# Advancements in Programmable Hydrogels: Synthesis, Characterization, and Their Applications in Medicine

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**Abstract.** This article establishes an integrated framework for programmable hydrogels, clarifying design principles, characterization methods, and core uses in healthcare and agriculture while assessing the contribution of nanotechnology. Hydrogels are three-dimensional hydrophilic polymer networks whose properties can be tuned by chemical crosslinking, physically assembled networks, and hybrid strategies—including 3D/4D printing—to control stiffness, toughness, and responsiveness to pH, temperature, light, electric or magnetic fields, and biological cues. Incorporating nanomaterials such as metallic or magnetic nanoparticles, carbon nanostructures, and DNA architectures enhances mechanical strength, conductivity, biocompatibility, and logic-encoded responsiveness, enabling dynamic "smart" behavior. Optimization relies on multiscale characterization combining mechanical testing, thermal analysis (DSC/TGA), imaging (SEM/TEM), atomic force microscopy, and swelling studies to link structure, stability, and morphology with function. Applications include controlled drug delivery, biomimetic scaffolds for adhesion and tissue regeneration, biosensing interfaces, soft robotic actuators, and targeted agro-environmental systems. Advances at the intersection of materials science, nanotechnology, and advanced fabrication point to a new generation of multifunctional hydrogels with strong translational potential, while highlighting remaining challenges in durability, long-term biocompatibility, manufacturing reproducibility, and precise spatiotemporal control of responses. An earlier version of this work was posted as a preprint on ChemRxiv [1].

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# 1 Introduction

Hydrogels are three-dimensional, hydrophilic polymer networks that can retain large amounts of water, mimicking natural tissue environments. They can be derived from natural biomaterials like collagen and alginate or synthetic polymers like polyethylene glycol and polyacrylamide. Key properties include mechanical strength, biodegradability, and biocompatibility, which can be tailored for various applications. Their high water content facilitates nutrient and waste exchange, promoting cell growth and supporting tissue formation, making them ideal for biomedicine, sensing, and tissue engineering applications [2]. A hydrogel is an insoluble three-dimensional network of polymers capable of absorbing biological fluids. It is formed through physical or chemical cross-linking, with chemical hydrogels relying on covalent forces and physical hydrogels on weaker secondary forces. Key properties of hydrogels include their swelling capacity, mechanical strength, and biological compatibility, which influence their morphology and structure. These attributes enable hydrogels to mimic the extracellular matrix (ECM), making them suitable for various applications in medicine and other fields [3]. Hydrogels are special materials that can hold water and form three-dimensional networks. They possess unique properties, including high water content, flexibility, and biocompatibility, making them suitable for various applications. Recent advancements have led to the development of smart hydrogels that can respond dynamically to environmental stimuli, enhancing their functionality in precision medicine, tissue engineering, and wearable technology. These adaptable properties drive innovation across multiple scientific fields [4].

Hydrogels are versatile biomaterials characterized by their polymer chains, cross-linking modalities, and porous architectures, enabling remarkable water absorption capabilities. They exhibit biocompatibility and responsiveness to environmental stimuli, making them adaptable for various applications. Hydrogels can be classified into natural and synthetic types, with cross-linking achieved through chemical, physical, or enzymatic methods. Their unique properties facilitate extensive use in biomedical, agricultural, environmental, consumer product, and biotechnological sectors, highlighting their significant impact across diverse fields [5]. Hydrogels are multifunctional biomaterials characterized by their high water absorption capacity, biocompatibility, and tunable mechanical properties. They can swell significantly in water while maintaining their structure, making them suitable for various applications. Their unique properties include stimuli responsiveness, which allows them to react to environmental changes. Hydrogels have evolved from early synthetic gels to advanced smart and biomimetic hydrogels, enhancing their versatility in drug delivery, tissue engineering, wound healing, and agriculture [6]. Hydrogels can be classified into hydrogels, copolymer hydrogels, and multipolymer hydrogels.

Programmability in hydrogels is an important factor that improves their usefulness and application in various domains, including biomedicine, soft robotics, and tissue engineering [7]. Programmable hydrogels may be made to respond to particular stimuli like temperature, pH, light, and chemical signals, giving you great control over their characteristics and behaviors [8]. Their versatility makes them excellent for developing dynamic systems replicating natural biological processes [7]. Programmable hydrogels can be employed in drug delivery systems to regulate the release of therapeutic drugs in response to certain inputs [9]. They're also utilized in tissue engineering to make scaffolds that promote cell proliferation and tissue creation [7]. In soft robotics, programmable hydrogels enable the development of flexible and adaptive robots capable of performing complicated tasks in changing situations. These robots can be utilized in biomedical devices, active implants, and sensors [9, 7]. Programmable hydrogels can be designed to detect specific biological signals, making them useful in biosensing applications for medical diagnostics [9].

Beyond biomedical applications, programmable hydrogels are increasingly investigated for environmental and agricultural engineering. Their ability to retain water, respond to chemical stimuli, and release active agents in a controlled manner makes them promising materials for soil conditioning, controlled fertilizer delivery, agrochemical release, water remediation, and environmental sensing. These emerging applications position programmable hydrogels as key materials for sustainable development and ecological transition.

Many studies highlight major hydrogel advances, demonstrating how programmability and nanotechnology may improve their functionality for various applications. Pruksawan et al. [7]. explore using encoded building block design and 3D printing to produce programmable hydrogel-based soft robots. They showed that the technique enables the production of adaptable, single-component hydrogels with configurable actuation properties. Hanif et al. (2023) [9] investigated the creation of physically crosslinked all-DNA hydrogels with variable shape and biodegradability. DNA sequences may be programmed to produce soft hydrogels with certain characteristics. Omidian and Wilson (2024) [10] have examined the incorporation of quantum dots into hydrogels to improve their chemical stability, mechanical strength, and heat resistance. [11] discussed the integration of different nanoparticles into hydrogel networks to develop nanocomposites with better characteristics and specific functionality.

This review overviews recent progress in programmable hydrogels and their innovative applications.

## 2 Fundamentals of Programmable Hydrogels

### 2.1 Composition and characteristics of hydrogels

Hydrogels are utilized in wound care, drug delivery, tissue engineering, and contact lenses, among other areas [12]. Hydrogels are composed of hydrophilic polymers that form a cross-linked network, allowing them to absorb and retain large amounts of water, which enhances their compatibility with biological tissues. Hydrogels are described as crosslinked polymeric networks that contain a significant amount of water. This unique structure is crucial for their function as drug delivery systems [13].

Hydrogels can be composed of naturally derived polymers, synthesized polymers, polymerizable synthetic monomolecules, or mixtures of these [14]. Hydrogels are primarily composed of hydrophilic polymer networks capable of retaining significant water content, which imparts softness and biocompatibility. These polymers can be classified as synthetic, such as polyethylene glycol (PEG) [15], polyacrylamide (PAAm) [16], or natural, including alginate and gelatin [17]. The tunable mechanical properties of hydrogels are influenced by factors like crosslinking density and polymer type, which allow customization for specific applications [18].

This adaptability is crucial in fields like tissue engineering, drug delivery, and wound healing, where specific mechanical characteristics are required to mimic natural tissues or enhance therapeutic efficacy [19]. Hydrogels exhibit key functional characteristics such as swelling or deswelling in response to environmental stimuli like pH, temperature, and light. This responsiveness makes them ideal for applications in drug delivery, tissue engineering, and biosensors, enhancing their versatility and effectiveness [20]. Additionally, modifications such as embedding nanoparticles or incorporating bioactive molecules enhance their functionality, enabling advanced applications in regenerative medicine and responsive systems [21].

### 2.2 Mechanisms of programmability

Hydrogels are programmable through multiple methods that allow them to respond to varied stimuli. Dong et al. (2021) [22] reported that hydrogels can be programmed to respond to specific chemical stimuli, such as pH, ionic strength, or the presence of particular proteins. For example, pH-sensitive hydrogels, which may swell or contract in response to changes in pH, are ideal for drug delivery systems [23]. Chatterjee and Hui (2021) [24] demonstrated that at certain temperatures, thermoresponsive hydrogels change into a different phase. These hydrogels may be designed to undergo gelation or sol-gel transitions, which can be utilized in applications such as tissue engineering and controlled medication delivery. Electrically and magnetically sensitive hydrogels can respond to electric or magnetic fields, respectively [25]. Mechanically active hydrogels can respond to mechanical forces, such as stretching or compression [22]. However, photoresponsive hydrogels can change their properties in response to light, such as UV or visible light [26]. Ooi et al. (2017) [27] reported that some hydrogels are designed to respond to biological stimuli, such as enzymes or cell-secreted factors.

### 2.3 Classification of programmable hydrogels

Hydrogels have emerged as a flexible and promising drug delivery medium, with unique properties such as biocompatibility, biodegradability, and controlled release of medicinal chemicals [28]. These materials are highly appreciated for their capacity to replicate natural tissues and respond to a variety of stimuli, which may be used to improve medication delivery efficiency and efficacy [29].

Table 1 classifies programmable hydrogels based on their responsiveness to external stimuli, highlighting their mechanisms and applications. Thermoresponsive hydrogels change properties with temperature, useful in drug delivery and tissue engineering [29], while pH-sensitive hydrogels respond to pH changes, making them ideal for targeted drug release and biosensors [30, 31]. Photoresponsive hydrogels, activated by light, are applied in smart lenses and photo-controlled therapies [32]. Electric field-sensitive hydrogels exhibit unique properties that significantly enhance their performance as actuators and artificial muscles [33, 34], whereas magnetic-sensitive hydrogels, embedded with magnetic nanoparticles, enable targeted drug delivery and tissue scaffolding [35]. Lastly, dual or multi-responsive hydrogels, capable of responding to multiple stimuli, are versatile for adaptive drug delivery and robotics [36].

These hydrogels demonstrate significant promise for advanced biomedical, engineering, and environmental applications, with ongoing research addressing challenges like biocompatibility and mechanical robustness.

**Table 1.** Types of programmable hydrogels and their applications

| Type of Hydrogel | Description | Example Applications | References |
|---|---|---|---|
| **Thermoresponsive** | Change properties with temperature changes; transition at critical solution temperatures. | Drug delivery, tissue engineering | Hoare and Kohane, 2008; [28]. |
| **pH-sensitive** | Swell or shrink in response to pH changes, due to ionizable groups in their structure. | Controlled drug release, biosensors | Suhail et al., 2023 ; [31]. |
| **Photoresponsive** | Respond to specific light wavelengths; enable reversible property modifications. | Smart lenses, photo-controlled drug delivery | Nicoletta et al., 2012 ; [32]. |
| **Electric field-sensitive** | Alter shape or size in response to electric fields, often using ionic species. | Actuators, artificial muscles | Bai et al., 2025; [33]. |
| **Magnetic-sensitive** | Integrate magnetic nanoparticles; respond to external magnetic fields. | Targeted drug delivery, tissue scaffolding | Liu et al., 2020) |
| **Dual or Multi-responsive** | Exhibit responsiveness to two or more stimuli (e.g., temperature and pH). | Multifunctional biomaterials | Knipe and Peppas, 2014; [36]. |

## 3 Synthesis of Programmable Hydrogels

The synthesis of programmable hydrogels employs various techniques, including chemical crosslinking [37], physical network formation [38], and hybrid methods [8]. These approaches enable the creation of hydrogels with tailored mechanical properties and responsive behaviors, essential for applications in soft robotics, tissue engineering, and beyond [35].

Chemical crosslinking mechanisms involve various approaches to form covalent bonds between polymer chains, resulting in enhanced structural stability and integrity. This process can be achieved through reactions between complementary functional groups, radical polymerization, or the use of ultraviolet light, each catalyzing the formation of crosslinks that bolster the material's properties [39]. The synthesis typically necessitates three essential components: a monomer that forms the base polymer, an initiator that triggers the polymerization process, and a crosslinking agent that facilitates the bonding between polymer chains, with precise ratios of these elements being crucial for maintaining the overall integrity and functionality of the hydrogel [39].

The synthesis of programmable hydrogels through physical network formation techniques is increasingly recognized for its diverse applications in biosensing, tissue engineering, and soft robotics. These hydrogels can be precisely engineered to exhibit tailored properties via methods such as DNA assembly, which utilizes self-assembling DNA building blocks based on Watson-Crick base pairing to ensure programmable interactions, and functionalization with nanomaterials to enhance mechanical properties and biocompatibility, making them ideal for biosensing [40]. Topological engineering techniques have also been developed to manipulate surface topology, creating supramolecular linkages with tunable adhesion properties and enabling dynamic adhesion suitable for smart devices [23]. Moreover, mechanical property sculpting through sequential photopolymerization fosters the design of

hydrogels with interpenetrating double networks, yielding a wide range of customizable mechanical characteristics such as stiffness and toughness without complicated formulations [38]. The synthesis of programmable hydrogels through hybrid approaches effectively merges physical network formation and chemical crosslinking techniques, thereby producing materials that exhibit enhanced functionality and adaptability for applications in soft robotics, biomedical devices, and biosensing. This hybrid methodology utilizes non-covalent interactions, such as hydrogen bonding, to form a flexible network, an example being the incorporation of cellulose nanocrystals, which improves mechanical properties while maintaining environmental responsiveness [8]. Additionally, chemical crosslinking introduces covalent bonds that stabilize the hydrogel structure, as seen in DNA hydrogels, where base pairing facilitates programmable assembly and disassembly, essential for biosensing [40]. The integration of these techniques enables the development of hybrid hydrogels that can respond dynamically to multiple stimuli, such as temperature and pH, allowing for precise control over their physical properties [8]. Natural polymers such as collagen, gelatin, alginate, and hyaluronic acid, as well as synthetic polymers such as polyethylene glycol (PEG) [15], polyvinyl alcohol (PVA), and polyacrylamide (PAAm) [16], are important ingredients in the production of programmable hydrogels. Natural polymers are biocompatible and biodegradable, but synthetic polymers have adjustable mechanical qualities and stability [17]. Recent innovations in synthesis methods, particularly in 3D printing and fabrication, have greatly improved the control over the structure and properties of hydrogels, facilitating the creation of complex biomaterials suitable for various biomedical applications such as tissue engineering and drug delivery. Techniques like inkjet printing enable high spatial resolution in constructing hydrogels with functional particulates, essential for advanced biomaterials [41]. Direct ink writing provides an affordable and scalable approach using injectable hydrogels as inks, allowing for the development of engineered biostructures with specific mechanical properties [42]. Furthermore, additive manufacturing methods, including extrusion and stereolithography, enhance the reproducibility and precision of hydrogel fabrication, leading to the creation of 3D/4D smart hydrogels for targeted applications [43]. In tissue engineering, 3D-printed hydrogels are particularly valuable as they can mimic the extracellular matrix, promoting cell growth and tissue regeneration [44].

## 4 Design and Functionalization of hydrogels

Smart stimuli-responsive hydrogels (Figure 2) have gained prominence due to their ability to react to external stimuli such as pH, temperature, and light. These hydrogels can be designed to undergo reversible shape changes or alterations in their physical properties in response to environmental changes, making them useful for applications like controlled drug delivery, where the release of therapeutics can be timed or targeted based on physiological conditions [45]. Designing smart hydrogels involves a deep understanding of both material science and the intended application domain. Key principles include the selection of appropriate monomers and crosslinkers, incorporation of responsive elements (such as pH-sensitive groups), and ensuring biocompatibility for biomedical applications. The integration of 3D printing technologies allows for the fabrication of complex structures with precise geometric control, further enhancing the functionality of the resulting hydrogels [42, 43].

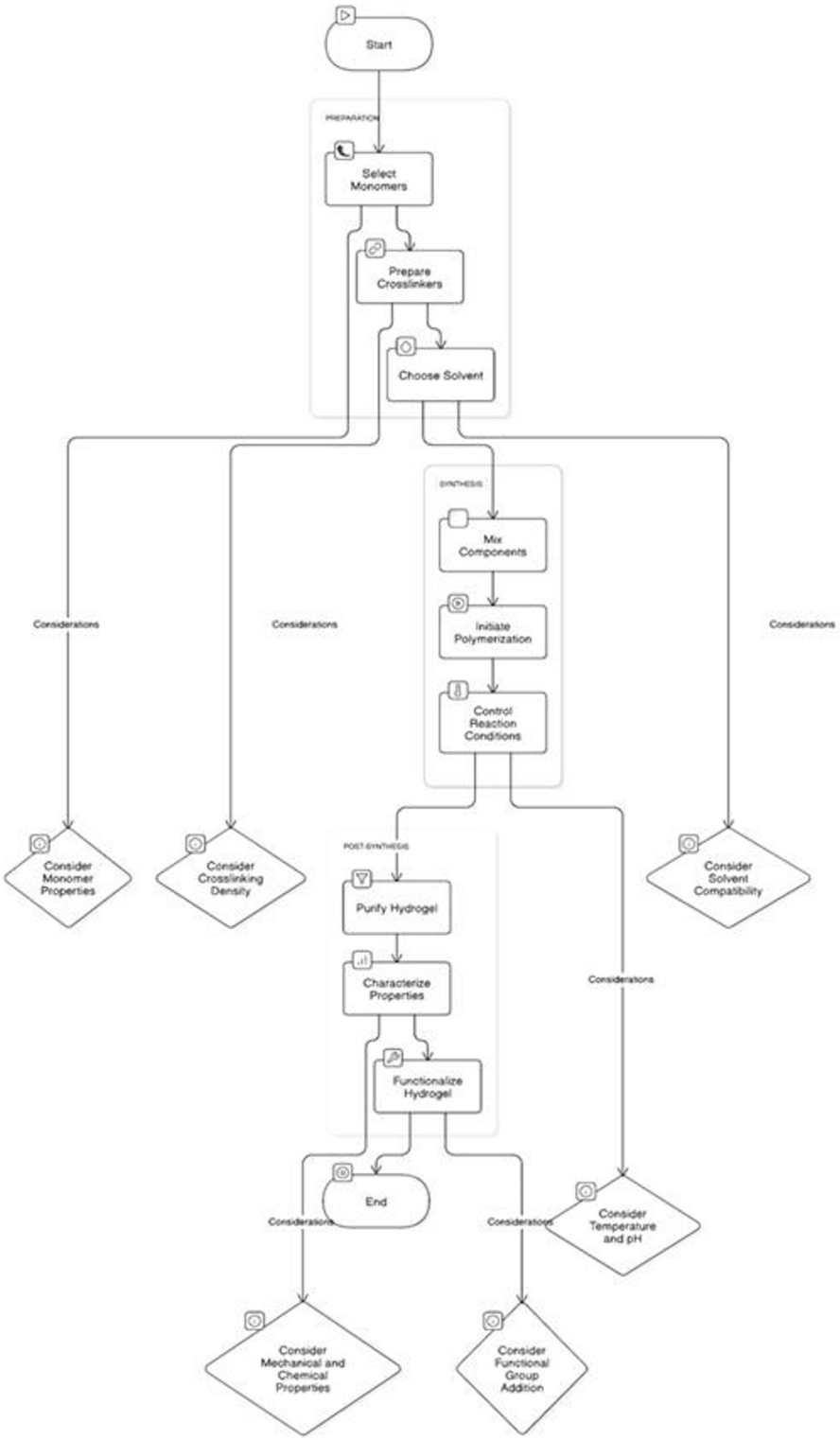


**Fig. 1.** Schematic Overview of Programmable Hydrogel Synthesis

Nanomaterials play a crucial role in enhancing the properties of hydrogels. The inclusion of nanoparticles, such as gold nanoparticles and carbon nanotubes, can significantly improve mechanical strength, electrical conductivity, and biocompatibility. Functionalization techniques, such as surface modification and covalent bonding, allow for the seamless incorporation of these nanomaterials into the hydrogel matrix, thereby tailoring their properties for specific applications [30]. For instance, gold nanoparticles can facilitate photothermal therapies in tumor treatments, while carbon nanotubes can enhance the electrical properties of hydrogels for neural applications [46]. The multifunctionality of elaborated hydrogels significantly enhances their applications in drug delivery systems and tissue engineering [47]. These hydrogels are designed to provide controlled release profiles, which minimize side effects while maximizing therapeutic efficacy [48]. Additionally, their ability to mimic the extracellular matrix (ECM) promotes cell adhesion, growth, and differentiation, making them invaluable in regenerative medicine [49].

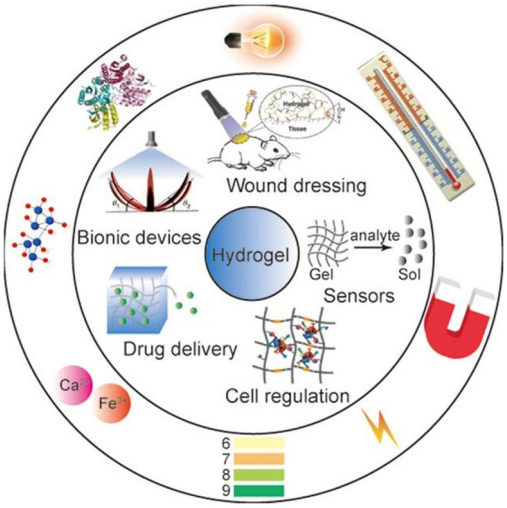


**Fig. 2.** Stimuli-responsive hydrogels: Fabrication and biomedical applications [50]

## 5 Characterization of Programmable Hydrogels

Characterizing programmable hydrogels is critical for knowing their characteristics and capabilities, allowing their optimization for varied applications in medicinal sectors, soft robotics, and environmental sustainability [22]. To effectively analyze these materials, several characterization approaches that examine their mechanical, thermal, morphological, and functional properties are used [51].

### 5.1 Characterization techniques

The mechanical performance of hydrogels is typically evaluated through compression and tensile tests, which measure parameters such as elasticity and tensile strength [31]. These tests help determine how hydrogels respond to applied forces, crucial for applications in tissue engineering where mimicking the mechanical characteristics of natural tissues is essential [52]. Understanding swelling behavior is important because it offers information about the hydrogel's capacity to absorb water. This is frequently evaluated by measuring the equilibrium swelling ratio, which reveals how much water a hydrogel can hold under given conditions. Evaluating swelling kinetics can also indicate the influence of environmental

stimuli, such as pH and temperature [53]. TGA and DSC are routinely used to evaluate the thermal stability of hydrogels. TGA evaluates weight loss as a function of temperature, showing degradation temperatures, whereas DSC offers information on phase transitions, such as glass transition temperatures, which are critical for assessing the thermal behavior of hydrogels [54]. SEM and TEM can be used to characterize the morphology of hydrogels. These approaches enable the viewing of the hydrogel's surface and interior architecture, which helps to comprehend porosity, network creation, and the distribution of embedded nanoparticles [55].

### 5.2 Assessing Functionality

Programmable hydrogels are intended to respond to a variety of external stimuli, including pH, temperature, and light changes. Functional testing frequently includes dynamic studies to investigate how these hydrogels modify their characteristics (e.g., swelling, shape) in response to various stimuli. This is crucial for applications like drug delivery systems [56]. Biocompatibility testing is critical for hydrogels used in medical applications. Standard testing includes cytotoxicity assays, hemocompatibility evaluations, and in vivo investigations to confirm the hydrogels are non-toxic and encourage cell attachment and proliferation [57]. Recent advances in hydrogel characterization include novel technologies like atomic force microscopy (AFM) for assessing nanoscale mechanical properties and sophisticated imaging techniques that give deep insights into hydrogel hierarchy. For example, [58] used AFM to analyze regional variation in mechanical characteristics at the nanoscale, providing a better knowledge of how hydrogel qualities might be tailored for specific applications. Furthermore, the use of artificial intelligence in interpreting data from various characterization approaches is gaining traction, potentially improving predictive modeling for hydrogel behaviors [59].

## 6 Role of Nanotechnology in Programmable Hydrogels

Nanotechnology plays a transformative role in enhancing the properties and functionalities of programmable hydrogels. By integrating nanomaterials such as nanoparticles, nanotubes, and quantum dots into hydrogel matrices, researchers have achieved significant improvements in mechanical strength, responsiveness to stimuli, electrical conductivity, and biocompatibility, key factors in biomedical and environmental applications.

Nanoparticles, including metallic (e.g., gold, silver) and magnetic types (e.g., iron oxide), are commonly embedded into hydrogels to confer multifunctionality. For instance, gold nanoparticles (AuNPs) enable photothermal responsiveness, making them ideal for targeted cancer therapy where local heating induced by near-infrared irradiation triggers drug release or induces cell death [46]. Similarly, magnetic nanoparticles facilitate remote control of hydrogel behavior via external magnetic fields, enhancing drug targeting, guiding scaffold orientation, or actuating motion in soft robotics [35].

The incorporation of quantum dots (QDs) into hydrogels introduces optical and electronic properties that enhance biosensing capabilities. [10] demonstrated that QD-functionalized hydrogels exhibit increased fluorescence, stability, and chemical robustness, opening new pathways for real-time diagnostics and environmental monitoring.

Carbon-based nanostructures such as carbon nanotubes (CNTs) and graphene oxide (GO) are also widely used to reinforce hydrogels mechanically and electrically. These nanomaterials create conductive networks within the hydrogel, enabling their use in neural tissue engineering, wearable biosensors, and actuating devices [11]. Their high aspect ratio and surface area facilitate interactions with polymer chains, improving not only stiffness and toughness but also cell adhesion and proliferation.

Nanotechnology also enables programmability at the molecular level. For example, DNA nanostructures can be embedded in hydrogels to design logic-encoded responsiveness, enabling the hydrogel to execute specific responses based on molecular cues [9]. Such "smart" hydrogels are capable of recognizing biological markers or environmental changes and responding through swelling, drug release, or mechanical actuation.
Finally, nanotechnology facilitates controlled release and targeted delivery of bioactive compounds within hydrogels. By loading nanoparticles with drugs or growth factors, hydrogels can act as reservoirs with precisely tunable release profiles, triggered by pH, temperature, enzymatic activity, or external fields [15, 10].

## 7 Conclusion

Programmable hydrogels represent a significant achievement in biomaterials research, with unique features that are especially useful in health and agriculture. Their capacity to imitate natural tissue conditions while responding to varied stimuli makes them extremely adaptable to a wide range of applications, including medication delivery systems, tissue engineering, and sustainable farming techniques. These hydrogels are synthesized using novel approaches such as chemical crosslinking and hybrid methods, allowing for molecular customization of mechanical characteristics and functionality and allowing for fine control over their behavior in response to environmental changes. Furthermore, the use of nanotechnology improves their mechanical and biological properties, paving the path for more effective and precise treatment solutions. Characterization methods give essential insights into hydrogel performance and stability, ensuring that they fulfill the high demands of current applications. As research in this field advances, future innovations will most likely focus on enhancing biocompatibility, mechanical robustness, and smart functions, extending the range of possibilities for programmable hydrogels. Finally, further research and development of programmable hydrogels have the potential to revolutionize healthcare treatments and agricultural techniques, resulting in better patient outcomes and more sustainable production methods. The synergistic interaction of material science, nanotechnology, and tissue engineering heralds intriguing potential for generating next-generation biomaterials that successfully solve some of society's urgent concerns.

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