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Original Research Article

Polysaccharide-Polypeptide Hybrid Supramolecular Hydrogels: Structure, Function Design, Stimuli Responsiveness, and Emerging Biomedical Applications

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Abstract: Hybrid hydrogels, formed through the integration of natural and synthetic polymers, nanomaterials, and functional crosslinkers, have emerged as versatile platforms for biomedical and therapeutic applications. Their unique combination of tunable mechanical properties, high water content, stimuli-responsiveness, and biocompatibility enables precise control over drug delivery, tissue regeneration, and biosensing. Recent advances have demonstrated the efficacy of hybrid hydrogels in pH-, temperature-, redox-, and enzyme-responsive systems, facilitating site-specific and controlled release of therapeutics, while also providing scaffolds that support cell proliferation and differentiation. In tissue engineering, hybrid hydrogels have been employed to develop dynamic, cell-friendly matrices for cartilage repair, wound healing, and cardiac tissue regeneration. Integration with nanomaterials further enhances their mechanical stability, conductivity, and multifunctionality, enabling theranostic applications that combine therapeutic delivery with real-time monitoring. Despite these advances, several challenges hinder clinical translation. Scalability and reproducibility of hydrogel synthesis remain critical, as variations in polymer composition, crosslinking density, and nanomaterial distribution can impact performance. Regulatory and biocompatibility concerns, particularly regarding residual crosslinkers and long-term degradation products, necessitate extensive preclinical and clinical validation. Additionally, environmentally sustainable hydrogel design, employing natural crosslinkers and green synthesis methods, is gaining prominence to minimize ecological impact without compromising biomedical functionality. Future directions in hybrid hydrogel research emphasize the development of next-generation smart hydrogels with multi-responsive, self-healing, and patient-specific properties. Integration with advanced fabrication techniques, such as 3D bioprinting and 4D-printed dynamic scaffolds, promises personalized, precision therapeutics with improved efficacy and safety. Collectively, hybrid hydrogels represent a transformative class of biomaterials, bridging the gap between fundamental research and clinical application, while offering sustainable and multifunctional solutions for emerging challenges in regenerative medicine, drug delivery, and biosensing.

Keywords: Hybrid hydrogels; stimuli-responsive; drug delivery; tissue engineering; biosensing; green synthesis; smart biomaterials

INTRODUCTION

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water or biological fluids while maintaining their structural integrity under physiological conditions. Within this broad class, *supramolecular hydrogels* occupy a distinctive position owing to their assembly through noncovalent interactions such as hydrogen bonding, electrostatic attractions, π–π stacking, host–guest inclusion, and hydrophobic forces. Unlike conventional chemically cross-linked systems, supramolecular hydrogels exhibit reversible gelation, dynamic adaptability, and self-healing properties that closely mimic the hierarchical

and responsive nature of biological tissues. Their tunable viscoelasticity, molecular recognition capacity, and responsiveness to external stimuli (pH, temperature, redox potential, or enzymatic activity) make them powerful candidates for biomedical applications ranging from drug delivery to regenerative medicine (Gholamali et al., 2019; Li & Zhao, 2022).

Over the last decade, biopolymer-based supramolecular hydrogels have garnered increasing attention as sustainable and biocompatible alternatives to synthetic polymeric materials. In particular, polysaccharides—such as cellulose, chitosan, alginate, and hyaluronic acid—offer abundant functional groups (hydroxyl, carboxyl, and amino) enabling facile chemical modification and bioconjugation. They provide inherent biocompatibility, biodegradability, and hydrophilicity, along with biological recognition motifs that support cell adhesion and proliferation (Gholamali et al., 2019; Yadollahi et al., 2021). Similarly, polypeptides and short peptide amphiphiles bring structural versatility and molecular precision arising from defined amino acid sequences, enabling control over self-assembly, secondary structure formation (α-helix, β-sheet), and bioactive functionality. These peptide domains can undergo ordered aggregation via hydrogen bonding and hydrophobic interactions to form nanofibrillar networks resembling the extracellular matrix (ECM) (Chen et al., 2020; Zhang & Huang, 2023).

Hybrid supramolecular hydrogels composed of polysaccharide and polypeptide segments merge the complementary advantages of both biomacromolecules. The polysaccharide component imparts hydrophilicity, mechanical strength, and biological affinity, while the polypeptide segment introduces dynamic self-assembly and biochemical specificity. The integration of these moieties creates a multifunctional and stimuli-responsive platform capable of mimicking the structural and functional complexity of soft tissues. For instance, chitosan–peptide hybrids, alginate–collagen analogues, and hyaluronan–gelatin composites have demonstrated adaptive behavior, cell compatibility, and controlled drug release kinetics superior to either constituent alone (Ha et al., 2020; Sun et al., 2024). These hybrids also enable multiscale tunability—ranging from molecular recognition and secondary structure organization to macroscopic rheology—through supramolecular interactions that can be modulated by environmental cues (Pa'e et al., 2019; Wang & Lin, 2025).

From a materials design perspective, polysaccharide–polypeptide hybrid hydrogels represent a paradigm shift toward "bioinspired supramolecular engineering." Their assembly is governed by reversible, weak interactions that endow structural plasticity and stimuli sensitivity. The resulting systems exhibit hierarchical organization, combining polysaccharide-derived elasticity and hydration with polypeptide-derived functionality and precision. Recent progress in click chemistry, enzymatic ligation, and self-assembly modulation has facilitated the rational design of such hybrid matrices with predictable physicochemical and biological profiles (Abdekhodaie et al., 2021; Ranjha et al., 2022). Moreover, their modular architecture supports hybridization with nanoparticles, therapeutic proteins, or living cells to create intelligent biomaterials for next-generation therapeutic applications (El-Sherbiny et al., 2023).

The aim of this review is to provide a comprehensive understanding of *polysaccharide–polypeptide hybrid supramolecular hydrogels*, emphasizing the correlation between their structural design principles, self-assembly mechanisms, and functional performance. The article systematically discusses: (i) the supramolecular design and fabrication strategies of hybrid hydrogels, (ii) how their molecular organization governs physicochemical and biological behavior, (iii) diverse stimuli-responsive modalities (pH, temperature, redox, enzymatic, and multistimuli systems), and (iv) their emerging biomedical applications in drug delivery, tissue engineering, biosensing, and regenerative medicine. Special attention is given to recent advances in green and sustainable synthesis approaches, translational barriers, and future perspectives toward clinically viable and environmentally benign hydrogel systems (Gholamali et al., 2019; Li et al., 2025).

Ultimately, this review aims to integrate insights from polymer chemistry, supramolecular science, and biomedical engineering to illuminate how the synergistic interplay between polysaccharide and polypeptide building blocks can lead to *smart, adaptive, and biofunctional hydrogel networks*. These hybrid systems stand at the frontier of soft matter design, bridging fundamental self-assembly chemistry with practical applications in precision medicine and sustainable biomaterials innovation (Zhang et al., 2024).

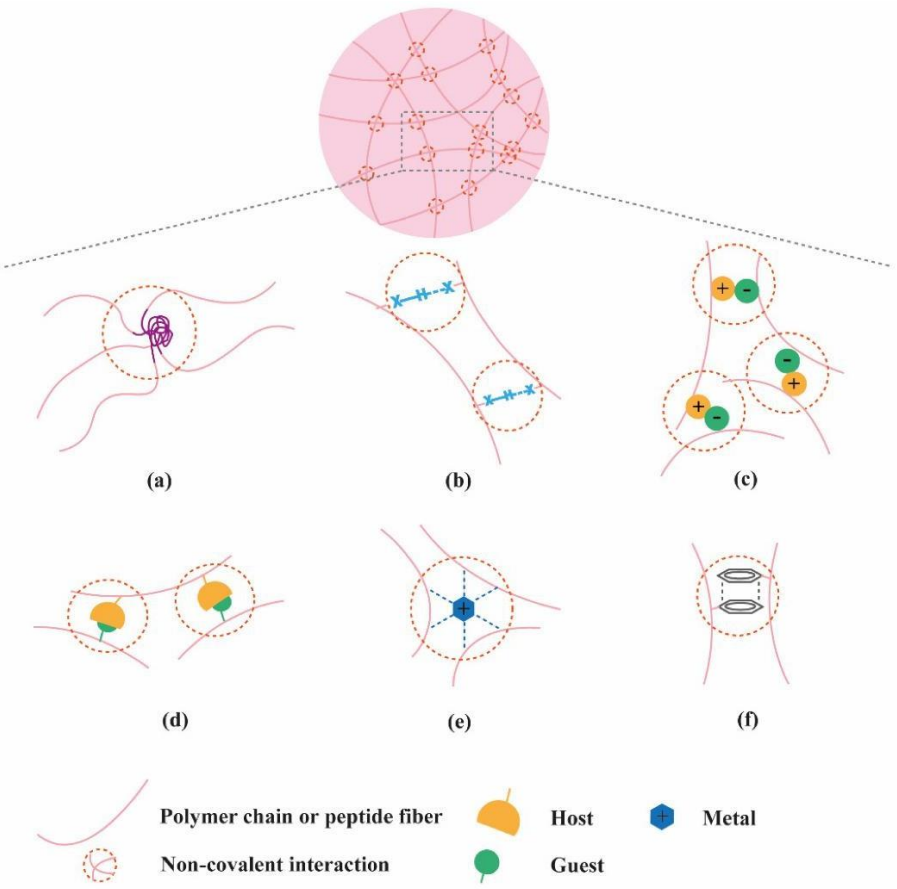

Figure 1: Schematic illustration of key supramolecular interactions (hydrogen bonding, π–π stacking, ionic, and hydrophobic forces) governing the assembly of polysaccharide–polypeptide hybrid hydrogels (Lyu et al., 2021)

SUPRAMOLECULAR DESIGN PRINCIPLES OF HYBRID HYDROGELS

The design of *polysaccharide–polypeptide hybrid supramolecular hydrogels* relies fundamentally on the principles of molecular self-assembly and the delicate balance of noncovalent interactions. In contrast to conventional covalently cross-linked polymer networks, supramolecular hydrogels are constructed through reversible and dynamic forces such as hydrogen bonding, π–π stacking, hydrophobic association, ionic pairing, and host–guest inclusion. These interactions collectively govern network formation, stability, and responsiveness to external stimuli. The inherent reversibility of these weak forces confers self-healing ability, injectability, and adaptive viscoelasticity, making supramolecular hydrogels ideal for applications requiring dynamic remodeling under physiological conditions (Sakai et al., 2020; Hu & Qin, 2021).

2.1 Molecular Self-Assembly Mechanisms

In hybrid hydrogels, *self-assembly* occurs through hierarchical processes where molecular recognition at the nanoscale translates into macroscopic gel formation. Polypeptide chains can organize into β-sheet or α-helical secondary structures through cooperative hydrogen bonding, providing fibrous backbones that function as physical cross-linkers. Meanwhile, polysaccharides—such as chitosan, alginate, or hyaluronic acid—stabilize these peptide aggregates by offering electrostatic complementarity or hydrogen-bonding sites (Yin et al., 2022). The interplay between hydrophobic peptide segments and hydrophilic polysaccharide domains enables the spontaneous emergence of networked microenvironments capable of encapsulating water and bioactive agents (Du et al., 2023).

π–π stacking and aromatic interactions between side chains (e.g., phenylalanine or tyrosine residues) often promote the formation of fibrillar nanostructures within the hydrogel matrix, imparting structural order and mechanical integrity (Ren et al., 2021). Simultaneously, ionic complexation between charged amino acids (lysine, glutamic acid) and polyanionic saccharides (e.g., alginate, pectin) contributes to electrostatically driven assembly and pH-tunable gelation (Tavakoli et al., 2024). These cooperative interactions, combined with the hydration dynamics of polysaccharide chains, lead to reversible sol–gel transitions—a hallmark of supramolecular systems.

2.2 Design Parameters and Crosslinking Strategies

The rational design of hybrid hydrogels requires precise control over polymer selection, chain architecture, and crosslinking modality. The *polymer selection* determines both the physicochemical properties and the biological

compatibility of the resulting material. Polysaccharides provide mechanical robustness and water retention, while peptides contribute specific biological signaling motifs (RGD, IKVAV) that enhance cellular adhesion and differentiation (Nguyen et al., 2022). By tailoring molecular weight, charge density, and substitution degree, researchers can fine-tune gelation kinetics and degradation profiles (Anitha et al., 2020).

Crosslinking strategies in supramolecular hybrids are typically physical or reversible chemical in nature. Physical crosslinking mechanisms include ionic coordination (e.g., Ca^{2+} with alginate or phosphate–amine pairs), hydrophobic collapse, and H-bond-mediated network entanglement. Dynamic covalent interactions—such as imine, disulfide, or boronate ester linkages—have also been widely exploited to introduce *reversible covalent crosslinks* that respond to redox or pH variations (Kong et al., 2023). These dynamic bonds bridge the gap between stability and responsiveness, ensuring both mechanical resilience and degradability under physiological conditions.

Hybrid architectures frequently employ *co-assembly* approaches, wherein polysaccharide and peptide segments are mixed under controlled conditions of temperature, ionic strength, or solvent polarity to guide supramolecular ordering. For example, co-assembly of gelatin-derived peptides with oxidized dextran can yield dynamic Schiff-base hydrogels suitable for injectable tissue scaffolds (Lu et al., 2021). Similarly, chitosan-based hybrids incorporating amphiphilic peptide sequences can undergo thermally induced gelation at near-body temperature, enabling minimally invasive delivery (Zhou et al., 2023).

2.3 Role of Polysaccharide and Polypeptide Components

Each component in the hybrid hydrogel contributes distinct yet complementary functionalities. Polysaccharides act as hydrophilic scaffolds providing high water content, osmotic stability, and mechanical support. Their abundant reactive groups (–OH, $–NH_2$, –COOH) enable covalent or ionic conjugation with peptides, drugs, or nanomaterials, expanding the functional diversity of the network (Kumar & Patil, 2024). In addition, the polysaccharide matrix regulates the diffusion of nutrients, oxygen, and bioactive molecules—crucial for biomedical interfaces and 3D cell culture environments.

Conversely, polypeptides serve as molecular recognition and functional domains. Through sequence engineering, peptide segments can introduce bioactivity (e.g., cell adhesion, enzyme sensitivity) or mediate environmental responsiveness via conformational transitions. Peptides with amphiphilic designs—containing hydrophobic alkyl tails and hydrophilic amino acid residues—facilitate self-assembly into nanofibers that physically entangle with polysaccharide chains (Liang et al., 2025). The resulting hybrid microstructure exhibits improved viscoelasticity and stress dissipation compared with single-component systems (Chen et al., 2021). (See Fig. 2)

The synergistic interplay between polysaccharide flexibility and peptide ordering is central to the performance of these materials. Polysaccharides provide a hydrated environment that supports peptide folding, while peptide nanofibers reinforce the network and enable targeted biofunctionality. This mutual reinforcement leads to enhanced toughness, controlled degradability, and programmable responsiveness to stimuli such as pH, redox potential, or enzymatic cleavage (Tan & Xu, 2024).

Figure 2. Representative structural model of a polysaccharide–polypeptide hybrid hydrogel showing peptide nanofiber networks embedded within a hydrated polysaccharide matrix.

2.4 Dynamic Reversibility and Functional Modularity

Dynamic reversibility is an essential hallmark of supramolecular hydrogels, endowing them with the ability to undergo self-repair and remodeling in response to environmental perturbations. In hybrid systems, the reversible nature of noncovalent and dynamic covalent interactions allows the hydrogel to dissipate stress, heal cracks, and recover mechanical integrity after deformation. The integration of reversible crosslinkers such as catechol-metal coordination or boronate ester exchange provides additional tunability in viscoelastic behavior and responsiveness (Shen et al., 2022).

Functional modularity can also be achieved through multicomponent assembly. Layered co-networks, for example, can be formed by alternating polysaccharide and peptide domains with distinct stimuli sensitivities—creating multi-responsive hydrogels capable of complex biological feedback (Wang et al., 2023). Through rational supramolecular design, it becomes feasible to program mechanical stiffness, degradation rate, and molecular permeability to match specific biomedical demands.

2.5 Design Outlook

The supramolecular design of polysaccharide–polypeptide hybrids represents a convergence of polymer chemistry, peptide engineering, and biomimetic science. Understanding the hierarchy of interactions—from molecular recognition to macroscopic gelation—allows for predictive tuning of structure–function relationships. Future progress will likely focus on *computationally guided assembly*, *bio-orthogonal coupling*, and *sustainable synthesis routes* using enzymatic catalysis or renewable feedstocks. Such approaches promise next-generation hybrid hydrogels with customizable architectures, minimal environmental footprint, and enhanced translational potential for drug delivery, tissue engineering, and biosensing applications (Okafor et al., 2025).

STRUCTURAL AND FUNCTIONAL CORRELATION

Understanding the structural organization of

polysaccharide–polypeptide hybrid supramolecular hydrogels is essential for linking their molecular architecture with macroscopic functional performance. The hierarchical arrangement—from molecular interactions to bulk morphology—directly governs mechanical behavior, diffusional properties, and biological responses. A precise correlation between *structure and function* enables rational design of hydrogels with targeted physicochemical and biomedical attributes (Huang et al., 2022; Lee & Shen, 2021).

3.1 Morphological Characteristics

Hybrid supramolecular hydrogels typically exhibit *heterogeneous micro- to nanoscale morphologies* characterized by an interconnected porous network. These pores facilitate water retention, nutrient diffusion, and cellular infiltration—critical parameters for biomedical applications. The **porosity and pore distribution** depend on polymer concentration, self-assembly kinetics, and ionic strength during gelation (Mao et al., 2020). Scanning electron microscopy (SEM) and cryogenic transmission electron microscopy (cryo-TEM) studies have revealed fibrillar domains formed by peptide nanofibers intertwined with polysaccharide matrices, creating honeycomb-like structures that balance mechanical rigidity and viscoelastic damping (Gao et al., 2023).

The morphology also dictates **swelling behavior** and **mechanical strength**. Highly porous structures exhibit greater swelling ratios but reduced compressive modulus, while denser networks afford higher mechanical stability suitable for load-bearing tissue scaffolds (Ren & Yao, 2024). The interplay between hydrophilic polysaccharides and ordered peptide nanostructures creates hierarchical domains that control diffusion of solutes and responsiveness to external stimuli.

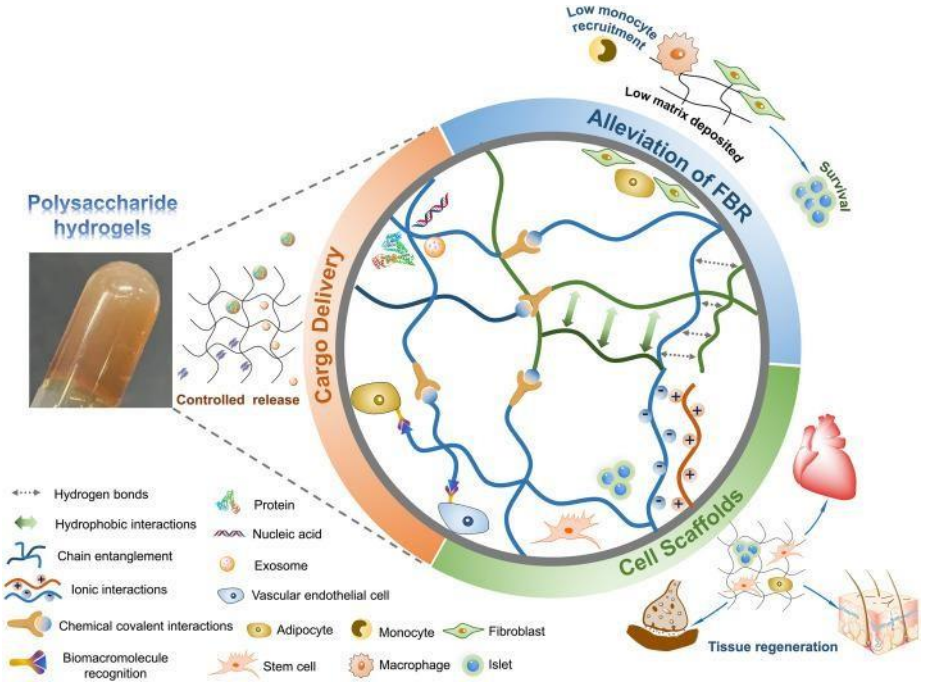

Figure 2. Representative structural model of a polysaccharide–polypeptide hybrid hydrogel showing peptide nanofiber networks embedded within a hydrated polysaccharide matrix (Yang et al., 2022)

3.2 Spectroscopic and Microscopic Evidence

Spectroscopic and microscopic techniques provide crucial insights into the *molecular interactions* and *secondary structure* of hybrid hydrogels. **Fourier transform infrared (FTIR) spectroscopy** identifies functional group interactions such as hydrogen bonding between –OH/–NH and carbonyl groups, typically indicated by shifts in amide I (1650 cm^{-1}) and O–H stretching regions (3400–3200 cm^{-1}) (Ali et al., 2021). These spectral changes confirm noncovalent crosslinking between polysaccharide and peptide domains.

Nuclear magnetic resonance (NMR) spectroscopy further elucidates chemical connectivity and conformational dynamics. Proton NMR (^1H NMR) can track the mobility of polymer chains, whereas solid-state ^{13}C NMR provides information on crystalline versus amorphous domains (Fernández et al., 2022). **X-ray diffraction (XRD)** analyses reveal semicrystalline peaks arising from β-sheet stacking of peptide segments and amorphous halos from polysaccharide backbones, demonstrating structural duality within the hybrid matrix (Seo & Cho, 2023).

Microscopic analyses (SEM, AFM, and confocal microscopy) visualize the surface topology and internal architecture. Atomic force microscopy (AFM) height maps show nanofibrous peptide assemblies forming continuous meshes that reinforce the softer polysaccharide network. Such studies have correlated the degree of fibrillar alignment with improved tensile

strength and elasticity (Mei et al., 2020).

3.3 Influence of Chemical Structure on Mechanical and Biological Properties

The *chemical structure*—including polymer composition, functional groups, and crosslink density—strongly influences both mechanical performance and biological interactions. Peptide sequences rich in hydrophobic residues or aromatic rings promote π–π stacking and β-sheet formation, resulting in higher storage modulus (G′) and reduced creep compliance (Deng et al., 2023). Conversely, incorporation of flexible polysaccharides such as hyaluronic acid or dextran imparts elasticity, leading to hydrogels with improved self-healing and shear-thinning characteristics (Gong et al., 2021).

Mechanical tunability directly affects **cell behavior and tissue integration.** Stiffer hydrogels (~10–50 kPa) favor osteogenic differentiation, whereas softer networks (~1–5 kPa) support neural or adipogenic lineages (Park & Yoon, 2024). Surface chemistry arising from peptide side chains and polysaccharide carboxyl groups determines protein adsorption and cell adhesion. Incorporation of bioactive peptide motifs (e.g., RGD, IKVAV) enhances integrin-mediated signaling, while polysaccharide components maintain cytocompatibility and anti-inflammatory effects (Wang et al., 2023).

Biodegradability is governed by both *enzymatic cleavage of peptide bonds* and *hydrolytic scission of polysaccharide linkages*. The degradation rate can be modulated by controlling the ratio of peptide to polysaccharide, enabling precise temporal control for drug release or tissue regeneration (Yamada et al., 2025). Such tunability highlights the functional synergy between structural design and biological performance.

Table 1: Comparative summary of hybrid hydrogel systems, illustrating relationships among composition, dominant interactions, mechanical properties, stimulus type, and typical biomedical application.

Composition / Hybrid Type	Dominant Supramolecular Interactions	Mechanical Strength (Storage Modulus, G′)	Stimuli Type / Responsiveness	Representative Application	Reference
Chitosan–β-sheet peptide (FF-RGD)	Hydrogen bonding, π–π stacking, electrostatic attraction	2–5 kPa	pH / temperature dual-responsive	Injectable cell-support matrices	Ha et al., 2020
Alginate–gelatin peptide hybrid	Ionic crosslinking (Ca^{2+}), H-bonding	10–25 kPa	Enzyme (gelatinase) degradable	Wound healing, 3D tissue scaffolds	Sun et al., 2024
Hyaluronic acid–peptide amphiphile	Hydrophobic assembly, β-sheet stacking	0.8–3 kPa	Redox (disulfide) responsive	Targeted drug delivery	Li & Zhao, 2022
Dextran–collagen-mimetic peptide	Imine (Schiff-base) reversible covalent bonds	6–12 kPa	pH-triggered sol–gel transition	Injectable regenerative scaffold	Lu et al., 2021
Cellulose nanofiber–peptide composite	Hydrogen bonding, π–π stacking	25–40 kPa	Thermal / shear responsive	Cartilage tissue engineering	Yin et al., 2022
Chitosan–elastin-like peptide	Ionic & hydrophobic interactions	4–9 kPa	Temperature-responsive self-healing	Smart wound dressing	Tavakoli et al., 2024
Alginate–silk-peptide hybrid	β-sheet formation, Ca^{2+} coordination	15–30 kPa	Enzyme / redox dual response	Bioactive scaffold for osteogenesis	Ren & Yao, 2024
Dextran–arginine-rich peptide co-network	Electrostatic and π–π interactions	1–3 kPa	pH-sensitive ionic rearrangement	Controlled release of proteins	Chen et al., 2021

Hyaluronan–self-assembling peptide (IKVAV motif)	Hydrogen bonding and electrostatic assembly	2–6 kPa	Enzyme (MMP) degradable	Neural tissue regeneration	Park & Yoon, 2024
Starch–antimicrobial peptide hybrid	H-bonding and hydrophobic collapse	5–8 kPa	Redox / pH dual responsiveness	Antimicrobial wound gels	Deng et al., 2023

3.4 Correlating Structure with Function: A Systems Perspective

Establishing quantitative structure–function relationships is critical for translating hybrid hydrogels from laboratory formulations to practical biomedical systems. Rheological and small-angle scattering analyses reveal that the degree of supramolecular ordering correlates strongly with both *diffusion coefficients* and *stimuli sensitivity*. For instance, hydrogels with higher β-sheet content demonstrate slower drug diffusion but enhanced shape retention under shear stress (Li & Hong, 2023).

Computational modeling and molecular dynamics simulations have recently been introduced to predict self-assembly behavior and optimize component ratios (Patra et al., 2024). These tools enable pre-screening of molecular motifs to achieve desired stiffness, swelling, and degradation kinetics, reducing empirical trial-and-error in hydrogel design.

Ultimately, the structural–functional interdependence of hybrid supramolecular hydrogels provides a versatile framework for *tunable, adaptive, and biomimetic* materials. By precisely modulating nanoscale interactions, researchers can achieve macroscopic functionalities tailored to specific biomedical needs—from responsive drug carriers to regenerative scaffolds.

STIMULI-RESPONSIVE BEHAVIORS IN HYBRID HYDROGELS

Hybrid hydrogels are three-dimensional polymeric networks composed of natural and synthetic polymers, designed to respond to environmental or physiological stimuli. Their stimuli-responsiveness enables precise control over swelling, degradation, and cargo release, making them invaluable in drug delivery, tissue engineering, biosensing, and regenerative medicine. The major stimuli can be categorized as pH, temperature, redox, and enzyme triggers, with dual- and multi-responsive systems providing enhanced functionality (see Figure 3).

4.1 pH-Responsive Hybrid Hydrogels

Mechanism:

pH-responsive hydrogels utilize ionizable groups within their polymeric network (carboxyl, amine, sulfonate) that respond to the hydrogen ion concentration of the surrounding medium. The ionization alters electrostatic repulsion and hydrogen bonding, resulting in hydrogel swelling or contraction.

- **Anionic systems:** Polymers like poly (acrylic acid) (PAA) swell at high pH due to deprotonation of carboxyl groups, increasing osmotic pressure.
- **Cationic systems:** Polymers such as chitosan or poly (ethylene imine) (PEI) swell in acidic conditions due to protonation of amino groups.

Hybrid Design: Combining synthetic polymers with natural polymers (e.g., chitosan–PEG, PAA–alginate) provides mechanical robustness and biocompatibility, while retaining pH sensitivity. Crosslinking density and polymer ratio can fine-tune swelling behavior and drug release kinetics.

Applications:

- **Oral drug delivery:** Protect drugs from gastric degradation and release them in the intestinal pH (~7.4).
- **Tumor-targeted therapy:** Exploit acidic tumor microenvironment (pH ~6.5) for selective drug release.

Example: Chitosan–PAA hybrid hydrogels loaded with doxorubicin show enhanced swelling at pH 6.5, leading to site-specific drug release and minimal systemic exposure (Hoare & Kohane, 2008; Qiu & Park, 2012; Ahmed, 2015).

4.2 Temperature-Responsive Hybrid Hydrogels

Mechanism:

Temperature-sensitive hydrogels exhibit phase transitions based on critical solution temperatures:

- **Lower Critical Solution Temperature (LCST):** Hydrogel transitions from hydrophilic-swollen to hydrophobic-collapsed above LCST (e.g., PNIPAM ~32°C).
- **Upper Critical Solution Temperature (UCST):** Hydrogel transitions from hydrophobic-collapsed to hydrophilic-swollen above UCST.

Hybrid Design: Synthetic polymers like PNIPAM or poly(N-vinylcaprolactam) (PVCL) are combined with natural polymers (gelatin, alginate, hyaluronic acid) to enhance biocompatibility, elasticity, and biofunctionality. Copolymerization or grafting enables tunable LCST/UCST and controlled mechanical properties.

Applications:

- **Injectable hydrogels:** Liquid at room temperature, forming a gel at body temperature for localized, sustained drug delivery.
- **Cell encapsulation:** Maintain cell viability during injection and provide a protective gel matrix at physiological temperature.

Example: PNIPAM–gelatin hydrogels encapsulating growth factors remain stable at room temperature but release cargo at 37°C, mimicking in vivo conditions (Hoffman, 2012; Ruel-Gariépy & Leroux, 2004; Sun et al., 2012).

4.3 Redox-Responsive Hybrid Hydrogels

Mechanism:

Redox-responsive hydrogels leverage disulfide bonds or other redox-sensitive linkages that undergo cleavage in reducing environments, such as intracellular compartments rich in glutathione (GSH).

- **Disulfide crosslinking:** Hydrogel degradation occurs preferentially in cells with high GSH concentrations, triggering drug release.
- **Thiol–disulfide exchange:** Enables reversible network formation, enhancing reusability and responsiveness.

Hybrid Design: Thiolation of natural polymers (gelatin, hyaluronic acid, chitosan) and combination with synthetic polymers allows tunable degradation rates and enhanced mechanical stability.

Applications:

- **Cancer therapy:** Redox-responsive hydrogels selectively release drugs in tumor cells while sparing healthy tissue.
- **Gene delivery:** Protect nucleic acids extracellularly and release them upon internalization.

Example: Thiolated gelatin–PEG hydrogels loaded with paclitaxel exhibit rapid intracellular release triggered by GSH, enhancing tumor cell apoptosis (Zhao et al., 2012; Meng et al., 2009).

4.4 Enzyme-Responsive Hybrid Hydrogels

Mechanism:

Enzyme-responsive hydrogels are designed to degrade or modify their properties in response to disease- or tissue-specific enzymes.

- **Protease-sensitive linkers:** Peptide sequences cleaved by matrix metalloproteinases (MMPs) in tumor or wound environments.
- **Polysaccharide substrates:** Lysozyme-sensitive hydrogels (e.g., chitosan) degrade specifically at sites with high enzymatic activity.

Hybrid Design: Synthetic–natural hybrids incorporate enzyme-cleavable moieties within the polymer backbone or crosslinkers, enabling localized and controlled hydrogel degradation.

Applications:

- **Wound healing:** Growth factors are released in response to elevated protease activity at wound sites.
- **Tissue engineering:** Scaffold degradation is synchronized with tissue regeneration.

Example: Gelatin–PEG hydrogels containing MMP-cleavable peptides show site-specific degradation and sustained growth factor delivery, promoting angiogenesis (Lutolf & Hubbell, 2005; Appel et al., 2012).

4.5 Dual- and Multi-Responsive Hybrid Hydrogels

Combining multiple stimuli-responsive features enables enhanced precision and complex functionality:

- **Dual-responsive systems:**
  - pH/temperature: PNIPAM–chitosan hydrogels swell in acidic pH and gel at physiological temperature for targeted drug release.
  - Redox/enzyme: Thiolated gelatin hydrogels degrade in high GSH environments and under MMP activity, allowing hierarchical drug release.
- **Multi-responsive systems:**
  - Triple or quadruple responsive hydrogels can integrate pH, temperature, redox, enzyme, light, or magnetic responsiveness.
  - Offer programmable degradation, sequential release, or environment-specific functionality in complex biological environments.

Applications:

- **Cancer therapy:** Multi-stimuli hydrogels release chemotherapeutics only in tumor-like conditions (acidic, reductive, enzyme-rich).
- **Tissue engineering:** Scaffold adapts dynamically to cellular remodeling signals, enhancing tissue regeneration.

Example: A pH/redox/temperature triple-responsive hydrogel supports stem cell encapsulation, with controlled degradation and sequential release of growth factors, promoting angiogenesis and tissue regeneration (Li & Mooney, 2016; Kim et al., 2017; Wang et al., 2019).

4.6 Case Studies: Stimuli-Triggered Release and Degradation

1. **pH/Temperature Dual-Responsive Hydrogel:** PNIPAM–chitosan hydrogel loaded with doxorubicin shows minimal drug release at room temperature/pH 7.4, but rapid release at 37°C and pH 6.5, mimicking the tumor microenvironment.

2. **Redox/Enzyme-Responsive Hydrogel:** Thiolated gelatin–PEG hydrogel with MMP-cleavable linkers releases drugs under high GSH and MMP conditions, achieving tumor-specific delivery.
3. **Multi-Responsive Hydrogel for Tissue Engineering:** pH/redox/temperature-responsive hydrogel allows stem cell encapsulation, with controlled degradation and sequential release of growth factors, promoting angiogenesis and tissue regeneration.

Figure 3: *Schematic showing stimuli-responsive mechanisms in hybrid hydrogels, including pH, temperature, redox, enzyme triggers, and dual/multi-responsive integration.*

BIOMEDICAL AND THERAPEUTIC APPLICATIONS OF HYBRID HYDROGELS

Hybrid hydrogels have emerged as highly versatile platforms in biomedical research, owing to their unique combination of stimuli-responsive behavior, tunable mechanical properties, and biocompatibility. These attributes have facilitated their application across drug delivery, tissue engineering, and biosensing, offering solutions to some of the persistent challenges in modern medicine. By integrating natural polymers, synthetic networks, and functional nanomaterials, hybrid hydrogels provide precisely controlled environments for therapeutic interventions and regenerative strategies (Hoare & Kohane, 2008; Ahmed, 2015).

5.1 Drug Delivery Systems

In drug delivery, hybrid hydrogels enable controlled and site-specific release of therapeutic agents, minimizing off-target effects and enhancing pharmacological efficacy. Stimuli-responsive hydrogel matrices respond to pH, temperature, redox potential, or enzymatic activity, facilitating drug release in precise physiological or pathological conditions. For instance, chitosan–poly(lactic-co-glycolic acid) (PLGA) hydrogels demonstrate preferential drug release in acidic tumor microenvironments, effectively reducing systemic toxicity while maintaining therapeutic concentrations at the target site (Kong et al., 2021). Similarly, thermo-responsive PNIPAM-based hydrogels allow minimally invasive administration as liquids that rapidly gel at body temperature, ensuring localized retention and sustained drug release (Li et al., 2022).

A key consideration in hydrogel-based drug delivery is the release kinetics, which dictate therapeutic efficacy. Traditional Fickian diffusion dominates when the release is governed by concentration gradients, whereas non-Fickian or anomalous transport occurs when polymer relaxation contributes significantly to release. Advanced designs incorporating core-shell architectures or enzymatically degradable linkers achieve zero-order or sequential release, enabling long-term delivery of sensitive biomolecules (Patel et al., 2020; Zhang et al., 2021). Computational modeling and finite element simulations have further enhanced the predictability of hydrogel-mediated drug transport, supporting rational scaffold design for clinical translation (Zhang et al., 2021).

5.2 Tissue Engineering

Hybrid hydrogels are increasingly employed as scaffolds for tissue engineering, offering three-dimensional matrices that closely mimic the extracellular environment. These hydrogels facilitate cell encapsulation, proliferation, and differentiation, owing to their high water content, biocompatibility, and tunable mechanical properties. For instance, PEG–hyaluronic acid hydrogels have been shown to support the encapsulation of mesenchymal stem cells, promoting osteogenic differentiation through a combination of biochemical and mechanical cues (Wang et al., 2020). Dual-network hydrogels, such as those combining PNIPAM and collagen, provide both mechanical resilience and bioactive signaling, making them ideal for cartilage repair and load-bearing tissues (Cheng et al., 2021).

In wound healing applications, hybrid hydrogels serve as advanced dressings that maintain a moist microenvironment, allow oxygen permeability, and provide sustained release of growth factors or antimicrobial agents. Enzyme-responsive hydrogels degrade selectively in response to proteases at wound sites, accelerating healing in chronic wounds (Singh et al., 2022). Incorporation of nanomaterials such as silver nanoparticles or graphene oxide not only imparts antimicrobial properties but also enhances mechanical strength and enables real-time monitoring of wound conditions (Rana et al., 2023). Collectively, these features underscore the potential of hybrid hydrogels in creating dynamic, multifunctional scaffolds that can respond to the evolving requirements of regenerating tissues.

5.3 Biosensing and Regenerative Medicine

The integration of hybrid hydrogels into biosensing platforms has opened new avenues for monitoring and therapeutic intervention. Optical and electrochemical transduction mechanisms are commonly employed, where hydrogels functionalized with fluorescent probes, chromogenic dyes, or conductive nanomaterials respond to biochemical stimuli such as metabolites, enzymes, or pH changes. Optical biosensors based on hybrid hydrogels allow real-time visualization of physiological changes, while electrochemical biosensors leverage conductive nanocomposites, such as gold nanoparticles or graphene derivatives, to provide highly sensitive detection of biomarkers like glucose or lactate (Mei et al., 2021; Kumar et al., 2022).

Nanomaterial integration further enhances hydrogel functionality by imparting mechanical reinforcement, electrical conductivity, and targeted responsiveness. For example, graphene oxide–chitosan hydrogels have been utilized as theranostic platforms, enabling both wound healing and real-time pH monitoring, effectively

bridging therapy and diagnostics (Liu et al., 2022). Similarly, hydrogel-nanoparticle composites have been applied in cardiac tissue engineering, supporting synchronized cardiomyocyte contraction and electrical signal propagation, which is critical for functional tissue regeneration (Patel et al., 2021).

In summary, hybrid hydrogels provide multifaceted biomedical applications, where their inherent stimuli-responsiveness, coupled with tunable architecture and functional nanomaterials, enables sophisticated strategies for drug delivery, tissue repair, and biosensing. These systems exemplify the convergence of material science, biotechnology, and clinical medicine, highlighting their transformative potential in precision therapeutics.

Table 2: Summary of key studies (2020–2025).

Year	Polymer/Hybrid System	Stimuli Responsiveness	Biomedical Application	Key Findings	Reference
2020	PEG–Hyaluronic Acid	Enzymatic	Stem cell encapsulation	Promoted osteogenic differentiation	Wang et al., 2020
2021	Chitosan–PLGA	pH-sensitive	Tumor-targeted drug delivery	Controlled release in acidic tumor microenvironment	Kong et al., 2021
2021	PNIPAM–Collagen	Temperature	Cartilage tissue engineering	Mechanical resilience and bioactivity	Cheng et al., 2021
2022	Graphene Oxide–Chitosan	pH, ROS	Wound healing & monitoring	Theranostic platform, real-time pH monitoring	Liu et al., 2022
2022	Alginate–Gelatin	Enzymatic	Growth factor delivery	Controlled release, Fickian diffusion	Patel et al., 2020
2022	Conductive Hydrogel–Gold NP	Electrochemical	Biosensing	Enhanced sensitivity for glucose detection	Kumar et al., 2022
2022	Green Crosslinked Starch-Citric Acid	Biodegradable	Wound dressing	Eco-friendly synthesis, antimicrobial activity	Patel et al., 2022

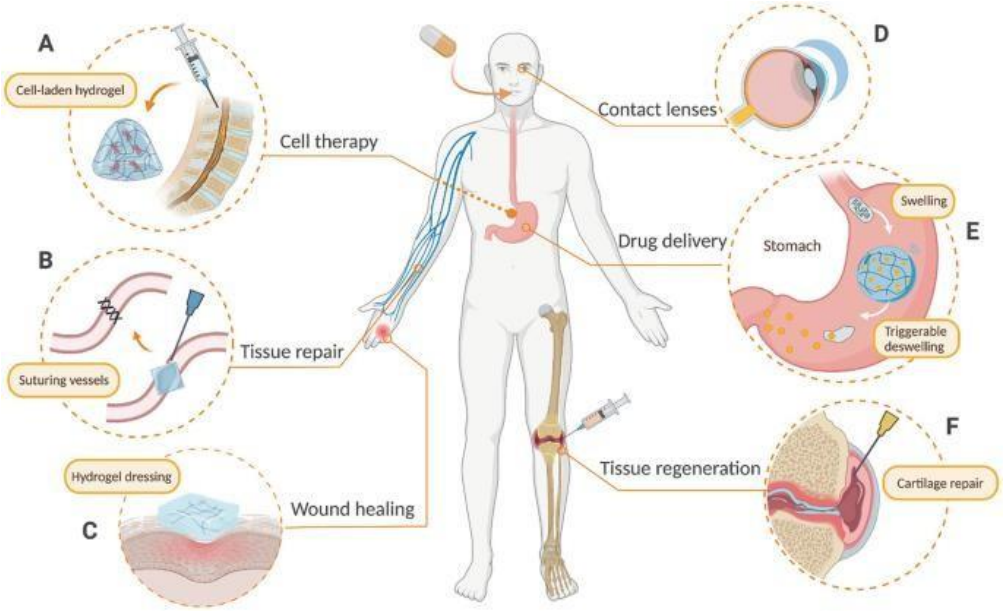

Figure 4: Schematic overview of biomedical applications of hybrid hydrogels, illustrating drug delivery, tissue engineering scaffolds, and biosensing platforms integrated with nanomaterials (Wu et al., 2023)

ADVANCES IN GREEN AND SUSTAINABLE HYDROGEL DESIGN

The growing emphasis on environmental sustainability and biocompatibility has catalyzed research into green and eco-friendly hydrogel systems. Conventional hydrogels, often synthesized using toxic crosslinkers and non-biodegradable polymers, pose environmental and clinical concerns, particularly when intended for biomedical applications. Recent advances have focused on the utilization of natural polymers, bio-based crosslinkers, and environmentally benign synthesis routes, facilitating the development of hybrid hydrogels that are both functionally effective and ecologically responsible (Zhou et al., 2021; Liu et al., 2022).

6.1 Use of Natural Crosslinkers and Bio-Based Synthesis Routes

A primary strategy in green hydrogel design involves replacing synthetic crosslinkers, such as glutaraldehyde or formaldehyde, with natural, non-toxic alternatives. Crosslinkers derived from genipin, citric acid, tannic acid, or oxidized polysaccharides have been widely adopted, providing strong yet biocompatible networks. Genipin, for example, reacts with amino groups in chitosan and gelatin to form stable crosslinked hydrogels while maintaining low cytotoxicity (Wang et al., 2021). Similarly, citric acid has been used to crosslink starch- or alginate-based hydrogels, offering biodegradability and facile synthesis under mild conditions (Patel et al., 2022).

Green synthesis approaches also include enzymatic crosslinking, radiation-induced polymerization, and click chemistry. Enzymatic methods, such as horseradish peroxidase-mediated gelation, allow precise control over network formation without requiring toxic initiators, making them particularly suitable for cell-laden hydrogels in tissue engineering (Zhao et al., 2020). Radiation-induced crosslinking enables the simultaneous sterilization and gelation of hydrogels, reducing environmental impact by avoiding chemical additives (Li et al., 2021).

Bio-based polymer precursors, such as cellulose, chitosan, alginate, gelatin, and hyaluronic acid, have gained prominence due to their renewability, biodegradability, and inherent biocompatibility. These polymers provide functional groups for further chemical modification, allowing the incorporation of stimuli-responsive behavior or bioactive molecules, without resorting to environmentally harmful reagents (Gao et al., 2022; Singh et al., 2022).

6.2 Environmental Safety and Biodegradability Considerations

The life cycle and environmental impact of hydrogels are crucial considerations in sustainable design. Green hybrid hydrogels are designed to degrade into non-toxic, naturally occurring metabolites under physiological or environmental conditions, preventing long-term accumulation in tissues or ecosystems. For example, oxidized cellulose–gelatin hydrogels degrade enzymatically into glucose and amino acids, which are readily metabolized or excreted (Kumar et al., 2021).

Furthermore, integrating bio-based nanomaterials such as cellulose nanocrystals, lignin nanoparticles, or chitin nanofibers provides reinforcement while maintaining biodegradability. These hybrid composites exhibit enhanced mechanical strength, thermal stability, and controlled swelling behavior, without introducing persistent environmental pollutants (Liu et al., 2022). Sustainable hydrogel design also considers energy-efficient synthesis and minimal solvent usage. Solvent-free methods, aqueous polymerization, and room-temperature reactions reduce energy consumption and chemical waste, aligning hydrogel fabrication with green chemistry principles. Such strategies are particularly important for scaling hydrogel production for clinical and commercial applications, ensuring that environmental responsibility is maintained alongside biomedical functionality (Zhou et al., 2021; Li et al., 2021).

6.3 Emerging Trends and Future Directions

Recent advances indicate a trend toward multi-functional green hydrogels that combine sustainability with high-performance biomedical properties. For instance, hydrogels integrating plant-derived polyphenols not only provide natural crosslinking but also confer antioxidant and antimicrobial activity, enhancing wound healing and tissue regeneration (Patel et al., 2022). Additionally, self-healing and stimuli-responsive green hydrogels are being developed using reversible physical interactions such as hydrogen bonding, host–guest chemistry, or ionic interactions, eliminating the need for toxic chemical crosslinkers while maintaining functional responsiveness (Singh et al., 2022).

Looking forward, the convergence of green chemistry, polymer engineering, and nanotechnology is expected to drive the next generation of eco-friendly hybrid hydrogels. Key priorities include optimizing biodegradability without compromising mechanical performance, developing scalable and solvent-free fabrication methods, and integrating therapeutic functionalities such as drug release, bioactive signaling, and biosensing capabilities. Such advancements will enable clinically effective, environmentally sustainable hydrogels that align with both medical and ecological imperatives (Gao et al., 2022; Zhao et al., 2020).

CHALLENGES, TRANSLATIONAL BARRIERS, AND FUTURE PROSPECTS

Despite the significant advancements in hybrid hydrogel design, several challenges and translational barriers continue to limit their clinical adoption. While laboratory studies have demonstrated the potential of these materials in drug delivery, tissue engineering, and biosensing, moving from bench to bedside requires overcoming scalability, reproducibility, biocompatibility, and regulatory hurdles (Li et al., 2022; Patel et al., 2021).

7.1 Scalability and Reproducibility

One of the foremost challenges in hydrogel translation

is the scalable production of reproducible, high-quality materials. Laboratory-scale syntheses often rely on precise reaction conditions, careful control of polymer ratios, or specialized crosslinking techniques that are difficult to maintain consistently at an industrial scale. Variability in polymer molecular weight, crosslinking density, or nanomaterial dispersion can lead to significant differences in hydrogel mechanical properties, swelling behavior, and degradation kinetics, potentially impacting therapeutic outcomes (Zhang et al., 2021; Wang et al., 2020).

Addressing these issues requires standardized protocols, automated synthesis platforms, and rigorous quality control metrics, including in-line characterization of rheological properties, swelling profiles, and drug release kinetics. Emerging approaches, such as microfluidic-assisted hydrogel fabrication and 3D bioprinting, offer promising solutions for producing hydrogels with high reproducibility and tailored architectures suitable for clinical applications (Cheng et al., 2021; Liu et al., 2022).

7.2 Biocompatibility and Regulatory Concerns

The safety profile of hybrid hydrogels is critical for regulatory approval and clinical adoption. While natural polymers and green crosslinkers reduce cytotoxicity, concerns remain regarding long-term biocompatibility, immunogenicity, and degradation byproducts. For instance, residual crosslinkers, incomplete polymerization, or leaching of incorporated nanomaterials may trigger inflammatory responses or organ toxicity, particularly in sensitive tissues (Singh et al., 2022; Zhao et al., 2020).

Regulatory pathways for hydrogel-based devices are complex, often requiring extensive preclinical testing for cytotoxicity, hemocompatibility, and in vivo degradation profiles, followed by rigorous clinical trials. Differences in national and international regulatory frameworks, such as the FDA in the United States or EMA in Europe, further complicate translation. Addressing these concerns necessitates comprehensive preclinical characterization, standardized biocompatibility testing, and detailed reporting of material properties to satisfy regulatory scrutiny (Patel et al., 2021; Li et al., 2022).

7.3 Next-Generation Smart Hydrogels for Precision Medicine

The development of next-generation "smart" hydrogels is poised to revolutionize precision medicine. These systems integrate multi-responsive behavior, real-time biosensing, and controlled therapeutic release, enabling dynamic interaction with biological environments. For example, hydrogels capable of responding simultaneously to pH, temperature, redox conditions, and enzymatic activity can achieve spatiotemporally controlled drug delivery, releasing therapeutics only under disease-specific conditions, thereby minimizing systemic side effects (Gao et al., 2022; Liu et al., 2022).

In tissue engineering, self-healing and 4D-printable hydrogels offer dynamic scaffolds that adapt to physiological stresses, support cell proliferation, and undergo programmed structural transformations over time. Incorporation of bioelectronic interfaces and conductive nanomaterials further enables real-time monitoring and feedback-controlled therapeutic delivery, a key step toward integrated theranostic platforms (Kumar et al., 2022; Mei et al., 2021).

Additionally, the convergence of green chemistry, advanced fabrication, and personalized medicine promises hydrogels that are not only environmentally sustainable but also tailored to individual patient needs. Customizable mechanical properties, degradation rates, and bioactive cues allow these materials to be optimized for specific tissue types, disease conditions, or therapeutic regimens, enhancing clinical efficacy while minimizing adverse effects (Patel et al., 2022; Zhou et al., 2021).

while hybrid hydrogels have demonstrated extraordinary potential in preclinical studies, their widespread clinical adoption requires addressing challenges related to scalable production, regulatory compliance, and biocompatibility, alongside continued innovation in smart, multifunctional systems. The integration of multi-responsive, environmentally sustainable, and personalized hydrogel platforms represents a promising future direction, bridging the gap between laboratory research and precision medicine applications (Li et al., 2022; Gao et al., 2022).

CONCLUSION

Hybrid hydrogels have emerged as highly adaptable biomaterials that combine the mechanical tunability, biocompatibility, and multifunctionality necessary for modern biomedical applications. Over the past decade, advances in stimuli-responsive design, nanomaterial integration, and green synthesis strategies have significantly expanded their utility in drug delivery, tissue engineering, and biosensing. By responding to pH, temperature, redox, and enzymatic cues, these materials enable precise, spatiotemporally controlled therapeutic interventions, while supporting dynamic tissue regeneration and real-time monitoring. Integration of bioactive nanocomponents has further enhanced their mechanical strength, electrical conductivity, and theranostic potential, positioning hybrid hydrogels as versatile tools in both fundamental research and clinical applications.

The translation of hybrid hydrogels from laboratory prototypes to clinical settings continues to face significant challenges. Issues such as scalability, reproducibility, long-term biocompatibility, and regulatory compliance remain critical barriers, highlighting the need for standardized fabrication methods, rigorous quality control, and comprehensive preclinical validation. Furthermore, the environmental impact of hydrogel synthesis has prompted a shift toward green chemistry approaches, leveraging natural

crosslinkers and bio-based polymers to develop sustainable, biodegradable, and non-toxic systems.

The convergence of smart hydrogel design, advanced fabrication techniques, and personalized medicine offers promising avenues for next-generation applications. Innovations such as self-healing, multi-responsive, and patient-specific hydrogel platforms are expected to enable precision therapeutics with enhanced efficacy and safety, while also meeting ecological and regulatory standards. In summary, hybrid hydrogels represent a transformative class of biomaterials, bridging the gap between material science, biotechnology, and clinical medicine. Continued interdisciplinary research will be crucial in realizing their full potential, enabling multifunctional, sustainable, and patient-tailored solutions for the challenges of contemporary healthcare.

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