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Review Article

## Hydrogels: A Comprehensive Review of Structure, Properties, and Multifaceted Applications

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### Abstract

Hydrogels, three-dimensional networks of hydrophilic polymers capable of absorbing and retaining significant amounts of water, have transitioned from laboratory curiosities to cornerstone materials in modern technology and medicine. Their unique biocompatibility, tunable physical and chemical properties, and stimuli-responsive nature have made them indispensable in fields ranging from drug delivery and tissue engineering to soft robotics and sustainable agriculture. This review provides a systematic overview of hydrogel classification, cross-linking mechanisms, and fundamental properties. We then delve into their advanced applications across biomedical and non-biomedical sectors, highlighting recent breakthroughs. Finally, we discuss the current challenges and future perspectives for the next generation of "smart" hydrogel systems.

**Keywords:** Hydrogel, Cross-linking, Stimuli-responsive, Biomaterial, Drug Delivery, Tissue Engineering, Soft Robotics, Agriculture.

## 1. Introduction

First described in the scientific literature in the 1960s, hydrogels have since evolved into a diverse class of materials. Their defining characteristic is their ability to swell in water without dissolving, a property stemming from hydrophilic functional groups (e.g., -OH, -COOH, -CONH<sub>2</sub>, -SO<sub>3</sub>H) on their polymer chains, while cross-links maintain their structural integrity. This combination results in a solid-like, yet highly hydrated, material that mimics the water content and soft, porous nature of natural biological tissues, making them exceptionally biocompatible<sup>1</sup>.

**Historical Context:** While the term "hydrogel" and its modern scientific investigation are often credited to Wichterle and Lim's seminal 1960 work on poly(2-hydroxyethyl methacrylate) (pHEMA) for contact lenses, the concept is much older. Natural hydrogels like gelatin have been used for centuries. The 1960s mark the beginning of their rational design as synthetic biomaterials.

**The Swelling Paradox:** The sentence "swell in water without dissolving" captures a critical chemical balance. The **hydrophilic functional groups** (e.g., -OH, -COOH) provide the thermodynamic driving force for water absorption (hydration). However, the **cross-**

**links** (covalent bonds or strong physical interactions) form a pervasive network that prevents the individual polymer chains from solvating and separating entirely, thus preventing dissolution. The equilibrium between these opposing forces—the osmotic pressure driving water in and the elastic retractive force of the polymer network resisting expansion—determines the final swelling ratio<sup>2</sup>.

**Mimicking Biology:** The statement about mimicking biological tissues is paramount to their success in medicine. Many human tissues are essentially natural hydrogels:

**The Extracellular Matrix (ECM):** A complex hydrogel of collagen, hyaluronic acid, and other proteins that provides structural and biochemical support to cells.

**Cartilage:** A classic example of a tough, water-saturated (~70-80% water) hydrogel that cushions joints.

The Vitreous Humor of the eye is a hydrogel. By replicating this high water content (often >90% water), hydrogels achieve a similar soft, wet, and porous microstructure. This minimizes the mechanical mismatch at the tissue-implant interface (a problem with hard materials like metals or ceramics), reducing friction and scar tissue formation. The porosity allows for the diffusion of nutrients, oxygen, and waste

products, which is essential for supporting encapsulated cells or healing surrounding tissue. This is the root of their exceptional biocompatibility.

The past two decades have witnessed an explosion in hydrogel research, driven by advances in polymer chemistry, nanotechnology, and a growing understanding of biological interfaces. Modern hydrogels are no longer simple, inert sponges; they are engineered to be "smart" or "intelligent," responding dynamically to environmental cues such as pH, temperature, light, or specific biomolecules<sup>3</sup>.

#### Drivers of Innovation:

- **Polymer Chemistry:** The development of "click" chemistry (e.g., CuAAC, SPAAC, thiol-ene), controlled radical polymerization (e.g., ATRP, RAFT), and new biocompatible cross-linking methods (e.g., enzymatic cross-linking) have allowed for precise control over network structure, functionality, and mechanical properties with minimal byproducts.
- **Nanotechnology:** The incorporation of nanomaterials (e.g., cellulose nanocrystals, clay nanoplatelets, graphene oxide, silica nanoparticles) has led to the creation of **nanocomposite hydrogels** with unprecedented strength, toughness, and functionality (e.g., electrical conductivity, enhanced drug loading).
- **Understanding Biological Interfaces:** Research in cell biology has revealed the critical importance of not just chemical signals but also physical cues (matrix stiffness, topography, viscoelasticity). This has driven the design of hydrogels that can precisely present biochemical cues (e.g., peptide sequences like RGD for cell adhesion) and mimic the mechanical properties of specific tissues (e.g., a soft brain-like gel vs. a stiffer bone-like gel)<sup>4</sup>.

**From "Inert Sponges" to "Intelligent" Systems:** The shift in paradigm is profound.

- **1st Generation:** Passive materials (e.g., early contact lenses, simple wound dressings). Their function was primarily based on their static swelling and diffusion properties.
- **2nd & 3rd Generation ("Smart" or "Responsive"):** Dynamic materials that act as actuators, sensors, and controlled-release systems. Their response is often a dramatic, non-linear change in volume (swelling/collapsing) or sol-gel transition.
- **Examples of Stimuli-Responsiveness:**

**pH:** A gel containing poly(acrylic acid) will swell in the basic environment of the intestine (COOH groups deprotonate to COO<sup>-</sup>, increasing electrostatic repulsion) but remain collapsed in the acidic stomach. This is ideal for targeted drug delivery.

**Temperature:** A gel like poly(N-isopropylacrylamide) (PNIPAAm) is swollen below ~32°C (its LCST) and collapses above it. This can be used for injectable drug

delivery (liquid injects, gel forms in the body) or as an actuator.

**Light:** A hydrogel with incorporated light-responsive molecules (e.g., spiropyran) can be made to swell or contract with precise spatiotemporal control using specific wavelengths of light, enabling exquisite control in microfluidic valves or for studying cell mechanics.

**Biomolecules:** A hydrogel with immobilized enzymes or molecularly imprinted networks can respond to specific biomarkers. The classic example is a glucose-responsive gel for insulin delivery, which swells in the presence of high glucose levels, releasing insulin<sup>5</sup>.

## 2. Classification and Synthesis of Hydrogels

This section is critical because the classification criteria directly determine a hydrogel's properties, functionality, and ultimate application.

### 2.1 Classification by Source

This defines the raw materials and heavily influences biocompatibility, biodegradability, and bioactivity<sup>6</sup>.

#### Natural Hydrogels:

- **Origin:** Derived from organisms (animals, plants, algae, microbes).
- **Mechanism:** They are often biopolymers that naturally form hydrogels in their biological roles (e.g., collagen in the extracellular matrix).
- **Examples & Details:**

**Collagen/Gelatin:** Collagen is the most abundant protein in the human body. Gelatin is its denatured form. Both are excellent for cell culture and tissue engineering due to the presence of cell-adhesion motifs (e.g., RGD sequences).

**Alginate:** A polysaccharide from brown algae. Forms gentle ionic gels with divalent cations like Ca<sup>2+</sup> (the "egg-box" model). Excellent for cell encapsulation but inert (often requires modification to support cell adhesion).

**Chitosan:** Derived from chitin (shellfish exoskeletons). A cationic polysaccharide unique among natural polymers. Has inherent antimicrobial properties and mucoadhesiveness.

**Hyaluronic Acid (HA):** A glycosaminoglycan found throughout the body (e.g., skin, joints). Imparts superb lubricity and is involved in cell signaling. Degraded by hyaluronidase enzymes.

**Fibrin:** Formed from fibrinogen and thrombin during the blood clotting process. Naturally promotes wound healing and is often used as a biological sealant.

- **Advantages:** Inherent biocompatibility, biodegradability, and bioactivity. Often exhibit low immunogenicity.
- **Disadvantages:** Batch-to-batch variability, potential pathogenicity, limited mechanical strength, and sometimes unpredictable degradation rates<sup>7</sup>.

### Synthetic Hydrogels:

- **Origin:** Man-made polymers, designed and synthesized in the lab.
- **Mechanism:** Their properties are a result of precise chemical design rather than biological evolution.

- **Examples & Details:**

**Poly(ethylene glycol) (PEG):** The "gold standard" for synthetic biomaterials. Highly hydrophilic, biocompatible, and **bio-inert** ("stealth" polymer that resists protein adsorption and cell adhesion). This inertness is an advantage for certain applications (e.g., preventing biofouling) but a disadvantage for others (often must be modified with peptides to support cells).

**Poly(acrylic acid) (PAA):** A polyelectrolyte that swells significantly at high pH due to ionization of its carboxylic acid groups. The basis for superabsorbent polymers (e.g., in diapers).

**Poly(vinyl alcohol) (PVA):** Can form hydrogels through repeated freeze-thaw cycles (physical cross-linking via crystallization) or chemical cross-linkers. Known for its high mechanical strength and elasticity<sup>8</sup>.

**Poly(hydroxyethyl methacrylate) (pHEMA):** The first synthetic hydrogel developed for biomedical use (contact lenses). Balances water content and mechanical stability.

- **Advantages:** Reproducibility, tunable properties (mechanics, degradation), high purity, and robust mechanical strength.
- **Disadvantages:** Lack of inherent bioactivity, potential toxicity from unreacted monomers or cross-linkers<sup>9</sup>.

### Hybrid Hydrogels:

- **Origin:** A combination of natural and synthetic polymers.
- **Mechanism:** Aims to create a synergistic material. The synthetic component provides structural integrity and tunability, while the natural component provides bioactivity.
- **Examples:** PEG-collagen, PLA-hyaluronic acid, PVA-alginate.
- **Advantages:** Customizable "designer" materials that can be tailored for specific biological and mechanical requirements.
- **Disadvantages:** More complex synthesis and characterization<sup>10</sup>.

## 2.2 Classification by Cross-Linking Method

This is the most critical technical distinction, defining the very nature of the polymer network.

### Physical (Reversible) Gels:

- **Definition:** Networks held together by transient, non-covalent interactions. These bonds can break and re-form, allowing for dynamic behavior.

- **Types & Mechanisms:**

**Ionic Interactions:** Cross-linking via ionic bonds. *Example: Sodium Alginate + CaCl<sub>2</sub> solution.* Divalent Ca<sup>2+</sup> ions bridge guluronic acid units on different alginate chains.

**Hydrogen Bonding:** Polymer chains associate through H-bonds, which are highly temperature-sensitive. *Example: Agarose* forms a thermo-reversible gel; heated to dissolve, gels upon cooling<sup>11</sup>.

**Hydrophobic Associations:** Blocks of hydrophobic polymers aggregate in water to form physical cross-links. *Example: Pluronic F127* (PEO-PPO-PPO triblock copolymer) is a liquid at low temperatures but forms a gel at body temperature as the PPO blocks aggregate.

**Crystallization:** Physical cross-links are crystalline domains within the polymer matrix. *Example: PVA* subjected to **freeze-thaw cycling**. Water freezes, concentrating the PVA solution into unfrozen regions, promoting crystal formation<sup>12</sup>.

**Molecular Entanglements:** Simple physical intertwining of long polymer chains. More common in high-viscosity solutions than true gels.

- **Advantages:** Often **injectable** (can be shear-thinning) and **self-healing**. Typically avoid the need for potentially toxic chemical cross-linkers.
- **Disadvantages:** Generally **mechanically weak** and unstable, can dissolve upon dilution or changes in environment (e.g., pH, temperature).

### Chemical (Permanent) Gels:

- **Definition:** Networks formed by strong, covalent bonds between polymer chains. These are permanent under physiological conditions<sup>13</sup>.
- **Synthesis Methods:**

**Free Radical Polymerization:** A monomer (e.g., acrylamide), a cross-linker (e.g., bisacrylamide), and an initiator (e.g., ammonium persulfate) are dissolved in water. The initiator generates radicals that start a chain reaction, creating the network. Common for polyacrylamide gels.

**Chemical Reaction of Complementary Groups:** Pre-made polymers are functionalized with reactive groups and then cross-linked<sup>14</sup>.

**Amide Bond Formation:** -COOH (e.g., on hyaluronic acid) reacted with -NH<sub>2</sub> (e.g., on a lysine-containing peptide) using a carbodiimide catalyst like EDC.

**"Click" Chemistry:** Highly efficient, specific, and bioorthogonal reactions. *Example: Strain-Promoted Alkyne-Azide Cycloaddition (SPAAC).* An azide-modified polymer reacts with a dibenzocyclooctyne (DBCO)-modified polymer without any toxic catalysts.

**Michael Addition:** A nucleophile (e.g., a thiol group -SH) attacks an electron-deficient alkene (e.g., a vinyl sulfone or acrylate group). A very common and gentle method.

**Enzymatic Cross-linking:** Using enzymes (e.g., transglutaminase, horseradish peroxidase) to form specific cross-links between modified polymers. Offers high specificity and biocompatibility.

**High-Energy Irradiation:** Exposing a polymer solution (e.g., PVA) to gamma or electron beam radiation. This generates free radicals on the polymer chains, which then recombine to form covalent C-C bonds. A "clean" method with no chemical additives<sup>15</sup>.

- **Advantages: Superior mechanical strength, permanent stability, and structural integrity.**
- **Disadvantages:** Can be brittle, often require purification to remove toxic cross-linkers/catalysts, and are not inherently self-healing.

### 2.3 Other Classification Criteria

**Electrical Charge:** Crucial for interactions with biomolecules (proteins, cells) and for stimuli-responsiveness<sup>16</sup>.

- **Anionic:** Contain negatively charged groups (e.g.,  $\text{COO}^-$  in alginate, PAA). Swell at high pH.
- **Cationic:** Contain positively charged groups (e.g.,  $\text{NH}_3^+$  in chitosan). Swell at low pH.
- **Neutral:** No charged groups (e.g., PEG, PHEMA). Swelling is less sensitive to pH.
- **Ampholytic (Zwitterionic):** Contain both positive and negative charges on the same chain (e.g., polymers mimicking phosphatidylcholine). Exhibit exceptional anti-fouling properties<sup>17</sup>.

#### Structure:

- **Amorphous:** No long-range order in the polymer chains.
- **Semi-crystalline:** Has regions of crystalline order (like in freeze-thaw PVA) which act as physical cross-links.
- **Hydrocolloid Aggregate:** A suspension of particles that are themselves gels (e.g., used in some wound dressings).

**Physical Form:** Dictates the application modality.

- **Matrix/Bulk:** Large, monolithic structures (e.g., tissue engineering scaffolds).
- **Film/Membrane:** Thin sheets (e.g., wound dressings, biosensor coatings).
- **Microsphere/Nanoparticle:** Tiny spherical particles for drug delivery or cell encapsulation.
- **Fiber:** Electrospun or extruded fibers for creating woven or non-woven mats<sup>18</sup>.

## 3. Key Properties and Characterization

The performance of a hydrogel in any application is dictated by its physical and chemical properties. These properties are not independent but are deeply interconnected, often in a trade-off relationship (e.g.,

increasing cross-linking improves strength but reduces swelling)<sup>19</sup>.

### 3.1 Swelling Behavior

This is the most fundamental hydrogel property, defining its capacity to hold water.

**Mechanism:** Swelling is a balance between two opposing forces:

1. **The Osmotic Pressure ( $\pi_{osm}$ ):** The driving force for water to enter the network. It arises from the affinity of hydrophilic groups for water and the concentration difference of mobile ions between the gel and the external solution (Donnan effect).
2. **The Elastic Retractive Force ( $\pi_{el}$ ):** The resistance of the polymer network to expansion. As the network swells, the polymer chains stretch, reducing their entropy and creating a counteracting force that opposes further swelling<sup>20</sup>.

**Equilibrium Swelling Ratio (Q):** The point where  $\pi_{osm} = \pi_{el}$ . It is typically defined as the weight (or volume) of swollen gel divided by the weight (or volume) of dry gel.

#### Influencing Factors:

- **Cross-link Density ( $\nu$ ):** The single most important factor. A higher density of cross-links (shorter chains between junctions) creates a tighter network with a higher  $\pi_{el}$ , resulting in a lower equilibrium swelling ratio.
- **Polymer-Water Affinity:** The more hydrophilic the polymer (e.g., PEG, PAA), the higher the  $\pi_{osm}$  and the greater the swelling.
- **Ionic Charge:** Polyelectrolyte gels swell much more than neutral gels due to the Donnan effect. The fixed charges on the polymer chain attract counter-ions, creating a large osmotic pressure difference. For example, an anionic gel (like PAA) will swell immensely at high pH as its  $\text{-COOH}$  groups ionize to  $\text{-COO}^-$ .

#### Characterization:

- **Gravimetric Analysis:** The most common method. The dry weight ( $W_d$ ) of the gel is measured. It is then swollen in a solution until equilibrium is reached, the surface water is blotted, and the swollen weight ( $W_s$ ) is measured.  $Q = W_s / W_d$ .
- **Volumetric Analysis:** Measuring the dimensions of the gel in its dry and swollen states.

**Implication:** Swelling dictates the mesh size ( $\xi$ ) – the average distance between two cross-links. The mesh size controls the diffusion of nutrients, oxygen, drugs, and waste products through the gel, which is critical for drug delivery and cell viability<sup>21</sup>.

### 3.2 Mechanical Properties

For applications beyond simple diffusion, the hydrogel must withstand mechanical stresses.

**Key Metrics:**

- **Elastic (Young's) Modulus (E or G')**: Measures the **stiffness** or resistance to elastic deformation. It's crucial for mimicking the mechanical environment of tissues (e.g., brain tissue is ~0.1-1 kPa, muscle ~10 kPa, cartilage ~0.5-1 MPa).
- **Compressive Strength**: The load per unit area at which the material fails under compression (critical for cartilage and bone applications)<sup>22</sup>.
- **Tensile Strength**: The load per unit area at which the material fails under stretching.
- **Toughness**: The energy required to fracture the material. It combines both strength and ductility. Traditional hydrogels are weak and brittle; creating *tough hydrogels* is a major research focus.

**Tuning Mechanics:**

- **Cross-link Density**: Increasing cross-linking increases modulus (stiffness) but often reduces extensibility, making the gel brittle<sup>23</sup>.
- **Advanced Architectures**:

**Double Network (DN) Hydrogels**: Incorporate two interpenetrating networks: a rigid, highly cross-linked first network and a soft, ductile second network. The first network dissipates massive amounts of energy through its sacrificial bonds, leading to extremely tough materials.

**Nanocomposite Hydrogels**: Reinforcing the polymer network with nanoparticles (e.g., **Laponite clay nanosheets, cellulose nanocrystals, silica nanoparticles**). The nanoparticles act as multifunctional, high-strength cross-linkers and energy dissipation centers.

**Slide-Ring Gels**: Use cyclodextrin rings threaded onto polymer chains, allowing cross-links to move and distribute stress evenly<sup>24</sup>.

**Characterization:**

- **Rheology**: Measures the viscoelastic properties (storage modulus  $G'$  and loss modulus  $G''$ ). A frequency sweep determines if the material is a solid ( $G' > G''$ ) and how its mechanics change with deformation rate.
- **Uniaxial Compression/Tension Testing**: Standard mechanical tests to measure modulus, strength, and strain-at-break<sup>25</sup>.

**3.3 Biodegradability**

For temporary applications in the body, the hydrogel must safely break down and be cleared.

**Mechanisms:**

- **Hydrolysis**: Cleavage of chemical bonds by water. Common hydrolytically labile bonds include **esters, anhydrides, orthoesters, and polyphosphazenes**. The rate can be tuned by the chemistry and local pH.
- **Enzymatic Degradation**: Cleavage by specific enzymes. This is highly relevant for natural polymers

(e.g., **collagenase degrades collagen, hyaluronidase degrades HA**). For synthetic gels, peptide sequences cleavable by specific enzymes (e.g., matrix metalloproteinases - MMPs) can be incorporated into the cross-links<sup>26</sup>.

**Characterization:**

- **In Vitro**: Monitoring mass loss, swelling ratio change, or decrease in mechanical properties over time in a buffer (with or without enzymes).
- **Release Profiles**: Tracking the release of an encapsulated model drug or fluorescent tag as the gel degrades.

**3.4 Stimuli-Responsiveness ("Smart" Hydrogels)**

These materials transduce an environmental signal into a mechanical or chemical response.

**pH-Responsiveness:**

- **Mechanism**: relies on **polyelectrolytes**. Anionic gels (with -COOH groups) are protonated and collapsed at low pH. As pH increases, they deprotonate (-COO<sup>-</sup>), increasing charge repulsion and causing swelling. Cationic gels (with -NH<sub>2</sub> groups) do the opposite, swelling at low pH when protonated to -NH<sub>3</sub><sup>+</sup>.
- **Application**: Oral drug delivery for targeted release in the intestine (basic pH) instead of the stomach (acidic pH)<sup>27</sup>.

**Thermo-Responsiveness:**

- **Mechanism**: Governed by a critical solution temperature. The most common type has a **Lower Critical Solution Temperature (LCST)**.

Below LCST: Polymer is hydrated and soluble; the gel is swollen.

Above LCST: Polymer chains dehydrate and become hydrophobic, aggregating and causing the gel to collapse.

- **Example**: **PNIPAAm** has an LCST of ~32°C, making it ideal for biomedical applications near body temperature.
- **Application**: Injectable drug delivery (liquid sol injected, forms a gel depot at body temperature), smart actuators<sup>28</sup>.

**Photo-Responsiveness:**

- **Mechanism**: Incorporation of light-sensitive molecules (**chromophores**) like **spiropyran, azobenzene, or o-nitrobenzyl groups**. Upon light irradiation, these molecules undergo isomerization or cleavage, changing their hydrophobicity/volume and triggering a network response.
- **Application**: Ultra-precise spatiotemporal control in microfluidics, drug release (e.g., UV light-triggered release), and 4D printing (shape-morphing structures)<sup>29</sup>.

**Biomolecule-Responsiveness:**

- **Mechanism:** The most sophisticated response. Often uses specific binding events.

**Antigen-Antibody:** Cross-linking an antigen into the network; introduction of the antibody causes cross-linking and collapse.

**Lectin-Glucose:** The lectin Concanavalin A (ConA) binds to glucose. A gel with ConA and polymer-bound glucose will swell in the presence of free glucose due to competitive binding.

**Enzyme-Substrate:** Incorporating a peptide sequence that is a substrate for a specific enzyme (e.g., MMPs). Enzyme presence cleaves the cross-links, degrading the gel.

- **Application:** The "holy grail" of **self-regulating insulin delivery**. A gel that swells and releases insulin precisely in response to high blood glucose concentrations<sup>30</sup>.

## 4. Applications of Hydrogels

### 4.1 Biomedical Applications

**Drug Delivery:** Hydrogels provide localized and controlled release of therapeutics (drugs, proteins, genes), protecting them from degradation and reducing systemic side effects. Stimuli-responsive systems enable on-demand release<sup>31</sup>.

**Tissue Engineering and Regenerative Medicine:** Hydrogels serve as 3D scaffolds that mimic the native extracellular matrix (ECM), supporting cell adhesion, proliferation, and differentiation. They are used for engineering cartilage, bone, skin, blood vessels, and neural tissues. Bioprinting often uses hydrogel-based bioinks.

**Wound Healing:** Hydrogel dressings create a moist wound environment, manage exudate, provide a cooling sensation, and can be loaded with antimicrobials or growth factors to accelerate healing (e.g., for burn wounds).

**Contact Lenses and Ophthalmology:** Silicone hydrogels are the standard material for modern soft contact lenses due to their high oxygen permeability and comfort.

**Biosensors:** Hydrogels functionalized with enzymes or antibodies can be used in diagnostic sensors. Swelling or optical changes in the gel can be correlated to analyte concentration<sup>32</sup>.

### 4.2 Non-Biomedical Applications

**Agriculture:** As soil conditioners, hydrogels act as "water reservoirs," reducing irrigation frequency and improving soil retention of water and fertilizers, crucial for arid regions.

**Soft Robotics and Actuators:** Hydrogels that change shape in response to stimuli are used to create artificial muscles, grippers, and microfluidic valves that operate in aqueous environments.

**Water Purification:** Superabsorbent anionic hydrogels can absorb and trap heavy metal ions and dyes from contaminated water.

**Electronics:** Emerging applications include flexible, stretchable conductors, electrolytes for batteries, and transparent ionic touch panels.

**Food Industry:** Hydrogels like alginate and gelatin are used as thickeners, gelling agents, and for encapsulating flavors or probiotics<sup>33</sup>.

## 5. Current Challenges and Future Perspectives

Despite their immense potential, several challenges remain:

**Mechanical Performance:** Many highly swollen hydrogels are inherently weak and brittle. Developing robust, tough, and fatigue-resistant hydrogels that do not compromise swelling or biocompatibility is a major focus.

**Sophisticated Biofabrication:** Improving the resolution, vascularization, and functionality of hydrogel-based tissues through advanced 3D bioprinting techniques.

**Translation to Clinic:** Scaling up manufacturing under Good Manufacturing Practice (GMP), ensuring long-term stability and sterility, and conducting comprehensive in vivo safety and efficacy studies are significant hurdles.

**Dynamic and Adaptive Systems:** The future lies in creating hydrogels that can adapt to complex biological environments in real-time, perhaps by integrating feedback loops or learning behaviors.

Future research will likely focus on:

**Multi-Responsive and Logic-Gate Hydrogels:** Systems that respond to multiple stimuli in a programmable sequence.

**Living Hydrogels:** Networks that incorporate living cells not just as passengers, but as active components that remodel and regenerate the matrix.

**Energy-Harvesting Hydrogels:** Using mechanical movement or salinity gradients to generate electricity<sup>35</sup>.

## 6. Conclusion

Hydrogels represent one of the most versatile and dynamic classes of materials in the 21st century. From their humble beginnings, they have been engineered into sophisticated platforms that interface seamlessly with biology and technology. By continuing to address challenges in mechanics, fabrication, and translational science, the next generation of hydrogels promises to revolutionize healthcare, environmental sustainability, and soft machinery, solidifying their role as a key enabling technology for future innovation.

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