role in cell encapsulation, controlled release of bioactive agents and the formation of tissue scaffolds. The ability to encapsulate living cells or growth factors within the hydrogel matrix at physiological temperatures allows for efficient and non-invasive delivery of therapeutic cells to the target site. Once injected into the body, the hydrogel undergoes gelation, forming a stable scaffold that mimics the structural and biochemical properties of the ECM, allowing for enhanced cellular interactions, differentiation and tissue regeneration (Burdick and Prestwich, 2011; Dai et al., 2011; Zhang et al., 2024) These hydrogels also provide a favorable microenvironment for cell survival and differentiation, as their high-water content supports nutrient transport and metabolic waste removal (H. Kim et al., 2024a).

Furthermore, many thermoresponsive hydrogels can be functionalized with cell-adhesive peptides, such as the RGD motif (Arg-Gly-Asp), which promotes cell attachment, migration, and differentiation, enhancing the regenerative capacity of the engineered tissue (Annabi et al., 2014a; Peppas et al., 2006b; Prakash et al., 2024). This functionalization is crucial for directing specific cellular responses, particularly for tissues like cartilage, neural and bone where precise control of cell behaviour is essential for effective regeneration (Lin et al., 2023a; Wang et al., 2025a).

Recent advancements in polymer chemistry, nanotechnology, and bio-fabrication techniques such as 3D and 4D bioprinting have greatly expanded the potential applications of thermoresponsive hydrogels. These innovations allow for the creation of customized scaffolds that not only mimic the mechanical properties of native tissues but also respond dynamically to environmental cues such as pH, temperature and mechanical stress (Bae et al., 2024; Ramanathan, 2024; Wang et al., 2025b). For example, the incorporation of nanomaterials, such as graphene oxide or hydroxyapatite into thermoresponsive hydrogels has resulted in hybrid systems with enhanced mechanical strength, bioactivity and functionality. This has significantly increased their suitability for challenging tissue engineering applications like bone and cartilage regeneration (Li and Mooney, 2016; Zhou et al., 2024).

Despite their promising potential, several challenges remain in fully exploiting the capabilities of thermoresponsive hydrogels. These challenges include mechanical limitations such as low tensile strength and poor load-bearing capacity as well as biodegradation issues that can lead to premature degradation of the hydrogel in vivo(Al Mamun et al., 2025; Liu et al., 2023). Additionally, while the sol-gel transition is highly beneficial for injectable hydrogels, controlling the kinetics of this transition to ensure consistency and reliability in clinical applications remains a significant challenge (Y. Kim et al., 2023; Lin et al., 2023b). Clinical translation remains a major hurdle as well, requiring optimization of scaffold fabrication, biocompatibility, and long-term stability of thermoresponsive hydrogels under physiological conditions (Hoffman, 1995; H. Kim et al., 2024b).

This review aims to provide a comprehensive analysis of the current state of thermoresponsive hydrogels in tissue engineering. It explores the fundamental mechanisms behind their sol-gel transition, the types of polymers commonly used and their diverse applications in the regeneration of various tissues, including cartilage, bone, neural, cardiac and vascular systems. Furthermore, the review highlights recent advancements in hybrid and composite hydrogels, stimuli-responsive multifunctional scaffolds and bio-fabrication techniques, such as 3D and 4D bioprinting which have enhanced the functional versatility of thermoresponsive hydrogels in regenerative medicine. Finally, the manuscript discusses current limitations, future research directions and the potential for clinical translation of these promising materials (Al Mamun et al., 2025; H. Kim et al., 2024b; Liu et al., 2023).

2. Applications in Cell Encapsulation, Delivery and Microenvironment Engineering

Thermoresponsive hydrogels offer significant advantages in tissue engineering applications, particularly in the encapsulation, delivery and retention of cells, as well as the creation of controlled and supportive microenvironments for enhanced tissue regeneration. Their unique ability to undergo a sol-gel transition at physiological temperatures provides several benefits for cell-based therapies, including improved cell survival, precise localization and enhanced differentiation outcomes. Below, we explore these advantages in greater detail:

2.1 Improved Cell Survival During Injection

Cell therapy often requires the delivery of viable cells to damaged tissues while maintaining their functionality in a supportive microenvironment. One of the major challenges is ensuring that cells remain viable during the injection process and continue to survive once injected. Thermoresponsive hydrogels offer a solution by remaining in a liquid state at lower temperatures, which facilitates easier injection and more uniform distribution within the tissue. This state reduces the mechanical forces exerted on the cells during injection, preventing shear stress-induced damage and improving cell survival post-injection (H. Kim et al., 2024b). Furthermore, by protecting cells from immune attack and minimizing direct exposure to the body's immune system before gelation, thermoresponsive hydrogels enhance the overall viability and engraftment of the cells at the target site (Liu et al., 2023). This characteristic makes them ideal for minimally invasive delivery of therapeutic cells, reducing the trauma associated with surgical implantation.

2.2 Retention and Localization of Therapeutic Cells

A key challenge in cell-based therapy is the retention and long-term localization of therapeutic cells at the desired site. Thermoresponsive hydrogels provide a stable scaffold once gelled, ensuring that the cells are retained at the target tissue. This localized retention improves the efficiency of cell engraftment, which is critical for tissue regeneration. By keeping

the cells at the injection site, thermoresponsive hydrogels also enhance local paracrine factor release—molecules secreted by cells that promote tissue healing—and facilitate better tissue integration(Li and Mooney, 2016). This feature is particularly advantageous in regenerative therapies where sustained cellular activity at the injury site is required for effective tissue repair.

2.3 Tailored Microenvironments for Differentiation

The mechanical properties of thermoresponsive hydrogels can be tailored to match the specific requirements of different cell types, thus creating an ideal microenvironment for cellular differentiation. The softness and ECM-like water content of certain thermogels promote neural differentiation in softer matrices, while more rigid matrices support chondrogenesis and osteogenesis (Burdick and Prestwich, 2011). The ability to tune these properties allows for the development of specialized scaffolds for different tissue types, including nerve, cartilage and bone. In addition, many thermoresponsive hydrogels can be functionalized with bioactive molecules, such as cell-adhesive peptides like the RGD motif (Annabi et al., 2014b). These ligands promote cellular attachment and guide cellular behaviour, further enhancing the differentiation process and promoting tissue-specific functions. For example, the addition of RGD motifs to thermoresponsive hydrogels can direct cell adhesion, migration and differentiation, leading to more efficient tissue regeneration and better functional outcomes in a variety of tissue types.

2.4 Controlled Release of Cell-Secreted Factors

Thermoresponsive hydrogels also provide an effective system for the controlled release of growth factors and extracellular vesicles (EVs) secreted by therapeutic cells. By slowing the diffusion of these bioactive molecules, hydrogels create a localized reservoir of growth factors that can enhance tissue healing and regeneration over time (Dai et al., 2011) . This controlled release not only supports the survival and activity of the encapsulated cells but also accelerates tissue repair by maintaining a sustained delivery of essential factors in a spatially and temporally controlled manner. This feature is particularly valuable in applications requiring the regeneration of complex tissues, where the prolonged availability of growth factors can significantly improve the functional integration of the newly regenerated tissue.

These applications highlight the versatility of thermoresponsive hydrogels in cell encapsulation, delivery, and microenvironment engineering. Their unique combination of mechanical tunability, temperature sensitivity and biocompatibility makes them an indispensable tool for advancing tissue engineering strategies, from cell therapy to tissue regeneration.

Table 1: Thermoresponsive Hydrogels in Tissue Engineering: Polymer Systems, Key Features, Applications, Advantages and Citations

Hydrogel Type / Polymer System	Key Features / Mechanisms	Primary Tissue Engineering Applications	Advantages	Citation
PNIPAAm-based hydrogels	LCST near 32°C; reversible sol–gel	Cartilage, neural, drug delivery	Highly tunable	Hoffman, 1995
Pluronic (Poloxamer) hydrogels	Micellar thermogelation	Drug delivery	FDA-approved	Kretlow et al., 2007
PEG-based thermogels	Hydrophilic/hydrophobic tuning	Cartilage, bone	Biocompatible	Li & Mooney, 2016
Chitosan/β-GP systems	pH- and thermo-responsive gelation	Bone, cartilage	Mild gelation conditions	Dai et al., 2011
Elastin-like polypeptides	Tunable LCST via sequence design	Cardiac, neural	Excellent biocompatibility	Peppas et al., 2006
Gelatin/GelMA thermogels	Thermally reversible; RGD motifs	Cornea, cartilage	ECM-like behaviour	Annabi et al., 2014

Nanocomposite thermogels	Nanoparticle reinforcement	Cardiac, bone	Enhanced mechanical and functional properties	Wang et al., 2025
Injectable cartilage thermogels	Flowable then stiffen in situ	Cartilage	Minimally invasive filling	Kim et al., 2024
Bone-regenerative thermogels	Osteogenic additives	Bone healing	Supports mineralization & growth factor delivery	Al Mamun et al., 2025
Neural thermogels	Ultra-soft (<1 kPa)	Brain, spinal cord	Reduces inflammation, supports axons	Liu et al., 2023
Cardiac conductive thermogels	CNT/graphene inclusion	Myocardial repair	Enhances electrical signaling	Lin et al., 2023
Corneal thermogels	Transparent, shape-conforming	Sutureless corneal repair	Personalized grafts	Mahapatra & Singh, 2024
Wound healing thermogels	Moisture-retentive	Chronic wounds, burns	Sustained release of therapeutics	(M. Yu and Zhong, 2023)
Thermogels with poly(lactic acid)	Biodegradable; thermoresponsive	Skin, cartilage	Biocompatible & biodegradable	Zhang et al., 2023
Chitosan-based thermogels	Electrostatic gelation; LCST	Wound healing, cartilage	Biocompatible ; antimicrobial	Liu et al., 2024
Polyurethane thermogels	Thermo-responsive urethane linkages	Bone regeneration	High mechanical strength	(X. Yu et al., 2025)
Hyaluronic acid-based thermogels	Thermosensitive behaviour; RGD motifs	Cartilage, skin, neural	Excellent cell interactions	Wang & Xu, 2024
Poly(ethylene glycol)-based thermogels	Hydrophilic/hydrophobic balance	Cartilage, vascular	Non-toxic, biocompatible	(Lee et al., 2024)
Fibrin-based thermogels	Thermoresponsive gelation	Wound healing, cardiac	ECM-mimetic	Sorrell et al., 2023
Silk fibroin-based thermogels	Biodegradable; bioactive	Bone regeneration	Strong and biocompatible	(Shi et al., 2023)
Collagen-based thermogels	Thermally reversible	Cartilage, skin	Mimics native ECM	Hui et al., 2024
PVA-based thermogels	Crosslinkable; sol-gel transition	Cartilage, wound healing	Good elasticity	(Tran et al., 2024)

Poly(N-vinylcaprolactam)-based thermogels	Hydrophobicity; LCST	Drug delivery, cartilage	High thermoresponsiveness	(An et al., 2024)
Poly(2-hydroxyethyl methacrylate)-based thermogels	Hydrophilic/hydrophobic transition	Cartilage, bone	Tunable properties	(Zhang et al., 2024)
Polycaprolactone-based thermogels	Biodegradable; thermo-responsive	Bone, vascular	High strength	(Li et al., 2023)
Thermoresponsive hydroxyapatite-composite hydrogels	Osteoinductive, thermoresponsive	Bone regeneration	Enhanced osteogenesis	(Park et al., 2025)
Polypropylene fumarate-based thermogels	Biocompatible, crosslinked	Tissue regeneration	Supports cellular adhesion	(Tu et al., 2025)

3. Challenges and Limitations of Thermoresponsive Hydrogels in Tissue Engineering

While thermoresponsive hydrogels have demonstrated great potential in various tissue engineering applications, their successful translation from laboratory research to clinical settings remains hindered by several challenges and limitations. These challenges primarily revolve around mechanical properties, biodegradability, bioactivity, gelation kinetics, and clinical translation. Addressing these issues is essential to enhance the functionality, reliability, and safety of thermoresponsive hydrogels in regenerative medicine.

3.1 Mechanical Properties

One of the key challenges in the development of thermoresponsive hydrogels is their mechanical properties. While hydrogels mimic the hydrated ECM, they often suffer from low mechanical strength, especially under load-bearing conditions, which limits their application in tissues that require substantial structural support, such as bone and cartilage (Annabi et al., 2014). The inherent flexibility of hydrogels can be a disadvantage for tissues that need high mechanical stability or durability over time. Additionally, most thermoresponsive hydrogels lack the necessary elasticity or tensile strength to withstand the forces encountered in vivo, such as those seen in joint cartilage or the heart.

Strategies to improve the mechanical properties of these hydrogels include the crosslinking of polymer chains to form a more robust network structure, the incorporation of nanomaterials (e.g., graphene oxide, hydroxyapatite), or the design of hybrid systems that combine synthetic and natural polymers (Wang et al., 2025; Liu et al., 2023). However, while these strategies can improve mechanical stability, they can also complicate the synthesis process and introduce concerns about biocompatibility and biodegradability, as some crosslinking agents or additives may be toxic or resistant to biodegradation (Li & Mooney, 2016).

3.2 Biodegradability and In Vivo Stability

The biodegradation of thermoresponsive hydrogels is a critical factor for their long-term application in tissue engineering. Ideally, hydrogels should degrade in a controlled manner over time, matching the rate of tissue regeneration to ensure that the scaffold is no longer needed once the tissue has been sufficiently repaired or replaced. However, many thermoresponsive hydrogels degrade too slowly or too quickly, leading to a mismatch between degradation rate and tissue regeneration.

For example, while natural polymers like gelatin and chitosan are inherently biodegradable they may degrade too rapidly under physiological conditions leading to premature loss of mechanical integrity before the tissue has regenerated (Dai et al., 2011). On the other hand, synthetic polymers like PNIPAAm and Pluronics may not degrade sufficiently in vivo unless engineered for controlled degradation (Hoffman, 1995; Li & Mooney, 2016). Achieving precise control over the degradation kinetics remains a significant hurdle, particularly in tissues with complex healing dynamics.

Furthermore, some hydrogels particularly those made from synthetic materials, may degrade into byproducts that are not easily cleared from the body potentially leading to inflammatory responses or immune reactions (Kim et al., 2024). Therefore, the challenge lies in designing hydrogels that offer adequate structural support, yet degrade in a manner that does not trigger adverse immune responses.

3.3 Gelation Kinetics and Temperature Sensitivity

The gelation kinetics of thermoresponsive hydrogels play a crucial role in their clinical effectiveness. The sol–gel transition temperature (LCST) must be precisely controlled to ensure that the hydrogel forms at the target site and not before or after injection. If the transition occurs too rapidly or too slowly it can lead to premature gelation during injection or incomplete gelation at the target site compromising the functionality of the hydrogel (Peppas et al., 2006).

For instance, PNIPAAm-based hydrogels undergo gelation at a temperature near 32°C, which is close to human body temperature. However, slight variations in ambient temperature or local tissue temperature may affect the reliability of the gelation process leading to inconsistent scaffold formation (Hoffman, 1995). Additionally, factors such as ionic strength, pH and the presence of bioactive molecules (e.g., drugs, growth factors) can influence the gelation behaviour, making the process more difficult to control under physiological conditions (Kretlow et al., 2007).

Recent advancements in bio-fabrication techniques, such as 3D and 4D bioprinting, aim to address these challenges by offering more precise control over the local temperature and gelation kinetics during scaffold formation (Ramanathan, 2024). However, achieving consistent and reproducible gelation in a clinical setting remains a significant barrier.

3.4 Bioactivity and Cell Interactions

For thermoresponsive hydrogels to be effective in tissue engineering, they must provide a suitable microenvironment for cell growth, differentiation and tissue integration. While hydrogels can mimic the hydrated ECM, they often lack the bioactive cues necessary to promote the desired cellular behaviours. For example, while PNIPAAm is widely used for its tunable gelation properties, it is not inherently cell-adhesive, making it challenging to support cell attachment and migration (Li & Mooney, 2016). The addition of cell-adhesive peptides (e.g., RGD motifs) or the use of biofunctionalized hydrogels can enhance cellular interactions but these modifications can increase the complexity of the system and impact other properties, such as mechanical strength or biodegradability (Annabi et al., 2014).

Additionally, while thermoresponsive hydrogels can encapsulate cells, growth factors and drugs the controlled release of these bioactive molecules is often suboptimal. Many hydrogels do not exhibit sustained release profiles over the long periods required for tissue regeneration, leading to ineffective healing or premature degradation (Dai et al., 2011). The challenge, therefore is to design hydrogels that not only maintain mechanical stability and biodegradability but also provide a microenvironment that supports dynamic cellular behaviours and allows for controlled delivery of therapeutic agents.

3.5 Clinical Translation and Regulatory Hurdles

Despite the significant progress made in hydrogel design and fabrication technologies, the clinical translation of thermoresponsive hydrogels remains a major challenge. Issues such as regulatory approval, scalability of manufacturing and long-term safety must be addressed before these materials can be widely adopted in clinical practice (Wang et al., 2025). Regulatory bodies, such as the FDA, require extensive preclinical and clinical testing to ensure that new biomaterials are safe, effective and reliable.

In addition to regulatory concerns, the cost of producing high-quality thermoresponsive hydrogels remains prohibitive for large-scale applications. Many advanced hydrogel systems, especially those incorporating nanomaterials or bioactive molecules, require complex and costly synthesis processes that may not be feasible for mass production or for use in routine clinical applications (Liu et al., 2023). The development of cost-effective, scalable manufacturing processes is crucial for the widespread adoption of thermoresponsive hydrogels in clinical settings.

While thermoresponsive hydrogels have shown remarkable promise in tissue engineering, addressing their mechanical limitations, biodegradation challenges and gelation inconsistencies will be essential for their clinical success. Additionally, improving bioactivity, cell interaction and controlled release profiles will enhance the therapeutic potential of these hydrogels. Overcoming these challenges will require interdisciplinary approaches that combine polymer chemistry, nanotechnology and advanced manufacturing techniques, with a focus on clinical translation and regulatory compliance. Continued research and innovation in these areas will ultimately unlock the full potential of thermoresponsive hydrogels in regenerative medicine.

4. Future Prospects and Research Directions

The field of thermoresponsive hydrogels in tissue engineering is rapidly evolving, with significant advances in polymer chemistry, biofabrication technologies and functionalization strategies. As these hydrogels continue to show promise in a wide array of applications, future research efforts must address key challenges and unlock their full potential in regenerative medicine. This section outlines several important research directions and emerging trends that are expected to shape the future of thermoresponsive hydrogels in tissue engineering.

4.1 Advanced Biofabrication Techniques: 3D/4D Printing and Beyond

One of the most exciting areas of future development for thermoresponsive hydrogels lies in bio-fabrication, particularly 3D and 4D bioprinting. These advanced techniques enable the precise deposition of hydrogel materials to create complex, patient-specific scaffolds that mimic the structure of native tissues. 3D bioprinting allows for the layer-by-layer construction of scaffolds that incorporate cells, growth factors and other bioactive molecules, while 4D bioprinting adds the dimension of time by incorporating hydrogels that can undergo dynamic changes in response to environmental stimuli such as temperature or pH (Ramanathan, 2024).

These technologies enable the creation of anatomically accurate and functionally responsive tissue models, providing a promising solution for personalized medicine. For example, thermoresponsive hydrogels can be used as inks for bioprinting, where they can rapidly gel in situ after deposition, forming stable structures that support tissue growth. In the future, multi-material 3D/4D printing will allow for the integration of multiple hydrogel systems with different properties, creating hybrid scaffolds that better mimic the complex microenvironment of tissues, such as those found in cartilage, bone, neural tissue and vascular systems (Wang et al., 2025).

4.2 Hybrid and Nanocomposite Hydrogels

To overcome the mechanical and degradation limitations of pure thermoresponsive hydrogels, hybrid and nanocomposite materials represent a promising direction for future research. The integration of nanomaterials such as graphene, carbon nanotubes (CNTs), hydroxyapatite and silica nanoparticles into thermoresponsive hydrogels can significantly enhance their mechanical strength, bioactivity and tissue integration. These nanocomposites can provide not only improved structural stability but also enhanced cell signaling and functionalization, allowing for more effective tissue regeneration (Peppas et al., 2006).

In particular, conductive nanocomposite hydrogels are emerging as a solution for tissue engineering applications in electrically active tissues, such as cardiac and neural tissues. The incorporation of conductive materials (e.g., graphene oxide, CNTs) into thermoresponsive hydrogels can create electroactive scaffolds that promote electrical signaling, supporting the regeneration of myocardial and neural tissues (Lin et al., 2023). These smart materials can also respond to environmental changes, such as the application of external electrical fields or mechanical stimuli to guide tissue regeneration processes.

4.3 Functionalization for Improved Cell Interaction and Differentiation

Future efforts in thermoresponsive hydrogel research will focus on enhancing cell-material interactions to improve cell survival, differentiation and tissue integration. While many thermoresponsive hydrogels are biocompatible, they often lack specific bioactive cues required to guide cellular behaviour. Incorporating cell-adhesive peptides (e.g., RGD sequences) or growth factors into the hydrogel matrix will enable better cell attachment and differentiation (Burdick & Prestwich, 2011).

Furthermore, the integration of stem cells, gene delivery systems or exosomes within thermoresponsive hydrogels will enhance cell-based therapies for tissue regeneration. By combining hydrogels with bioactive molecules or genetic modifications, it is possible to create an environment that not only supports cell growth but also stimulates specific differentiation pathways, such as osteogenesis, chondrogenesis or neurogenesis. The future of thermoresponsive hydrogels

lies in their ability to mimic the native extracellular matrix (ECM) more accurately, providing cells with the appropriate mechanical, biochemical, and physical cues to regenerate functional tissues (Annabi et al., 2014).

4.4 Biodegradable and Biocompatible Crosslinking Strategies

As discussed, one of the major limitations of thermoresponsive hydrogels is their mechanical properties, which are often insufficient for high-load-bearing tissues. To improve the mechanical strength and structural integrity of hydrogels, biodegradable crosslinking agents and self-healing materials are being explored. Recent advancements have shown that dynamic covalent bonds (e.g., disulfide, boronic ester bonds) and supramolecular interactions (e.g., hydrogen bonds, host-guest chemistry) can improve the mechanical properties of hydrogels without compromising their biodegradability (Kim et al., 2024).

In addition, enzymatic crosslinking using enzymes that catalyse hydrogel formation in response to biological cues can enable on-demand gelation at the site of injury, minimizing the risks associated with premature gelation during injection. These biocompatible and biodegradable crosslinking methods will be crucial for creating functional scaffolds that provide the required mechanical support while gradually degrading as tissue regenerates.

4.5 Controlled and Sustained Drug Delivery

One of the key applications of thermoresponsive hydrogels in tissue engineering is their ability to encapsulate and release therapeutic agents, including growth factors, drugs and bioactive molecules. However, ensuring the controlled and sustained release of these agents over time is still a challenge. Future research will focus on designing hydrogel systems that can provide long-term release profiles without the risk of premature degradation or burst release (Dai et al., 2011).

Innovations in multi-stimuli-responsive hydrogels—those that can respond to temperature, pH, ion concentration or mechanical stress—will provide greater control over drug release. Such systems could be designed to release therapeutic agents locally and temporally, ensuring the sustained release of growth factors and other bioactive molecules over extended periods, matching the needs of tissue regeneration and repair (Li & Mooney, 2016).

4.6 Clinical Translation and Regulatory Approaches

As thermoresponsive hydrogels continue to show promise in preclinical studies, their clinical translation will require careful consideration of regulatory approval, scalability and long-term safety. Researchers must collaborate with regulatory bodies such as the FDA to develop clear guidelines for the testing and approval of these novel materials. Good manufacturing practices will need to be established to ensure that hydrogels can be produced at large scales with consistent quality, reproducibility and safety profiles (Liu et al., 2023).

Additionally, long-term biocompatibility studies as well as assessments of immune responses, inflammation and bioaccumulation of degradation products, must be conducted to ensure that thermoresponsive hydrogels can be safely used in humans without causing adverse effects (Wang et al., 2025).

The future of thermoresponsive hydrogels in tissue engineering lies in their ability to address current limitations in mechanical properties, biodegradability, bioactivity and clinical translation. With ongoing advancements in bio-fabrication, nanotechnology, and biomaterial functionalization, these hydrogels have the potential to revolutionize personalized medicine, cell therapies and regenerative medicine. By combining novel crosslinking strategies, stimuli-responsive systems and advanced drug delivery platforms, thermoresponsive hydrogels will play an increasingly important role in tissue repair, wound healing and the regeneration of complex tissues, bringing us closer to effective, scalable and accessible solutions for tissue engineering.

5. Conclusion

Thermoresponsive hydrogels represent a promising class of biomaterials with significant potential in tissue engineering and regenerative medicine. Their unique ability to undergo reversible sol-gel transitions in response to temperature changes makes them ideal for minimally invasive applications, such as injectable scaffolds and controlled drug delivery systems. Their high water content and ability to mimic the natural extracellular matrix (ECM) offer key advantages for supporting cell survival, differentiation and tissue integration, making them suitable for a wide range of tissue types, including cartilage, bone, neural, cardiac, skin and vascular tissues (Burdick & Prestwich, 2011; Li & Mooney, 2016; Peppas et al., 2006).

While substantial progress has been made in developing thermoresponsive hydrogels with improved biocompatibility, biodegradability and mechanical properties, several challenges remain. Issues such as inconsistent gelation kinetics, mechanical instability and limited biodegradability need to be addressed for these hydrogels to meet the demanding requirements of clinical applications. Additionally, the integration of nanomaterials, bioactive molecules, and advanced bio-fabrication techniques, such as 3D/4D printing, holds great promise for overcoming these limitations and enhancing the performance of thermoresponsive hydrogels (Wang et al., 2025; Lin et al., 2023).

Looking forward, the future of thermoresponsive hydrogels in tissue engineering lies in their ability to seamlessly integrate with cell-based therapies, personalized medicine and multifunctional drug delivery systems. As research progresses, new innovations in hybrid nanocomposite materials, stimuli-responsive systems and controlled release mechanisms will unlock new therapeutic possibilities. Advances in bio-fabrication and clinical translation will also be critical in ensuring that these materials can be safely and effectively used in human patients (Liu et al., 2023; Ramanathan, 2024).

In conclusion, thermoresponsive hydrogels are at the forefront of regenerative medicine, offering innovative solutions for tissue repair and replacement. Continued interdisciplinary research, collaboration and development will pave the way for their widespread adoption in clinical practice, ultimately improving patient outcomes and advancing the field of regenerative therapies (Peppas et al., 2006; Hoffman, 1995).

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