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Review **TDD**

Hydrogels: Innovations, Applications, and Future Directions in Biomedical Research

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Abstract

Hydrogels are intricate three-dimensional polymeric matrices that possess the ability to absorb and retain substantial quantities of water while preserving their structural integrity. Their biocompatibility, adjustable characteristics, and capacity to emulate the extracellular matrix (ECM) render them exceedingly valuable for biomedical applications, particularly in the domains of drug delivery, wound healing, and tissue engineering. This paper investigates the classification, synthesis methodologies, properties, and various applications of hydrogels, with particular emphasis on their function in controlled drug release and regenerative medicine. Progressions in intelligent hydrogels, self-repairing materials, conductive hydrogels, and designs amenable to 3D printing are transforming both medical and technological arenas. Notwithstanding challenges, such as mechanical fragility, finite lifespan, and intricate manufacturing processes, ongoing research endeavors, are addressing these constraints to enhance hydrogel efficacy. Prospective advancements in hydrogel technology are poised to yield substantial contributions to healthcare, sustainability, and other fields.

Keywords: Biomedical applications, drug delivery, hydrogels, smart hydrogels, tissue engineering

INTRODUCTION

Hydrogels are networks of hydrophilic polymers that can hold large volumes of water while preserving their structural integrity. Hydrogels have developed from simple water-absorbing polymers to extremely complex biomaterials with uses in wound healing, tissue engineering, drug delivery, and regenerative medicine since their inception in the 1960s [1]. They can enhance cellular connections, contain bioactive substances, and permit controlled drug release because of their special capacity to mimic the extracellular matrix (ECM). The origin, composition, crosslinking technique, and sensitivity to external stimuli can all be used to categorize hydrogels [2]. Their appropriateness for biomedical applications is largely determined by these classes. The potential of hydrogels in medical research and engineering has increased due to recent developments in the field such as smart, self-healing, conductive, and nanocomposite hydrogels [3].

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CLASSIFICATION OF HYDROGELS

Hydrogels can be classified based on different factors such as their origin, composition, physical structure, and responsiveness.

Hydrogels are categorized into many different groups depending on their origin, structure, preparation method, crosslinking mechanism, charge, responsive nature, physical aspect, and degradation (Table 1) [4].

Based on Origin

Basically, hydrogels have been divided into two groups based on their origin, that is, natural and synthetic hydrogels. Recently, significant development has been achieved in designing hydrogels using natural biomass resources [5].

- *Natural Hydrogels:* Made from biological materials like gelatin, chitosan, agar, and alginate. They are biodegradable and biocompatible; due to this, they are widely used in the hydrogel wound dressing.
- *Synthetic Hydrogels:* Made from lab-created polymers such as polyacrylamide (PAAm), polyethylene glycol (PEG), and polyvinyl alcohol (PVA). They have better mechanical strength, stability, and are easy to modify.
- *Hybrid Hydrogels:* A combination of natural and synthetic materials to enhance properties. These hydrogels offer enhanced mechanical strength, tunable degradation, and improved bioactivity.

Based on Polymer Composition

- *Homopolymer Hydrogels:* Made from a single type of polymer. These hydrogels can absorb and retain significant amounts of water while maintaining their structural integrity.
- *Copolymeric Hydrogels:* Made from two or more different monomers to improve properties. The combination of multiple monomers allows for the tuning of properties such as swelling, mechanical strength, biodegradability, and responsiveness to stimuli.

Interpenetrating polymer network (IPN) hydrogels represent sophisticated hydrogels composed of two or more distinct crosslinked polymer networks that exhibit physical entanglement without covalent linkage among them. This distinctive architecture significantly improves mechanical integrity, swelling characteristics, and reactivity to various stimuli, thereby rendering IPN hydrogels exceedingly advantageous in the realms of pharmaceutical delivery, regenerative medicine, wound management, and biosensing technologies.

Based on Physical Structure [6, 7]

- *Amorphous Hydrogels:* Have a non-structured, flexible gel-like form. It consists primarily of water and hydrophilic polymers. They are considered ideal candidates for dressings due to their excellent biocompatibility.
- *Crystalline Hydrogels:* A densely packed network structure of polymers with the order of crystallization makes up crystalline hydrogels. Have a more organized structure with better strength.
- *Semi-Crystalline Hydrogels:* They are developed by chemical crosslinking and have portions of both amorphous and crystalline. It gives a balance of flexibility and strength.

Table 1. Comparison of natural, synthetic, and hybrid hydrogels.

Property	Natural Hydrogels	Synthetic Hydrogels	Hybrid Hydrogels
Source	Biological (e.g., chitosan)	Lab-synthesized (e.g., PEG)	Mix of natural and synthetic.
Biodegradability	High	Variable	Moderate to high.
Mechanical strength	Low	High	Improved over natural.
Bioactivity	High	Low	Tunable.
Typical applications	Wound dressings, scaffolds	Contact lenses, sensors	Regenerative medicine.

Based on Crosslinking Type [6, 7]

- *Physical Hydrogels:* Formed through non-covalent bonds like hydrogen bonding or ionic interactions. They are reversible and can change state under different conditions.
- *Chemical Hydrogels:* Have covalent bonds, making them more stable and durable but less reversible.

They are formed by chemical gelation processes. The three main chemical gelation processes include condensation, vulcanization, and addition polymerization.

Based on Responsiveness [6, 7]

Conventional hydrogels swell after absorbing water but do not respond or change to the application of any external stimuli.

- *Smart (Stimuli-Responsive) Hydrogels:* They are like the conventional hydrogels except these gels change properties based on temperature, pH, light, or electric fields.

SYNTHESIS TECHNIQUES OF HYDROGELS

Hydrogels are synthesized using different methods depending on the desired properties and applications. The main techniques include free radical polymerization (FRP), crosslinking, and grafting [3, 7, 8].

FRP

This is the most common method for hydrogel synthesis. FRPs constitute a category of chain polymerizations wherein the growth of each polymer molecule transpires through the sequential addition of a monomer to a terminal free radical reactive site, which is referred to as the active centre.

Steps

- *Monomer Selection:* Common monomers include acrylamide (AAm), acrylic acid (AA), and N-isopropylacrylamide (NIPAM).
- *Initiator Addition:* Thermal or chemical initiators, like ammonium persulfate (APS), start the reaction.
- *Crosslinking:* Crosslinkers, like N, N′-methylenebisacrylamide (MBA), help form a stable network.
- *Polymerization:* The reaction forms a gel-like structure.
- *Applications:* Used in drug delivery, contact lenses, and wound dressings.

Physical Crosslinking

Physical methods use non-covalent interactions, like hydrogen bonding, ionic bonding, and hydrophobic interactions, to form hydrogels.

Methods

- *Ionic Gelation:* This method relies on the electrostatic interaction between two oppositely charged polymers to form hydrogels (e.g., alginate-calcium hydrogels).
- *Hydrophobic Interactions:* Certain polymers self-assemble in water. This process happens when hydrophobic regions of polymer aggregates try to minimize their exposure to the surrounding aqueous environment.
- *Crystallization:* Polymers arrange themselves into ordered crystalline structures within the polymer network.
- *Applications:* Used in tissue engineering and injectable hydrogels.

Chemical Crosslinking

Chemical crosslinking involves covalent bond formation between polymer chains using chemical crosslinkers. This makes hydrogels more stable and durable.

Methods

- *Aldehyde Crosslinking:* It comprises the formation of a covalent bond between aldehyde-functionalized polymers and nucleophilic groups. Generally, it uses glutaraldehyde to link polymers.
- *Enzymatic Crosslinking:* It is a highly specific method to form a hydrogel. In this method, enzyme-mediated reactions are used to create covalent bonds. It uses enzymes like horseradish peroxidase.
- *Photo-Polymerization:* It uses UV light and photo initiators to generate reactive species, leading to the crosslinking of polymer chains.
- *Applications:* Used in medical implants, tissue scaffolds, and biosensors.

Grafting Polymerization

Grafting adds hydrogel properties to an existing material by attaching polymer chains to a surface.

Methods

- *Plasma-Induced Grafting:* It uses plasma energy to activate a surface before polymer attachment.
- *Radiation-Induced Grafting:* It uses gamma rays or electron beams for surface modification.
- *Applications:* Used in water purification, coatings, and smart hydrogels.

Hybrid and Nanocomposite Hydrogels

Combines hydrogels with nanoparticles, fibres, or biopolymers to enhance properties like strength, conductivity, or responsiveness. Examples:

- *Graphene-Based Hydrogels:* Improve electrical conductivity.
- *Cellulose-Based Hydrogels:* Increase biodegradability and water retention.
- *Applications:* Used in biosensors, electronics, and regenerative medicine.

PROPERTIES OF HYDROGELS

Physical Properties

- *High Water Absorption:* Hydrogels can absorb and retain large amounts of water without dissolving [9].
- *Soft and Flexible:* Due to water content and the nature of their polymer network, hydrogels are soft and flexible. Their gel-like structure makes them similar to biological tissues.
- *Swelling and Shrinking:* Hydrogels show swelling and shrinking behavior that depend on different physiological conditions.
- *Porosity:* Hydrogels exhibit a porous structure, which influences their ability to carry molecules and cells. The porous structure also allows controlled diffusion of substances.
- *Mechanical Strength:* They have a varying mechanical strength ,ranging from soft to tough, depending on their polymer type and crosslinking density.

Chemical Properties [9, 10]

- *Biocompatibility:* Biocompatibility of the hydrogel is the foremost requirement of a drug delivery system. Many hydrogels are biocompatible, making them suitable for biomedical applications.
- *Biodegradability:* Some hydrogels break down naturally, making them environmentally friendly and finding application in drug delivery.
- *Crosslinking Nature:* Can be chemically or physically crosslinked for stability.
- *pH Sensitivity:* Some hydrogels swell or shrink depending on the surrounding pH.

Biological Properties [11, 12]

- *Non-Toxic:* Many hydrogels are non-toxic and suitable for medical applications.
- *Bioactivity:* Some hydrogels support cell growth, making them useful for tissue engineering.
- *Antibacterial Properties:* Some hydrogels contain antimicrobial agents for wound healing.

Responsive Properties (Smart Hydrogels) [13]

- *Temperature-Sensitive:* Some hydrogels expand or shrink based on temperature changes.
- *pH-Sensitive:* They react to changes in acidity or alkalinity.
- *Light-Sensitive:* Some hydrogels change properties when exposed to light.
- *Electric Field-Sensitive:* Can change shape or release drugs under an electric field.

DRUG DELIVERY APPLICATIONS OF HYDROGELS

Hydrogels are used in medicine to deliver drugs in a controlled and targeted way. They help release drugs slowly, protect them from the environment, and reduce side effects (Figure 1) [14–16].

Slow and Controlled Drug Release

Hydrogels can release drugs over time, reducing the need for frequent doses. Drug release depends upon the diffusion coefficient of molecules through the gel network. Some hydrogels release drugs in response to pH, temperature, or enzymes.

- *Example:* pH-sensitive hydrogels release drugs in the intestines instead of the stomach.

Injectable Hydrogels

They are designed on the principles of conversion into the gel inside the body (*in situ-gelling*). These are liquid when injected and turn into a gel inside the body. Gelation occurring outside the body can be easily transitioned to a fluidic state upon the application of adequate shear stress. They are used for cancer treatment, wound healing, and tissue repair.

- *Example:* Hydrogels used for local chemotherapy drug delivery.

Skin Patches (Transdermal Delivery)

Hydrogel patches deliver medicine through the skin without injections. Hydrogels encompass synthetic polymers such as PVA and poly (hydroxyalkyl methacrylate), as well as biopolymers, and are extensively employed as wound dressings. The modification of these kinds of polymers for transdermal drug delivery is a highly attractive aspect and can be utilized to administer proteins. They are used for pain relief, nicotine patches, and hormone therapy.

- *Example:* Lidocaine hydrogel patches for pain relief.

Eye Drops and Contact Lenses

Hydrogels are the principal materials of soft contact lenses because of their biocompatibility and transparent characteristics. Therefore, hydrogel contact lenses are extensively used in ophthalmic drug delivery. Hydrogels hold medicine longer in the eye, improving drug absorption. They are used for diseases like glaucoma, dry eyes, and other eye infections.

- *Example:* Drug-loaded contact lenses for glaucoma treatment.

Oral Drug Delivery (Capsules and Tablets)

pH-responsive swelling plays a crucial role in the efficacy of oral and cancer-targeted delivery systems. In this context, the expansion of the hydrogels within the acidic environment of the stomach is generally limited, thereby ensuring that the drug remains physically protected and encapsulated. As the hydrogels traverse the intestinal pathway, where the pH levels are neutral, the polymeric network can be engineered to undergo significant swelling, facilitating the rapid diffusion of the therapeutic agent. It is used for probiotics, insulin, and antibiotics.

- *Example:* Hydrogel capsules that release medicine in the intestines.

Wound Healing

Hydrogels are also used for the treatment of skin wounds. For this purpose, hydrogels are placed on the dynamic surfaces, and they must adhere and conform to such surfaces while being tough enough to tolerate the surface movement and deformation derived from the environment. Hydrogel bandages keep wounds moist and release antibiotics.

- *Example:* Silver nanoparticle hydrogels for antibacterial wound healing.

INNOVATIONS IN HYDROGEL DESIGN

Researchers are enhancing hydrogels to render them more intelligent, resilient, and functional. Presented herein are several intriguing recent advancements [17–20].

Smart Hydrogels

Stimuli-responsive hydrogels may be classified as advanced biomaterials, wherein external stimuli, including pH levels, temperature variations, electrical and magnetic fields, light exposure, and the concentrations of biomolecules, can be employed to facilitate the release of pharmacological agents.

- *Example:* pH-sensitive hydrogels release medicine only in the intestines.

Self-Healing Hydrogels

Self-healing hydrogels autonomously rejuvenate their structural integrity when compromised or subjected to physical trauma. It exhibits enhanced characteristics regarding durability and stability attributable to its ability to reconstitute its form, injectability, and elasticity, thus restoring its original mechanical properties.

- *Example:* Used in artificial skin and wound healing.

Conductive Hydrogels

Conductive hydrogels (CHs) exhibit elevated conductivity and notable electrochemical redox characteristics, enabling their application in the detection of electrical signals produced within biological systems, as well as in the administration of electrical stimulation to modulate cellular activities and functions, which encompass cell migration, cell proliferation, and cell differentiation. Such properties confer upon CHs distinct advantages in the realm of tissue repair.

- *Example:* Helps restore nerve signals in damaged tissues.

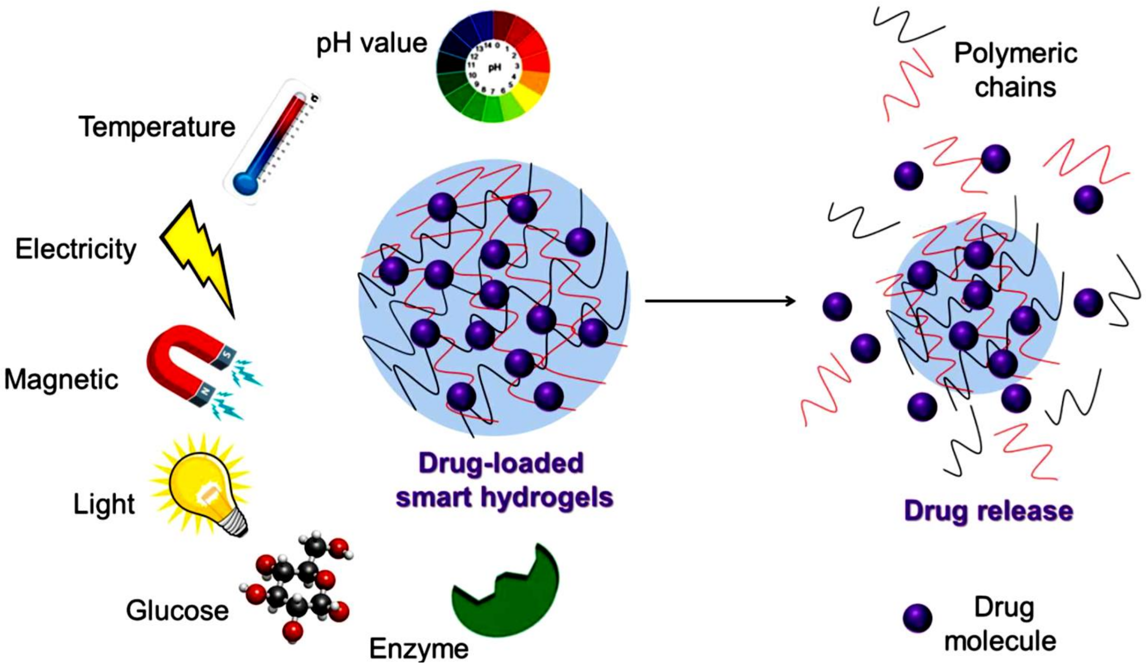

Figure 1. Various external stimuli, including pH, temperature, electricity, magnetism, light, and biomolecules (including glucose and enzymes), are controlling the drug release from a smart hydrogel [2].

3D Printable Hydrogels

Three-dimensional (3D) printing, recognized as a burgeoning and adaptable additive manufacturing technology, has been employed to produce hydrogel constructs characterized by intricate architectures, albeit these gels frequently exhibit mechanical fragility. In comparison to conventional processing methodologies, 3D printing offers significant advantages, including a simplified operational protocol, meticulous structural precision, and enhanced cost efficiency.

- *Example:* Used for growing artificial organs.

Stronger Hydrogels (Nanocomposites)

Nanocomposite hydrogels consist of 3D, crosslinked polymeric frameworks that integrate nanomaterials – such as clays, metallic nanoparticles, or carbon-based nanostructures—within their matrix to augment mechanical robustness, thermal resilience, and functional reactivity for sophisticated biomedical and engineering applications (Table 2).

- *Example:* Used for bone repair and wound healing.

Sticky Hydrogels

Sticky hydrogels are used for wound closure, tissue adhesives, and wearable bioelectronics. They are engineered polymer networks reinforced with nanoscale fillers and functional groups, like catechols or aldehydes, that make their adhesion strong and reversible to wet and dynamic biological surfaces.

- *Example:* Stops bleeding in surgeries.

Eco-Friendly Hydrogels

They are derived from natural sources like cellulose, chitosan, or alginate. Eco-friendly hydrogels are sustainable, biodegradable polymer networks designed to minimize environmental impact while maintaining functionality for applications such as agriculture, water purification, and biomedical devices.

- *Example:* Used for water storage in dry areas.

Table 2. Recent innovations in hydrogels.

Innovation Type	Function/Advantage	Example Use
Smart hydrogels	Stimuli-responsive drug delivery	Intestinal pH release.
Self-healing hydrogels	Auto-repair upon damage	Artificial skin, bandages.
Conductive hydrogels	Electrical signal transmission	Nerve regeneration.
3D printable hydrogels	Complex scaffold fabrication	Organ printing.
Nanocomposite hydrogels	Enhanced strength and functionality	Bone repair, wound care.
Sticky hydrogels	Adheres to wet tissues	Surgical adhesives.
Eco-friendly hydrogels	Sustainable, biodegradable sources	Water storage, agriculture.

APPLICATIONS BEYOND DRUG DELIVERY

Hydrogels are useful in many areas besides medicine. They can absorb water, stay flexible, and react to changes in the environment.

Wound Healing

Hydrogels provide a moist environment and increase contact time, which helps to facilitate the healing process [21].

- *Example:* Hydrogel bandages for burns and cuts.

Tissue Engineering

Hydrogels are being used as scaffold materials because they are structurally similar to the ECM of many tissues. They help to grow new skin, bone, or organs [22].

- *Example:* Used to create artificial skin for burn victims.

Contact Lenses

Soft contact lenses are constructed from hydrogel or silicone hydrogel substances, which are purposely engineered to retain a considerable volume of water, thereby facilitating their maintenance of softness, flexibility, and permeability. This elevated water content is instrumental in preserving the lenses' moisture levels throughout the day, mitigating dryness and discomfort, and rendering them more suitable for prolonged use [23].

- *Example:* Contact lenses that keep the eyes hydrated.

Agriculture (Water Storage)

Agricultural hydrogels retain water and swell to a larger size, which is several times their original size. On contact with water, they absorb huge amounts of moisture, retain it, and release it back to the soil to suffice the crop requirement during drought conditions [24].

- *Example:* Hydrogels that help crops to grow in dry areas.

Sensors and Electronics

Hydrogels possess the capacity to emulate the mechanical characteristics of biological tissues, rendering them suitable for applications in wearable and implantable sensor technologies. Their ability to respond to various stimuli, such as temperature, pH, or pressure, enables them to be utilized as intelligent sensors in the areas of healthcare monitoring, soft robotics, & environmental sensing applications [25].

- *Example:* Smart hydrogels for glucose monitoring.

Food Industry

In the food industry, hydrogels are used as moisture-retaining agents to help keep food moist and fresh for longer periods.

- *Example:* Edible coatings for fruits.

Water Purification

In water purification, hydrogels play a valuable role because of their high-water absorption capacity, tunable porosity, and ability to be functionalized with specific chemical groups. They can be engineered to selectively absorb or adsorb contaminants such as heavy metals, dyes, and organic pollutants from wastewater.

- *Example:* Hydrogel sponges that clean dirty water.

LIMITATIONS AND CHALLENGES

Hydrogels are very useful, but they also have some problems [26–30].

Weak Strength

Mechanical properties of many hydrogels depend on physical interactions rather than covalent bonds, which makes them prone to rupture easily under pressure.

- *Problem:* It cannot be used for strong materials like bone repair.

Short Lifespan

Some hydrogels have shorter lifespans due to their biodegradability, hydrolysis, and enzymatic breakdown, environmental conditions, and low cross-linking density.

- *Problem:* Not long-lasting for medical or industrial use.

Slow Response Time

The response of some hydrogels depends upon the external stimuli such as pH, temperature, light, or electric fields. If the response of the hydrogel towards external stimuli is delayed, then the required actions, such as drug release, also get affected.

- *Problem:* Delayed effect on drug delivery.

Hard to Make

The synthesis and processing of hydrogels is often challenging due to the complexity in the cross-linking, sterility and biocompatibility, and scalability.

- *Problem:* High cost and complex production.

Swelling and Shrinking

As hydrogels change their size based on water content, dimension instability, mechanical stress, impaired functionality, and storage problems are some of the major concerns.

- *Problem:* Hard control in medical implants (Figure 2).

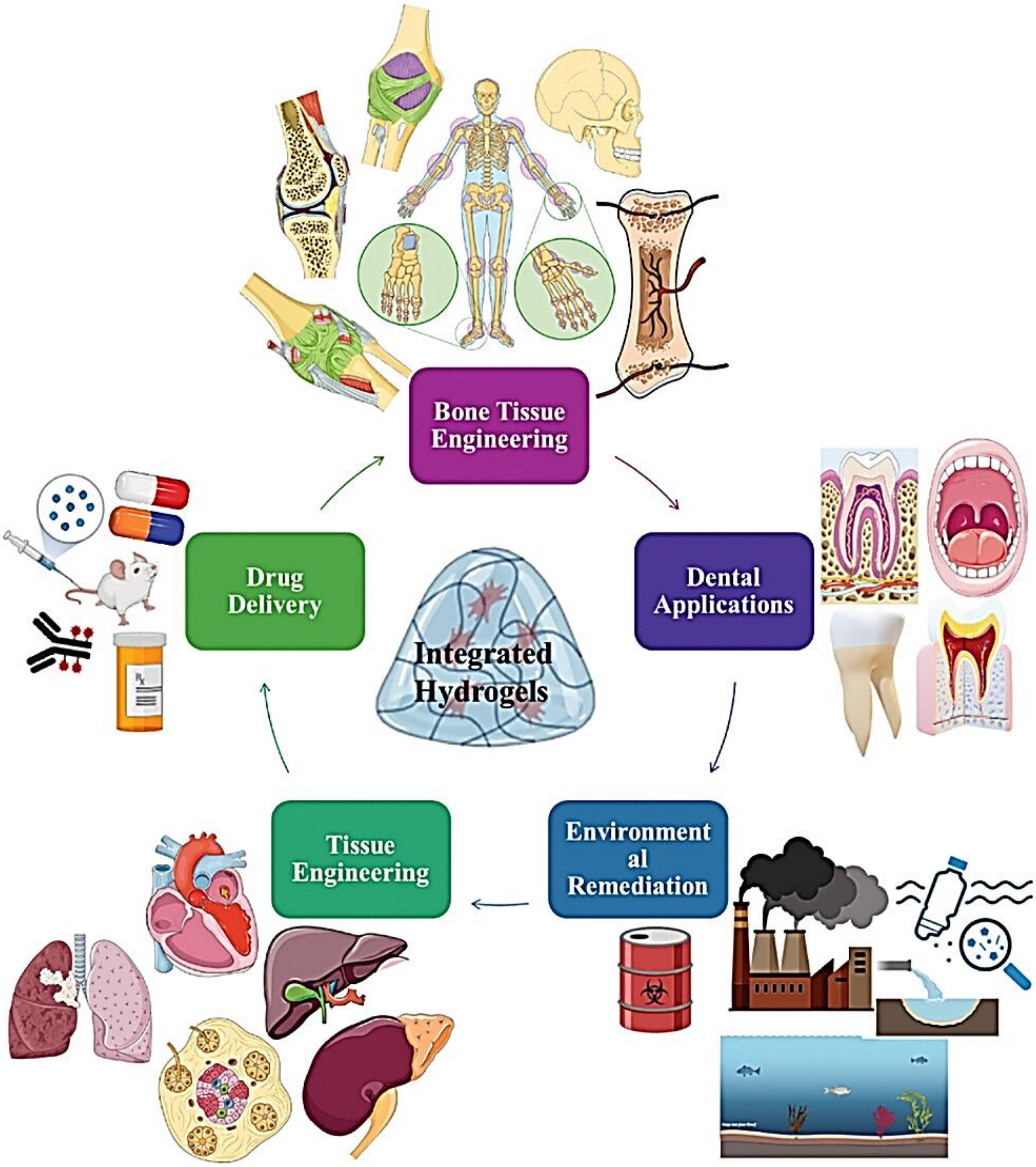

Figure 2. Multifunctional applications of integrated hydrogels [31].

CONCLUSIONS

Hydrogels are versatile materials with many uses in medicine, agriculture, electronics, and environmental science. Their ability to absorb and retain water, respond to external stimuli, and be biocompatible makes them valuable for uses such as drug delivery, wound healing, tissue engineering, and many more.

Despite various challenges, like complex manufacturing, scalability, low strength, and short lifespan, there are continuous efforts being made to develop stronger, smarter, and eco-friendly hydrogels. Future innovations will improve their durability, responsiveness, and applications in advanced medicine and technology.

With ongoing research, hydrogels will continue to transform healthcare, sustainability, and engineering, making life better in many ways.

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