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Stimuli-responsive hydrogel actuators for skin therapeutics and beyond

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Abstract

Stimuli-responsive hydrogels are innovative soft materials that have garnered significant attention in recent years. These hydrogels can undergo phase transitions or structural changes in response to external stimuli, offering considerable potential for use as actuators. They can effectively be used for drug delivery and disease treatment by responding flexibly to a variety of stimuli. This paper first categorizes the types of external stimuli that hydrogel actuators respond to and outlines their applications in skin therapeutics. It then reviews therapeutic potentials of hydrogel actuators beyond the skin, and discusses the challenges and future prospects for the development of stimuli-responsive hydrogel actuators.

Keywords: Hydrogel actuators, stimuli-responsive hydrogels, wearable hydrogels, drug delivery

INTRODUCTION

Stimuli-responsive hydrogels are intelligent soft materials that proactively react to various external environmental stimuli, such as temperature, light, pH, electricity, and magnetic fields[1]. Under these stimuli, hydrogels can exhibit reversible or irreversible behaviors such as expansion, contraction, and deformation, creating internal stress that drives their conversion[2]. Additionally, hydrogels possess flexibility, high water

content, excellent biocompatibility, and tunable physicochemical structures and properties[3]. These unique characteristics make stimuli-responsive hydrogels ideal for developing soft actuators. These actuators can employ diverse structural and functional designs to modify their physicochemical properties, detect environmental stimuli, undergo shape changes and movement processes, adapt to complex environments, and meet functional requirements under varying conditions[4].

The properties of stimuli-responsive hydrogel actuators are promising in the biomedical field, particularly in on-demand drug delivery[5]. These actuators possess mechanical and soft material properties, and their excellent biocompatibility makes them superior to similar products in biomedical applications[6]. Their structural similarity to the extracellular matrix (ECM) allows for safe and effective integration into the human physiological environment, adapting to diverse and complex conditions and facilitating drug acquisition and release[7]. Hydrogels have a porous network structure that can load drugs within the gel, with pore size adjustable by altering the hydrogel's crosslinking density[8]. Stimuli-responsive hydrogel actuators can contract, swell, and decompose by responding to external stimuli, enabling the controlled release of drugs to deliver the optimal dose to the target area at the appropriate time[9]. Furthermore, the drug delivery effect of hydrogel actuators can be precisely controlled in time and space, meeting various treatment needs, enhancing treatment efficacy, reducing adverse side effects, and ultimately achieving the goal of disease treatment.

This paper reviews the various types of external stimuli to which stimuli-responsive hydrogel actuators can respond, outlines their performance and application pathways, and highlights their biomedical applications in skin therapeutics and beyond [Figure 1].

TYPES OF STIMULI-RESPONSIVE HYDROGELS

Natural systems constantly respond and adapt to changes in their environment. Inspired by nature and bionics, various soft actuators have been designed and developed. Among them, hydrogel actuators demonstrate significant potential in drug delivery and biomedical engineering, owing to their resemblance to soft biological tissues, high water content, flexibility, and biocompatibility. Because hydrogel actuators can achieve specific responses to different stimuli, they are well-suited for applications in various biomedical engineering fields. Studies have shown that when biological tissues are affected by trauma or disease, their pH, temperature, enzyme levels, and other states change. As a "smart" stimuli-responsive material, hydrogel actuators can respond to various environmental stimuli, including pH, electricity, temperature, and light [Table 1]. The specific structure of stimuli-responsive hydrogel actuators allows for controllable target deformation and function [Figure 2], making them advantageous in drug delivery and disease therapy.

pH-responsive hydrogel actuators

Altered pH values are closely linked to many physiological processes. Under normal conditions, the pH ranges from gastric acid (pH 1-3) to the duodenum (pH 6) and the jejunum and ileum (pH 6-7.5)[36]. In abnormal conditions, such as inflammation, bacterial infection, wound healing, tumors, and other pathological environments, pH levels change correspondingly. pH-responsive hydrogels contain easily hydrolyzed units, including carboxyl, sulfonate, and amino moieties, which dissociate or protonate according to the environmental pH, leading to changes in electrostatic interactions and ultimately altering the volume of the hydrogel[37]. These hydrogels can exhibit swelling and deswelling deformation characteristics in response to pH changes under different physiological conditions, making them highly applicable in the biomedical field. pH-responsive hydrogel actuators can be classified as cationic or anionic based on their functions[38]. Their swelling mechanisms include changes in hydrophobic properties,

Table 1. Advantages, disadvantages, and biomedical applications of different stimuli-responsive hydrogel actuators

Stimulus-responsive	Advantages	Disadvantages	Biomedical applications	Ref.
pH	(1) High specificity (2) Precise release	(1) Difficult to biodegrade	(1) Cancer treatment (2) Periodontal disease (3) Gastrointestinal disease (4) Periocular disease (5) Diabetic wound healing	[10-14]
Temperature	(1) Easy to control (2) Simplicity of operator (3) Short response time (4) Wide application	(1) Poor biocompatibility (2) Unable to take active control	(1) Cancer treatment (2) Periodontal disease (3) Periocular disease (5) Diabetic wound healing	[15-18]
Electricity	(1) Actively controlled (2) Can adjust	(1) Gel fatigues easily (2) Requirements for instruments	(1) Wound healing (2) Drug delivery	[19,20]
Glucose	(1) Good biocompatibility (2) Long duration	(1) Slow response (2) Gel recovery was slower	(1) Periodontal disease (2) Diabetes mellitus (3) Diabetic wound healing	[21-23]
Enzyme	(1) High efficiency (2) High specificity	(1) Strict environmental conditions (2) Cause needs a prerequisite	(1) Cancer treatment (2) Periodontal disease (3) Gastrointestinal disease	[24-26]
Light	(1) Safe (2) Sensitive (3) Low cost	(1) Difficult to penetrate the tissue	(1) Cancer treatment (2) Periodontal disease	[27,28]
Magnet	(1) Actively controlled (2) Wireless and remote	(1) Not biodegradable	(1) Cancer treatment (2) Drug delivery	[29,30]
Redox	(1) Target release	(1) Unable to take active control	(1) Periodontal disease (2) Gastrointestinal disease (3) Diabetic wound healing	[31-33]
Ultrasound	(1) Safe (2) Trigger remotely	(1) Destroy the gel structure	(1) Gastrointestinal disease (2) Drug delivery	[34,35]

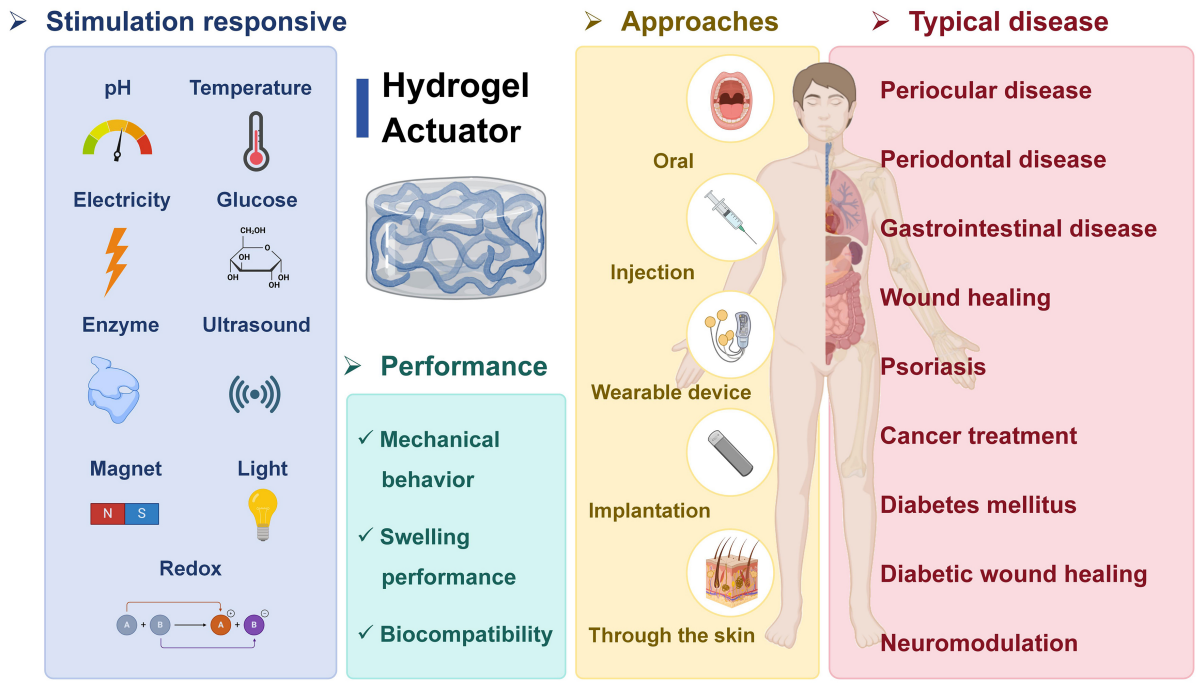

Figure 1. Stimuli-responsive hydrogel actuators for therapeutics, including the type of stimulus responses, hydrogel actuator performance, application, and treatable typical diseases. (Created in BioRender.com).

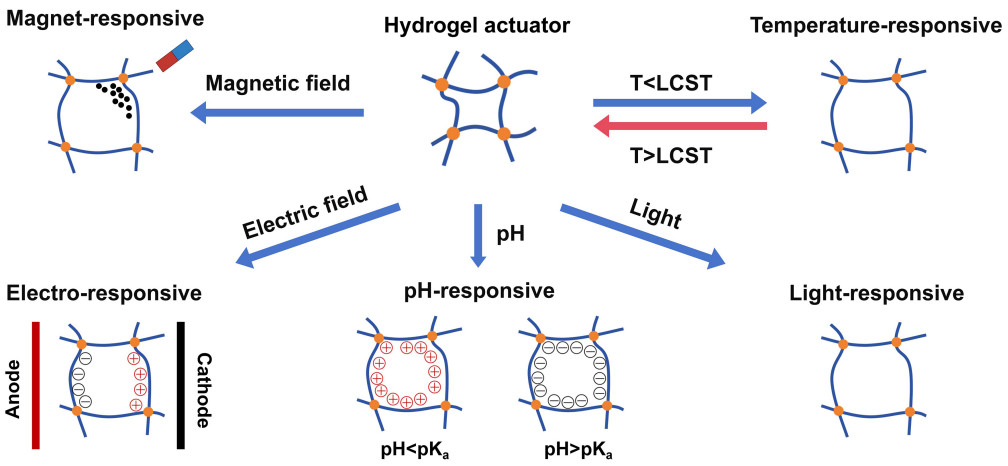

Figure 2. Schematic diagram of the actuation mechanism of stimulus-responsive hydrogel actuators.

intermolecular and intramolecular hydrogen bond complexing, and electrostatic repulsion[39]. When hydrogels synthesized from polymers with acidic or basic groups are used as actuators, the pH change in pathological environments can intelligently regulate the passive release of drugs. For example, in a wound with higher pH, the hydrogel expands due to electrostatic repulsion between ionized carboxyl groups, releasing more drugs. As the wound heals and pH decreases, the drug release also diminishes. The rate of drug release can be further regulated by changing the material ratio and composition of the hydrogel, thus achieving sensitive pH response and precise target function, ensuring maximum biosafety[40].

Temperature-responsive hydrogel actuators

Temperature-responsive hydrogels are capable of responding to changes in ambient temperature, offering easy control, simple operation, and short response times. These hydrogels possess both hydrophilic and hydrophobic groups, and temperature variations can affect hydrophobic interactions and hydrogen bonds between polymer chains. As a result, changes in temperature cause the hydrogel actuator to expand or contract due to alterations in enthalpy and entropy equilibrium, molecular rearrangement, and interactions between the hydrogel internal network structure and water[41]. Temperature-responsive hydrogel actuators are classified into positive and negative response types, including those with upper critical solution temperature (UCST) and lower critical solution temperature (LCST)[42]. Most temperature-responsive hydrogels have a LCST in water. When the temperature is below the LCST, the hydrophobic interaction between the hydrogel polymer chains weakens, causing the hydrogel network to expand. When the temperature rises to a state higher than the LCST, the hydrophobic interaction increases, causing the hydrogel network to shrink and transition into a gel state. Conversely, hydrogels with a UCST dissolve upon heating[43]. An important feature of temperature-responsive hydrogel actuators is their ability to transition from a liquid or semi-solid state at room temperature to a gel state at body temperature[44]. This feature allows the hydrogel to load therapeutic materials in a liquid state and form a gel, releasing the drug upon injection into the tissue[45]. For instance, during wound healing or tumor treatment, local inflammation can raise the wound temperature, causing the temperature-responsive hydrogel actuator to change its state and volume, thereby increasing drug release at the wound site. This feature makes temperature-responsive hydrogel actuators widely used in the field of biomedical engineering.

Electro-responsive hydrogel actuators

A hydrogel actuator that responds to external environmental changes by expanding or contracting is called an electro-responsive hydrogel actuator[46]. As a rare type of stimuli-responsive hydrogel actuator that can be

actively controlled, electro-responsive hydrogel actuators offer the advantage of highly controllable actuation states and adjustable actuation degrees. They can easily, remotely, and repeatedly generate stimulation signals, meeting therapeutic needs for *in vivo* applications and adjustable release. The most common way to achieve this is by introducing conductive polymer structures into the hydrogel scaffold[47]. This enables electro-responsive hydrogel actuators to respond to electrical signals while maintaining high hydrophilicity, biocompatibility, and the ability to deliver different molecules. The highly cross-linked polymer network of hydrogel actuators possesses mechanical properties similar to biological tissues, and the highly porous structure can store drugs. When an electrical signal is applied, the hydrogel aperture increases, and the hydrogel network expands. The expansion and collapse of the hydrogel actuator provide a switching system for drug release, meeting the need for intermittent and prolonged administration for medical conditions such as cancer, diabetes, and chronic pain. By adjusting the voltage, current density, and pulse conditions applied to the hydrogel actuator, on-demand drug release can be achieved. With the development of flexible electronics, even *in vivo* implantation is possible.

Glucose-responsive hydrogel actuators

As the primary energy source for normal physiological activities, glucose levels are typically regulated by a strict feedback mechanism[48]. The human pancreas controls the release of endogenous insulin by monitoring glucose levels in the body. In diabetic patients, this feedback regulation system becomes imbalanced, affecting insulin secretion. Glucose-responsive hydrogels can recognize and respond to various glucose molecules, such as phenylboronic acid (PBA), glucose oxidase (GOx), and glucose-binding molecules (GBM)[49]. These three mechanisms have been extensively researched. Therefore, glucose-responsive hydrogel actuators hold significant potential for insulin delivery. For instance, in diabetes, these hydrogel actuators can identify glucose molecules in the external environment, thereby altering their physicochemical structure and properties to facilitate insulin release and supplementation.

Enzyme-responsive hydrogel actuators

Enzymes are widely found in various human tissues and can directly reflect the body's health status. Due to their high sensitivity and selectivity in living organisms, enzyme-responsive hydrogel actuators have attracted considerable attention[50]. Drugs loaded in the hydrogel can initiate an enzymatic response under the recognition of a specific enzyme, releasing the drug to the corresponding target site. Enzyme-responsive hydrogels exhibit low swelling at low pH, which can protect protein drugs from digestion by proteolytic enzymes in the stomach. Existing enzyme-responsive hydrogels include enzyme reaction hydrogel nanoparticles (NPs), magnetic hydrogels, drug reaction hydrogels, and hydrogels for dual protein delivery[51]. These hydrogel actuators can be used in a wide range of biomedical engineering applications, such as wound healing, protein delivery, and antimicrobial scaffolds.

Light-responsive hydrogel actuators

Based on different wavelengths and energy levels, light stimulation sources can be divided into natural light, ultraviolet (UV) light, near-infrared (NIR) light, and infrared light[46]. Due to its rapid, non-contact, and sensitive characteristics, light stimulation has significant application potential in the biomedical field. Light-responsive hydrogels are categorized into two types: (i) hydrogels containing photoisomerization/photoionizing chromophores and (ii) hydrogels containing photothermal agents[52]. They can also be classified into UV-responsive hydrogels and visible light-responsive hydrogels based on the light stimulation sources. Visible light is particularly advantageous due to its accessibility, safety, and low cost. Light-responsive hydrogels can change their properties through three mechanisms in response to external light stimuli. First, photosensitive groups grafted onto the hydrogel initiate a response and deformation after absorbing photons with sufficient energy. Second, photoactive molecules within the hydrogel produce ions that react with the hydrogel network or alter its osmotic pressure, causing expansion. Finally, hydrogel

actuators containing photosensitivity factors can change their properties by absorbing photons to gain energy[53]. Light-responsive hydrogel actuators can achieve high sensitivity for remote control and operation without the need for complex external equipment[54]. They can produce the necessary structural or physicochemical changes under light irradiation to meet required treatment modes. Additionally, the light conditions can be externally adjusted, allowing the hydrogel actuator to respond dynamically to light of sufficient intensity and appropriate wavelength.

Magnet-responsive hydrogel actuators

Magnet-responsive hydrogel actuators can respond to applied magnetic field stimuli. Unlike other stimulation modes, magnet-responsive hydrogel actuators are modified by adding paramagnetic or ferromagnetic substances, which impart sensitivity and precision to external magnetic stimulation[55]. When exposed to a magnetic field, the magnetic material in the hydrogel network aligns with the field, causing part of the hydrogel structure to move. This alignment allows the magnet-responsive hydrogel actuator to respond and move according to the magnetic field guidance, achieving the desired actuation[56]. Additionally, magnetic stimulation can increase the temperature, causing the hydrogel to expand or contract[57]. The magnetic field can act as a remote switch to control the hydrogel actuator, making it suitable for remote actuation. Due to their superparamagnetism and biocompatibility, magnet-responsive hydrogels can be applied in biomedical fields, such as minimally invasive surgery and targeted drug administration[58].

Redox-responsive hydrogel actuators

Redox-responsive hydrogel actuators are achieved by redox reactions occurring in the internal network structure of the hydrogel. Adding redox-active components to the hydrogel network can control molecular interactions, thereby causing swelling or shrinking[40]. Redox points can be established through high concentrations of glutathione (GSH) in the cytoplasm and intracellular organelles[59]. In pathological environments, redox potential changes significantly[53], triggering the hydrogel's drug delivery. Significant differences in glutathione concentrations make redox-responsive nanohydrogels an intelligent platform for controlled and precise drug delivery. Oxidation-responsive hydrogel actuators respond to reactive oxygen species (ROS), facilitating hydrogel degradation and drug release. During drug delivery, redox-responsive hydrogel actuators respond to redox phenomena in specific regions and thus function effectively.

Ultrasound-responsive hydrogel actuators

Ultrasound is widely used in medical fields such as disease diagnosis and treatment due to its safety and non-invasive characteristics. It introduces biological effects into cells and tissues through three main mechanisms: heat, cavitation, and acoustic flow[49]. Similar to other exogenous stimuli, ultrasound can be used to remotely trigger on-demand administration and achieve deep tissue penetrating therapy. For both treatment and diagnosis, ultrasound can act on living tissues and cells either thermally or mechanically. Hydrogels serve as carriers for small bioactive molecules such as different drugs, growth factors, and antibodies[60]. Ultrasound can promote drug release without disrupting the gel network, allowing for spatially controlled delivery of therapeutic agents. This can be achieved through different methods, including pulsed, unidirectional burst release, and prolonged release after *in vivo* administration[61].

Multiple stimuli-responsive hydrogel actuators

Given the variability of disease environments and differences between individuals, it is essential to develop new hydrogels that can dynamically adapt to their surroundings. Multiple stimuli-responsive hydrogel actuators can respond simultaneously to various environmental stimuli, allowing for independent regulation of each stimulus. This combination of multiple stimuli enables more precise drug delivery, thereby achieving better therapeutic outcomes. In practice, while hydrogel actuators rely on two or more

stimuli, the synergistic response performance of each stimulus is crucial. Compared to single stimuli-responsive hydrogels, multiple stimuli-responsive hydrogels offer greater control over their behavior, enhancing overall performance and applicability.

PROPERTIES OF HYDROGEL ACTUATORS

Stimuli-responsive hydrogel actuators possess high water content, mechanical strength, and biocompatibility, enabling them to respond to external stimuli through phase or structural changes. Many studies have demonstrated the feasibility of stimuli-responsive hydrogel actuators. In this section, we summarize necessary characteristics of hydrogel actuators, and then discuss their applications in therapeutics.

Characteristics of hydrogel actuators

Mechanical behavior

The high water content and porous structure of hydrogels give them a softness similar to that of native tissue. Common parameters used to indicate the mechanical properties of hydrogels include stiffness, compressive strength, tensile strength, pore size, and toughness[47]. Conventional stimuli-responsive hydrogels often have weak mechanical properties, slow response times, and poor environmental tolerance, which limit their applications in soft actuators. Constructing reversible non-covalent bonds, such as hydrogen bonds, electrostatic interactions, and coordination bonds, can effectively enhance the mechanical properties of hydrogel actuators. This improvement is crucial for increasing the toughness of hydrogels, and these reversible non-covalent bonds can also impart self-healing properties[46]. Additionally, the crosslinking method significantly affects the mechanical properties of hydrogel actuators. Typical chemical cross-linking networks offer more stable and stronger mechanical properties, while physical cross-linking networks are flexible, stretchable, and sometimes self-healing[62]. Therefore, different crosslinking methods produce hydrogels with varying excellent physical and chemical properties[40]. Some studies have shown that NP doping and chemical cross-linking are also key methods to improve mechanical properties[63]. The application of hydrogel actuators in different biomedical fields requires diverse mechanical properties. For example, hydrogel stiffness is necessary for tissue matrix substitutes. Stiffness has been shown to affect cell activity and function, ultimately achieving cellular and tissue homeostasis. Furthermore, the porous structure is another vital feature of hydrogels, serving as transport channels for drugs and other substances, regulating many physiological activities, and determining the effects of biomedical applications. Elasticity in the interactions between hydrogel and tissue can regulate interactions with the surrounding matrix and may lead to variations in cell diffusion.

Swelling performance

Swelling capacity is a crucial property for biomedical applications. The swelling properties depend on their pore size, internal network structure, and hydrophilic and hydrophobic characteristics[64]. These properties result in different swelling behaviors, categorized into high swelling, non-swelling, and negative swelling[65]. For example, hydrophilic hydrogels with large mesh sizes are highly prone to swelling, whereas hydrophobic hydrogels with a higher degree of crosslinking exhibit minimal swelling. The swelling performance of hydrogels is crucial in the biomedical field, as it enables drug release, substance transfer, and absorption of wound secretions. Hydrogels with varying swelling levels have distinct application prospects. Hydrogels with high swelling properties are extensively used in wound healing and drug administration. In contrast, non-swelling hydrogels are crucial in tissue adhesives and bioelectronics due to their ability to maintain stable morphology and physical properties in physiological environments. Some hydrogels also exhibit negative swelling, which can be utilized for non-invasive wound closure and drug release.

Biocompatibility

Hydrogel actuators have high biocompatibility, which not only preserves the functions of encapsulated drugs and biomolecules but also reduces the inflammatory response when applied[66]. Furthermore, hydrogels exhibit antibacterial properties that are crucial in the biomedical field. The prevailing view is that hydrogels bind to the negatively charged bacterial cell walls, causing changes in membrane permeability. This inhibition of cellular DNA replication ultimately leads to cell death[67]. To achieve optimal functionality, further improvement and optimization of hydrogels are necessary.

Hydrogel actuators in skin therapeutics

Wearable hydrogel actuators

Hydrogels serve as an important bridge connecting electronics and biology due to their flexible properties in mechanics, electronics, and biology. Especially in wearable bioelectronics, they demonstrate better biocompatibility and flexibility compared to elastomer materials[68]. Hydrogel can be integrated with wearable electronics in various forms such as patches, tattoos, and fibers, and serve roles such as adhesion layers, stimuli-responsive elements, energy storage, and sensing components[69-79]. Hydrogel wearable devices enable continuous monitoring of physical and biochemical parameters of the human body. Furthermore, they are often used to modulate drug delivery and neural mechanisms. Their ease of integration with wireless communication also paves the way for applications in personal home monitoring and remote medical practices[80,81].

Transdermal hydrogel actuators

Using hydrogel as a wound dressing can keep the wound moist while promoting healing and avoiding secondary injury[82]. The mechanism involves the absorption and retention of wound exudates, which contribute to the proliferation of fibrocytes and migration of keratinocytes, thereby promoting healing[49]. Additionally, the hydrogel acts as a barrier, reducing infection risk due to its inherent antibacterial properties. In drug delivery, drugs, antibiotics, and other substances can be incorporated into the hydrogel for continuous treatment. Due to its flexibility, hydrogel can adapt to various wound surfaces, such as traumatic, burn, and diabetic wounds[83]. Hydrogel dressings are particularly advantageous for complex wounds, such as diabetic wounds, where traditional dressings are less effective. Traditional dressings often serve only as physical barriers and provide short-term drug supplements, which are insufficient for the high-glucose environment and biochemical disorders of diabetic wounds[84]. Hydrogel dressings, with their physicochemical properties similar to the natural ECM, can be easily loaded with drugs or cytokines for effective treatment[46]. Additionally, stimuli-responsive hydrogel actuators retain collagen properties and can change shape, size, or volume in response to stimuli, enhancing treatment effectiveness and drug utilization, and promoting wound healing.

Monitorable hydrogel actuator

Biosensors are able to sensitively monitor environmental and physiological indicators in humans and provide real-time feedback. The unique properties of stimuli-responsive hydrogel actuators, which can undergo reversible phase volume transitions under environmental stimuli, offer additional options for biosensors[85]. These hydrogels interact specifically with target biomolecules, enabling detectable physical or chemical changes within the hydrogel matrix. This specific detection method allows hydrogel actuators to accurately quantify interactions, thereby enabling the monitoring of various physiological indicators. Hydrogel sensors can track a range of physiological indicators and biomarkers in the human body, facilitating early health warnings, disease detection, and other functions[86]. The excellent mechanical properties and biocompatibility of hydrogel actuators make them suitable for safe, long-term use in the human environment. Furthermore, these actuators exhibit high sensitivity and specificity in response to environmental stimuli, making them particularly useful in disease monitoring applications, such as diabetes

management, where high precision is essential[87]. The integration of these unique properties with modern electronic technology broadens the application scenarios for hydrogels, offering promising prospects for the development of intelligent medical systems that integrate monitoring, diagnosis, and treatment.

Other hydrogel actuators

Ingestion

Oral administration is the most common method of drug delivery due to its convenience, non-invasiveness, and low cost. However, the harsh digestive environment of the gastrointestinal tract and the transport limitations of the gastrointestinal mucosa significantly affect drug absorption, particularly for biological agents[88]. Additionally, drugs administered orally have longer transport times and slower onset. Hydrogel actuators, which respond to external stimuli by swelling, can enter the gastrointestinal tract orally, shrink into a dense state to protect encapsulated drugs, and ensure targeted release at specific locations[89]. This approach also slows down the release rate, preventing premature drug release before reaching the target site. Some hydrogel actuators can quickly absorb gastric juice and respond to pH changes, minimizing damage to gastric wall cells[90]. Stimuli-responsive hydrogel actuators provide an effective means for treating gastrointestinal diseases, enabling a broader range of drugs to be used. Moreover, these systems can achieve gastrointestinal residence by utilizing pH or enzyme differences in the gastrointestinal environment for controlled, targeted drug release. Continuous and stable drug release during the treatment period improves drug efficacy. Therefore, hydrogel actuators are an excellent choice for oral drug delivery. By adjusting various parameters, hydrogels can be tailored for different physiological conditions, offering broad application prospects in the treatment of gastrointestinal diseases.

Injection

Compared to conventional implantable hydrogel actuators, injectable hydrogel actuators respond more easily to various stimuli and avoid frequent invasive surgeries, offering a novel approach for chronic disease treatment[19]. In drug delivery, hydrogels are excellent carriers due to their high water content and biocompatibility. Unlike traditional injectable drug methods, injectable hydrogels provide local, controllable, and continuous drug delivery[91]. Injectable hydrogels should be in a low-viscosity sol state before injection, and then gelate and cross-link through various chemical or physical interactions post-injection. Subsequently, the hydrogel should undergo gradient absorption and degradation, ensuring the byproducts are non-toxic[92]. Additionally, injectable hydrogels can dynamically adjust in response to different external stimuli, tailored to specific disease treatments. Among various stimuli-responsive modes, temperature and electrical stimuli are the most effective. Temperature-responsive hydrogel actuators can transition from liquid to solid as ambient temperature changes from room temperature to body temperature during injection. This allows drugs to be loaded into the hydrogel in a liquid state and continuously released at the target site once the hydrogel solidifies in the body. During wound healing, increased inflammation raises wound temperature, causing the hydrogel actuator to change volume and increase drug release at the wound[5]. Electrical stimulation is easier to produce and control compared to other stimuli-responsive modes, despite the poor degradability of conductive polymers.

Implantation

Implantable hydrogel actuators can be used for the diagnosis and treatment of various diseases. The implanted hydrogel exhibits stable mechanical properties, and its physical and chemical structure helps to minimize immune responses, provide a stable microenvironment, and ensure long-term retention at the target site. This stability enhances the effectiveness, reliability, and continuity of treatment[63]. The hydrogel's intrinsic properties allow it to mimic the mechanical and biochemical characteristics of human tissues, resulting in reduced nonspecific binding to interfering molecules and lower background signals. Flexibility, biodegradability, and non-toxicity are critical parameters of hydrogel actuators. As hydrogel technology

advances, its applications can extend to challenging deep areas such as the heart, lungs, and brain. The hydrogel actuator releases drug molecules into the surrounding tissue environment, achieving a therapeutic effect.

HYDROGEL ACTUATORS FOR THERAPEUTICS

The unique properties make hydrogel actuators promising for biomedical and drug delivery applications. These hydrogels can load various drugs and release them in response to specific external stimuli to achieve targeted functions. In this section, we summarize the typical diseases treated using hydrogel actuators as therapeutic methods [Table 2].

Skin diseases

Wound healing

As a barrier between the human body and the outside world, the skin is highly susceptible to injury. Modern clinical development of wound dressings has increasingly focused on combining excellent antibacterial properties with enhanced wound healing capabilities[108]. The functions of wound dressings include protecting wounds, reducing bacterial presence, and promoting healing. Hydrogels, with their beneficial properties, can simulate the ECM environment, allow sufficient gas exchange, absorb wound exudates, maintain a moist environment, and minimize the risk of bacterial infection[109]. Therefore, hydrogels are ideal for wound dressings. Furthermore, hydrogels can serve as a drug reservoir, enabling on-demand drug release and exchange of wound exudates in response to environmental stimuli to meet various demands[110]. Hydrogel actuator dressings can be applied to the skin, exerting contraction forces in response to temperature changes to promote wound closure. The hydrogel's inherent viscosity allows for rapid stress transfer to the wound edges[65]. In addition, drugs or other therapeutic agents can be incorporated into the hydrogel, promoting drug release through active contraction and facilitating wound healing.

Blacklow *et al.* developed an active adhesive dressing composed of a thermoresponsive adhesive hydrogel with high tensile strength, toughness, tissue adhesion, and antibacterial properties[93] [Figure 3A]. These dressings adhere to the skin, respond to skin temperature, and exert sufficient contraction forces to facilitate wound closure. The hydrogel's viscosity allows for rapid and effective transfer of these forces to the wound edges. This mechanical therapy provides a novel approach to traditional wound healing. Additionally, hydrogels themselves have inherent biological functions that promote wound healing. *In vitro* and *in vivo* studies have demonstrated their effectiveness in promoting skin wound contraction and wound healing.

Yang *et al.* developed a new NIR photoresponsive dressing material [Figure 3B] based on dodecyl-modified and chitosan (CS) hydrogel, photothermal agent, and antimicrobial drug (ciprofloxacin)[94]. The nanocomposite dressing is injectable, adaptive, and capable of rapid molding. Unlike traditional drug delivery strategies, the light stimulation response switch allows for precise control of drug release at the infection site, maintaining sufficient drug concentration for effective bacterial infection treatment. Under NIR light irradiation, WS_2 nanosheets generate significant heat, triggering the release of antibiotics at the wound site on demand. *In vitro* antibacterial tests and infected mouse wound models verified its excellent bactericidal effect. This synergistic therapy combines the photothermal effect and spatiotemporal control of drug release, effectively avoiding the disadvantages of two separate treatment modes and achieving the synergistic effect of antibacterial action and wound healing promotion in the dressing.

However, since hydrogel actuators apply contraction force based on temperature changes to promote wound closure, more temperature factors need to be considered. For instance, in cold environments, additional heating methods may be required. Additionally, the skin temperature of different parts of the

Table 2. The applications of hydrogel actuators in various diseases

Disease type	Disease characteristics	Trigger conditions	Types of hydrogel	Ref.
Wound healing	(1) Easy to produce (2) Easy to develop complications	(1) Temperature (2) Light	(1) Transdermal (2) Injection	[93,94]
Diabetic wound healing	(1) Hard to heal (2) Easy to infect (3) High-sugar wound environment	(1) pH (2) pH/glucose	(1) Transdermal	[95,96]
Periocular disease	(1) Complex physiological structure (2) Physiological factors restriction	(1)Temperature	(1) Transdermal	[97,98]
Periodontal disease	(1) Disruptive disease (2) Oral environment restriction	(1) pH/temperature (2) Temperature	(1) Transdermal (2) Injection	[11,99]
Psoriasis	(1) Chronic, autoimmune skin disease (2) Complex pathogenesis	(1) Enzyme (2) Temperature	(1) Transdermal (2) Injection	[100,101]
Cancer treatment	(1) High mortality (2) Difficult to treat (3) Easy to produce side effects	(1) Temperature (2) pH (3) Light	(1) Implantation	[91,102,103]
Diabetes mellitus	(1) Chronic metabolic disease (2) Highly dependent on insulin	(1) Glucose	(1) Implantation	[104,105]
Gastrointestinal disease	(1) High incidence (2) Long disease course (3) Harsh treatment environment	(1) pH (2) Enzyme	(1) Ingestion	[106,107]

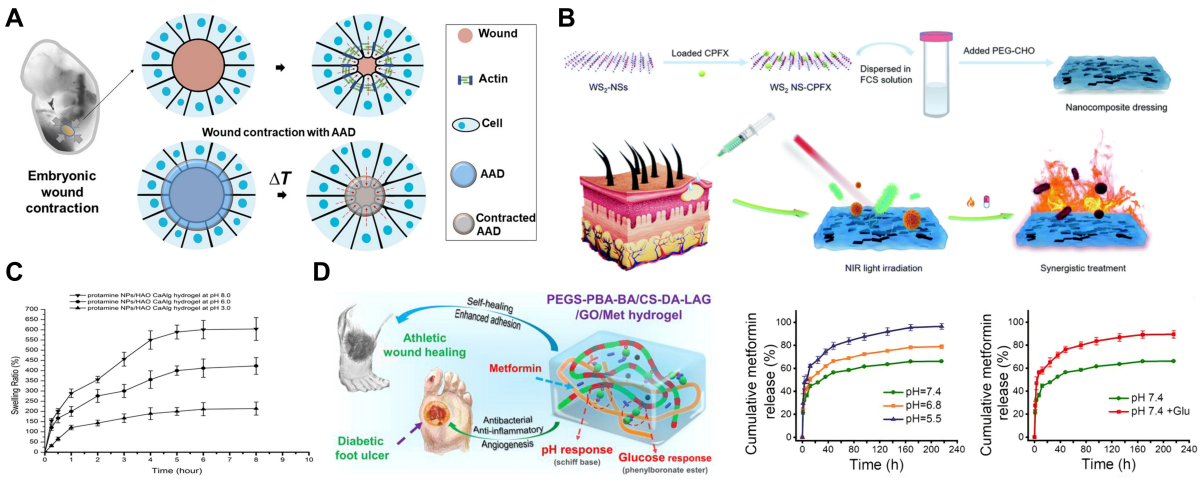

Figure 3. (A) Skin wounds of chicken embryo. AAD responds to skin temperature and promotes wound healing through active contraction[93]. Copyright 2019, AAAS; (B) Schematic of the nanocomposite dressing fabrication and the synergistic treatment of a bacterium infected wound[94]. Copyright 2020, RSC Publishing; (C) PH-responsive drug delivery of HAO from protamine NPs/HAO CaAlg hydrogel for a period of 8 h under different pH conditions[95]. Copyright 2019, Springer; (D) The schematic diagram of structure, pH and glucose-responsive mechanism of PC hydrogel and its application in diabetic foot ulcers and athletic wound healing. PH and glucose-responsive metformin release[96]. Copyright 2022, ACS Publications. AAD: Active adhesive dressings; HAO: hyaluronan oligosaccharides; NPs: nanoparticles; PC: PEGS-PBA-BA/CS-DA-LAG.

human body can vary. These factors need further investigation in future studies.

Diabetic wound healing

In the specific pathophysiological environment of diabetic wounds, there are higher requirements for hydrogel dressings. Diabetic wounds are characterized by disordered inflammation regulation, slow healing, susceptibility to infection, and impaired tissue remodeling[111]. Traditional wound dressings have limited functionality and are not suitable for the diabetic wound healing process. In contrast, stimuli-responsive hydrogel actuators can adapt to complex wound changes, rapidly monitor and respond to the diabetic environment, and improve therapeutic efficacy[46].

Wang *et al.* have proposed a novel alginate-based pH-responsive hydrogel and explored two major factors affecting diabetic wound healing[95] [Figure 3C]. Studies showed that the developed hydrogel contains drugs and NPs with the potent bactericidal properties of protamine, a major component of the hydrogel, effectively reducing wound infection caused by bacteria and promoting wound healing. Additionally, hyaluronic acid, another major component of the hydrogel, can enhance the expression of vascular growth factor, thereby promoting angiogenesis in skin wounds and further accelerating wound healing.

Liang *et al.* developed a pH/glucose dual-responsive hydrogel, phenylboronic acid and benzaldehyde difunctional polyethylene glycol-co-poly(glycerol sebacic acid) (PEGS-PBA-BA)/dihydrocaffeic acid and L-arginine co-grafting chitosan (CS-DA-LAG) (PC), tailored for the specific needs of diabetic foot wounds[96] [Figure 3D]. This hydrogel, utilizing metformin as a model drug, exhibits multiple functions, including antibacterial activity, hemostasis, and controlled drug release. Compared to other hydrogel dressings, PC hydrogel offers better adhesion, making it more suitable for human movement. The dual pH/glucose response enhances wound repair in the low pH and high glycemic environments characteristic of diabetic wounds. Experimental results demonstrated that this hydrogel could promote diabetic foot healing by reducing and inhibiting inflammation and enhancing angiogenesis.

The physiological environment of diabetic wounds is complex and variable, making the development of hydrogel actuators that are more sensitive to environmental changes and respond more rapidly a more challenging direction for future development.

Periocular disease

Eye infusion is now the conventional treatment for ocular diseases. However, local eye drops suffer from low patient compliance and reduced bioavailability due to tear drainage[112]. To address these issues, hydrogels have been increasingly incorporated into eye drop formulations. In this method, drugs are encapsulated in a hydrogel that is administered as a liquid at room temperature. Upon contact with body temperature, the hydrogel undergoes a reversible sol-gel phase transition, prolonging the retention time of the drug on the eye and enabling sustained release of the therapeutic agent[113].

Bellotti *et al.* proposed a temperture-responsive hydrogel based on poly(*N*-isopropylacrylamide) (pNIPAAm) and polyethylene glycol (PEG), incorporating a system containing a degradable microsphere made of polylactic acid-hydroxyacetic acid copolymer (PLGA)[97] [Figure 4A]. This hydrogel features lower LCST and gelation temperatures than other temperature-responsive hydrogels, ensuring rapid gelation after drug administration. It maintains stability under various conditions, and its drug release profile demonstrates continuous drug release capacity. This study addresses the issue of high-frequency administration required for ocular diseases, improving patient compliance. Moreover, it also shows a promising application in the treatment of various eye diseases.

Iohara *et al.* proposed a temperture-responsive hydrogel based on a hydrophobically modified polymer/α-cyclodextrin, demonstrating a reversible solution-gel transition within the physiological temperature range[98] [Figure 4B]. Diclofenac sodium was used as the model drug, and the application of hydrophobically modified hydroxypropyl methylcellulose (HM-HPMC)/α-cyclodextrin (α-CD) significantly enhanced the ocular absorption of diclofenac sodium. This study tested the efficacy of this thermoresponsive hydrogel in rabbit eyes. The system leverages the interaction between CD and the hydrophobically modified polymer to create a thermoresponsive hydrogel, promising numerous applications in the treatment of ocular diseases.

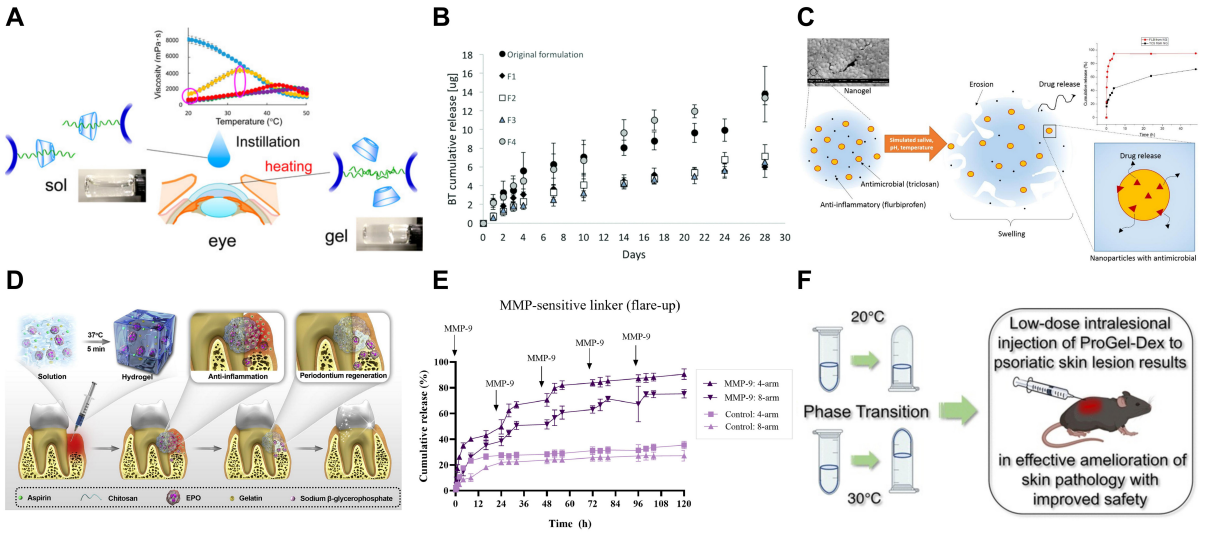

Figure 4. (A) HM-HPMC/α-CD rapidly forms a gel on the ocular surface, enhancing the ocular absorption of the drug[97]. Copyright 2019, RSC Publishing; (B) Drug release in different formulated hydrogels[98]. Copyright 2017, ACS Publications; (C) Hydrogels using model drugs play a dual role in treating periodontitis and antibacterial disease[11]. Copyright 2019, Elsevier; (D) The preparation and application of the CS/β-GP/gelatin hydrogels[99]. Copyright 2019, Elsevier; (E) Cumulative drug release after repeated MMP-9 exposure (↓) of the PEG hydrogels cross-linked with MMP-sensitive linker B. $N = 3$[101]. Copyright 2023, Elsevier; (F) Intradermal Injection of a Thermoresponsive Polymeric Dexamethasone Prodrug (ProGel-Dex) Ameliorate Dermatitis in an IMQ-Induced Psoriasis-like Mouse Model[100]. Copyright 2024, ACS Publications. HM-HPMC/α-CD: Hydrophobically modified hydroxypropyl methylcellulose/α-cyclodextrin; CS/β-GP: chitosan/β-sodium glycerophosphate; MMP-9: matrix metalloproteinase-9; PEG: polyethylene glycol; IMQ: imiquimod.

The application of hydrogel actuators in the treatment of periocular diseases still requires more clinical trial evidence to prove its safety and comfort when used in humans.

Periodontal disease

The unique physiological environment of the oral cavity fosters bacterial proliferation, disrupting the oral ecological balance and leading to dental caries, periodontitis, oral cancer, and other diseases. These conditions adversely affect patients' physical and mental health as well as their quality of life. Conventional treatments for periodontal disease are often ineffective due to saliva-induced drug dilution and loss of efficacy, and they can cause systemic toxicity[114]. Stimuli-responsive hydrogels, however, can respond to specific oral conditions, where external stimuli trigger behaviors such as deformation, drug release, or degradation. These hydrogels exhibit excellent bioadhesion, enabling precise control over drug delivery location and timing, which facilitates targeted and sustained drug release[115]. Consequently, they enhance drug utilization and duration, accelerating the recovery from periodontal diseases.

Aminu *et al.* prepared poly(ε-caprolactone) (PCL) NPs and directly loaded the anti-inflammatory drug halobetasol into a CS-based hydrogel, imparting dual anti-inflammatory and antibacterial effects[11] [Figure 4C]. The synthesized hydrogel exhibited dual stimuli-responsive effects to pH and temperature, enabling controlled drug release for the treatment of periodontitis inflammation and pain relief. This functionality was demonstrated *in vitro* and in rats, showing better therapeutic outcomes compared to the administration of the drugs alone.

Xu *et al.* developed an injectable mild hydrogel using CS, β-sodium glycerophosphate (β-GP), and gelatin[99] [Figure 4D]. This hydrogel enables the continuous release of aspirin and erythropoietin (EPO), which exhibit anti-inflammatory and tissue regeneration effects, respectively. The injectable thermal hydrogel

undergoes a sol-gel transition at body temperature, allowing it to fill small tissue voids of various shapes, such as those caused by periodontitis. The experimental results show that the hydrogel supports repeated and long-term administration, effectively terminating inflammation and promoting periodontal tissue regeneration.

The limitation of periodontal disease lesions makes injectable hydrogel actuators more competitive, as they can fill various small tissue pores. Therefore, future research should focus on further improving the degradation efficiency and ratio of hydrogel actuators to achieve rapid and complete degradation while meeting the therapeutic cycle.

Psoriasis

Psoriasis is a chronic autoimmune skin disorder influenced by both genetic and environmental factors. It is marked by excessive keratinocyte proliferation, the infiltration of inflammatory cells in the epidermis, and the formation of lesions with silvery scales[116]. The pathogenesis of psoriasis involves complex mechanisms, with the overactivation of the adaptive immune system via the *CARD14* gene being a leading explanation[117]. Many current psoriasis treatments have side effects; however, since 90% of cases are mild to moderate and predominantly localized, topical treatments remain the most commonly employed therapeutic approach[118]. Hydrogel actuators not only fulfill the requirements for psoriasis treatment but also offer more targeted and effective therapies based on the severity and specific needs of the patient.

Noddeland *et al.* developed enzyme-responsive hydrogels for the treatment of psoriasis by delivering the anti-inflammatory drug tofacitinib citrate[101] [Figure 4E]. When the enzyme-responsive hydrogel interacts with matrix metalloproteinase-9 (MMP-9), alterations in the concentration and structure of the multi-arm PEG within the hydrogel can modify its physical and mechanical properties. This interaction induces swelling and structural changes in the hydrogel, which in turn leads to drug release. Additionally, by fine-tuning specific formulation parameters, drug release can be further optimized to address the personalized treatment needs of individual patients.

Jiang *et al.* developed a thermoresponsive hydrogel, "ProGel-Dex", which is administered through intradermal injection, using dexamethasone as a model drug[100] [Figure 4F]. Its therapeutic efficacy and safety in the treatment of psoriasis were validated in a mouse model of psoriasis. ProGel-Dex is in liquid form at 4 °C, but once injected into the body, it forms a solid hydrogel, enabling sustained drug release at the pathological site. The unique thermoresponsive phase transition property of ProGel-Dex allows it to remain effective for one to four months, significantly extending the treatment duration.

Due to the complex pathogenesis and types of psoriasis, most experiments using hydrogel actuators for psoriasis treatment are based on acute inflammation models. Further research is needed to address the chronic and complex pathophysiology of psoriasis in humans.

Other diseases

Cancer treatment

In recent years, cancer has remained one of the leading causes of death. Chemotherapy, the main treatment for cancer, has significant drawbacks, including poor stability and systemic toxicity[119]. Stimuli-responsive hydrogel actuators offer a promising alternative for drug delivery. These hydrogels exhibit controlled volume or phase changes in response stimuli, allowing for precise control of drug release location and duration. Implantable or injectable hydrogels encapsulate drugs to target the tumor's surrounding or internal environment, ensuring targeted delivery to the tumor site[120]. This approach aims to achieve better

local tumor treatment and reduce drug toxicity to normal tissues. Achieving long-term, controllable, and sufficient drug delivery is crucial in this method.

Ahsan *et al.* developed a temperature-responsive injectable hydrogel for the effective and continuous delivery of the anticancer drug disulfiram (DSF) to cancer cells[91] [Figure 5A]. The hydrogel has excellent biocompatibility, with liquid injection at room temperature (25 °C) and rapid gel formation at body temperature (36.5 °C). The hydrogel relies on swelling for movement. Experiments showed that the hydrogel expanded most at 37 °C and pH 1.2, and less at 25 °C and pH 7.4, indicating that the drug can be rapidly released under acidic conditions and high temperatures. This confirms that DSF can be effectively delivered under physiological conditions.

Hu *et al.* synthesized a pH-sensitive carboxymethyl chitosan (CMCS) hydrogel through acid bonding[102] [Figure 5B]. Using doxorubicin (DOX) as a model drug, the hydrogel can be implanted at the tumor site in any shape. The hydrogel controls the release of the drug in response to pH levels. Within 144 hours, the hydrogel released only 29.9% of DOX at pH 7.4, while the cumulative release reached 49.3% and 65% at pH 5.0 and 6.5, respectively. *In vivo* studies showed that the implanted hydrogel significantly prolonged the release time of DOX and increased drug accumulation in the tumor area. Continuous drug release in the weakly acidic environment of tumor tissue effectively controlled tumor metastasis and inhibited tumor growth.

Gangrade *et al.* developed a self-repairing hydrogel that exhibits volume shrinkage under NIR laser irradiation, allowing for non-invasive administration of DOX to tumors[103] [Figure 5C]. After NIR radiation, the synergy between the locally induced high temperature by NPs and the DOX released by hydrogel contraction effectively kills tumor cells.

In future studies, multiple stimulus-responsive methods can be combined to achieve a synergistic effect in tumor treatment while further reducing side effects on surrounding healthy tissues.

Diabetes mellitus

Diabetes mellitus, a widespread global disease, poses a serious threat to public health. Individuals with diabetes require daily insulin injections to maintain normal blood glucose levels. However, frequent post-meal insulin injections not only diminish the patient's quality of life but also fail to dynamically adjust the insulin dose and timing, leading to unnecessary side effects[121]. Furthermore, poor blood sugar control can result in severe complications. Glucose-responsive hydrogel actuators can undergo subtle conformational changes in response to glucose, thereby promoting the precise release of insulin[104].

Ye *et al.* developed glucose-responsive hydrogels that undergo reversible rapid volume phase transitions in response to fluctuations in blood glucose concentration, with the potential to simulate pancreatic activity for regulating insulin delivery[105] [Figure 5D]. Hydrogels can control the rate of insulin release by adjusting the size of the gel network. When glucose is added in the range of 50.0 μM to 20.0 mM, the nanogel can expand and stabilize in less than one second. The insulin release rate may increase tenfold when transitioning from normal glucose levels (6.0 mM) to elevated glucose levels (15.0 mM). This self-regulating insulin delivery characteristic significantly enhances the efficacy of diabetes treatment.

Lee *et al.* synthesized a glucose-responsive hydrogel based on trehalose polymers for insulin delivery[104] [Figure 5E]. Hydrogels prepared from trehalose polymers and boric acid crosslinking agents can release insulin in a glucose-responsive manner. The two main mechanisms of insulin release by borate hydrogel are

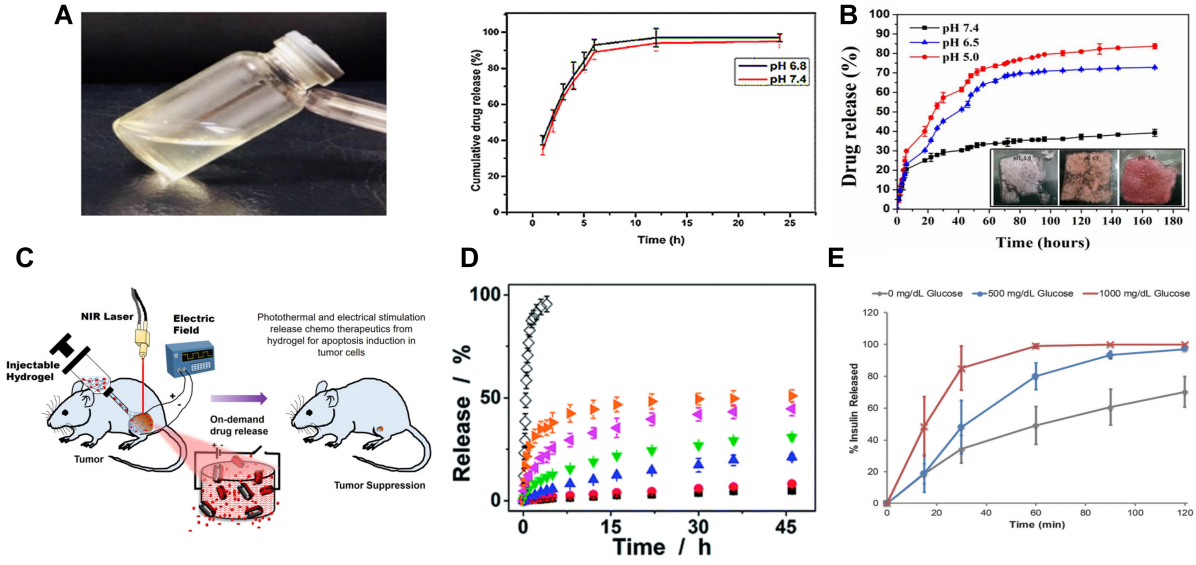

Figure 5. (A) Drug release profiles at different pH (n = 3)[91]. Copyright 2020, ACS Publications; (B) *In vitro* release profile of DOX from hydrogel-2 in PBS (0.01 M) at pH 7.4, 6.5 and 5.0 under 37 °C, and attached images of DOX-loaded hydrogels after incubation for 168 h[102]. Copyright 2017, Elsevier; (C) Photothermal and electrical stimulation release chemotherapeutics from hydrogel for apoptosis induction in tumor cells[103]. Copyright 2020, ACS Publications; (D) Releasing profiles of insulin from the ConA@poly(NIPAM) nanogels in the presence of 0.0 mM ((the prmM ((the prmM ((the premM ((the premM (◀), and 20.0 mM (▶) glucose in PBS of 7.4 at 37 °C. In the blank release (◊), the insulin solution was released to the PBS[105]. Copyright 2014, RSC Publishing; (E) Insulin released in D-PBS under different conditions[104]. Copyright 2018, Wiley. DOX: Doxorubicin; PBS: phosphate-buffered saline; D-PBS: Dulbecco's phosphate-buffered saline.

swelling and competitive binding. The swelling action is caused by the equilibrium movement of different boronic acid species when binding to diols such as sugars. Meanwhile, the borate-based polymer can form a hydrogel after complexing with a diol-containing polymer in the existence of insulin, which is then competitively replaced by glucose and releases insulin. Furthermore, trehalose hydrogels can protect insulin from heat stress, compensating for the limitation of most protein drugs at regulated temperatures to maintain their activity.

Since diabetic patients need repeated and large amounts of insulin intake after meals, future research should focus on further increasing the drug-loading capacity of hydrogel actuators to meet the long-term and higher dosage requirements for diabetes treatment.

Gastrointestinal disease

The therapeutic effect of orally ingested drugs is often compromised by the harsh environment of the gastrointestinal tract, which can also hinder drug absorption due to digestive conditions and gastrointestinal mucosal transport restrictions[122]. Additionally, there are variations in the gastrointestinal environment across different regions, including enzyme types and pH levels, which range from pH 1-3 in the stomach to pH 5-7.5 in the small intestine and pH 7.8-8 in the colon[123]. Other biological behaviors also influence the actual therapeutic effect. Stimuli-responsive hydrogels for oral administration have demonstrated good stability in the gastrointestinal environment, allowing precise drug release in response to specific conditions, thus achieving controlled drug delivery[124]. Moreover, researchers are developing gastrointestinal-resident stimuli-responsive hydrogel systems for long-term and stable drug delivery.

Ulcerative colitis (UC) is a bowel disease typically treated with corticosteroids and immunosuppressants. However, these drugs can cause significant side effects, including malignant tumors and infections.

Therefore, targeted local treatment is a more appropriate approach[13].

Huai *et al.* developed an alginate/hyaluronic acid hydrogel that responds to the colonic microenvironment[106] [Figure 6A]. This hydrogel demonstrates well-controlled drug release and significant biodegradability in inflammatory environments, minimizing early drug leakage in the gastrointestinal tract. Its mucosal adhesion and pH-sensitive properties enable targeted drug delivery and release at inflamed sites, allowing for smaller drug doses to achieve the same therapeutic effect. Therefore, this hydrogel holds promise as a novel oral antibody delivery system.

Wang *et al.* developed an intestinal enzyme-responsive hydrogel encapsulating the model drug imatinib for long-term controlled drug release and treatment of bowel cancer through oral administration[107] [Figure 6B]. The drug-loaded hydrogel responds to intestinal enzymes, triggering hydrolysis and subsequent drug release, significantly enhancing the tumor suppression effect of the model drug. Experiments show that this enzyme-responsive hydrogel can achieve the long-term synchronous release of kinase inhibitors (imatinib) and promoters (sodium deoxycholate) in the intestine, improving therapeutic efficiency. This method provides an effective way to enhance the bioavailability of oral hydrophobic anticancer chemotherapeutic drugs.

There are significant differences in conditions such as pH values or enzyme types in different parts of the gastrointestinal tract. Therefore, hydrogel actuators for treating gastrointestinal diseases should have more precise and sensitive responsive characteristics.

Neuromodulation

Implantable neural modulation devices, such as deep brain stimulators and vagus nerve stimulators, have been widely used to treat neurological disorders[125,126]. These devices are often made from rigid probes and are limited by lower sensitivity and mechanical compatibility with tissue. Reducing the mechanical mismatch at the electronics-tissue interface can significantly reduce adverse immune responses caused by chronic implantation[127,128]. Recent developments in soft elastic hydrogel materials have further enhanced the ability for localized low-voltage neural modulation, and they exhibit good biocompatibility and mechanical interface compatibility[81].

Liu *et al.* reported elastic microelectronics composed of a highly conductive hydrogel and an elastic fluorinated photoresist as a passivation insulation layer. The microelectronics has 10 kPa Young's modulus and a current injection density 30 times higher than platinum electrodes. Effectiveness has been validated by applying electrical stimulation to the mouse nerve[129] [Figure 6C]. Tringides *et al.* proposed a conducting supersoft viscoelastic hydrogel filled with carbon nanomaterials. This array is primarily made from hydrogels with highly tunable physical properties, allowing for independent variation of viscoelasticity and stiffness. It can be used for neural signal acquisition and electrical stimulation[130] [Figure 6D]. Yang *et al.* report a strategy for the construction of conductive and bioadhesive hydrogel neural interfaces with photopatternable, antifouling, soft, and elastic features. The prepared multifunctional hydrogel can achieve rapid adhesion and more stable electrical integration on moist tissues and has shown effectiveness in the electrical signal recording and stimulation of the rat sciatic nerve[131] [Figure 6E].

For actual clinical applications, further improvements are needed to enhance the usability and durability of implantable devices, while reducing potential immune responses in the biological system during long-term implantation.

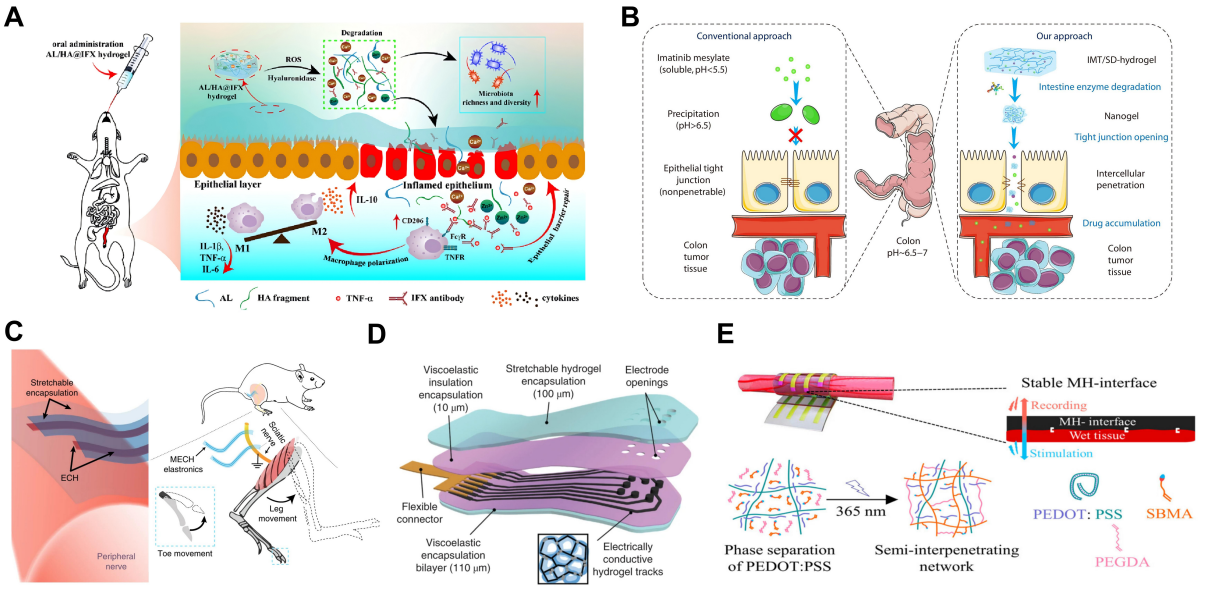

Figure 6. (A) Inflammatory microenvironment triggers hydrogel destruction and IFX releasing. AL/HA@IFX promot epithelial barrier reparation and modulating of gut flora[106]. Copyright 2023, Elsevier; (B) Schematic illustration of orally administrated IMT/SD-hydrogel at colon with intestine enzyme triggered release through epithelial adherens junctions for enhanced therapeutic efficiency[107]. Copyright 2022, Springer; (C) Schematic of the in vivo neural stimulation experiment with a MECH microelectrode[129]. Copyright 2019, Springer Nature; (D) Device and its various components[130]. Copyright 2021, Springer Nature; (E) Schematic illustration of chronic neuromodulation application with photopatternable MH to achieve robust electrical integration between implanted bioelectronics and peripheral nerves[131]. Copyright 2023, ACS Publications. IFX: Infliximab; AL/HA: an colon microenvironment-responsive; IMT/SD: imatinib and sodium deoxycholate; MECH: a micropatterned electrically conductive hydrogels.

CONCLUSION AND PERSPECTIVE

This article reviews a range of external stimuli capable of activating these hydrogels, summarizes their performance and application methods, and emphasizes their specific uses in biomedical engineering, with a focus on drug delivery. Despite advancements in the use of stimulus-responsive hydrogel actuators in biomedicine and targeted drug delivery, most biomedical applications remain at the proof-of-concept stage. Several challenges need to be overcome before transitioning from laboratory research to clinical practice.

Firstly, when transitioning hydrogels from experimental to clinical use, a broader range of application conditions and environments must be considered. This includes expanding the target population to include children and the elderly with weaker constitutions, ensuring stability, safety, and non-toxicity across various user groups. Additionally, it is crucial to ensure that hydrogel actuators maintain structural and functional stability even in extreme conditions.

Secondly, actual applications may demand more precise drug release timing, particularly for chronic diseases or conditions requiring implanted hydrogel actuators. Future research could explore increasing the drug-loading capacity of hydrogels or developing hydrogel actuators with multiple drug reservoirs to extend drug release times. Moreover, the complex mechanisms of many diseases pose greater challenges for controlling drug-loading capacity, release rates, and degradation rates of hydrogel actuators.

Thirdly, current hydrogel actuators rely heavily on aqueous environments because their volumetric changes are driven by water transfer within the hydrogel matrix. The slow diffusion rate of water hinders real-time responsiveness. Future research could focus on reducing the dependency of hydrogels on water environments or enhancing the water retention capabilities of hydrogels to mitigate this limitation.

Finally, the research trend in hydrogel actuators is shifting from single-stimulus responses to multi-stimulus responses. Although multi-stimulus-responsive hydrogel actuators overcome some limitations of single stimuli, they introduce additional complexity. It is necessary to consider the synergistic effects of multiple stimuli, the reliability of these actuators, and the potential interference between different stimuli.

A promising future direction in this field is to create intelligent hydrogel actuators with robust performance, multi-stimuli responsiveness, and precise, sustained release capabilities. These actuators may also incorporate more sophisticated hardware such as physiological sensors, and more advanced software such as artificial intelligence towards better automation and closed-loop therapy.

DECLARATIONS

Authors' contributions

Supervised this work and provided guidance: Guan Y, Nan K
Contributed to the discussion and writing of this manuscript: Du N, Fan Y, Huang H, Guan Y, Nan K

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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