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Preparation and application of electro-conductive hydrogels in biomedical engineering

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Highlights

- The conductivity of hydrogel can be realized by introducing conductive medium.
- Various properties of hydrogel can be adjusted by changing the proportion of ingredients.
- Electro-conductive hydrogels are widely used in biomedical engineering as biomaterials.

Abstract

Electro-conductive hydrogel is a new composite hydrogel with high electrical conductivity, extraordinary mechanical properties, and controllability. It can be equipped with specific materials to obtain specific properties, which has attracted considerable research attention due to its wide range of application as a biomaterial in the biomedical engineering field. It can be used as a patch to promote healing and as a dressing for burns and pressure wounds. In pharmaceutical science, it is widely studied as a carrier of targeted and quantitative drug release. In surgery, it can serve as a cell scaffold for implantable therapy. Currently, increasing research is focusing on the development of sensors as simulated skin for robots, as well as in health monitors for human activity and well-being. In this review, we summarize the classification and selection of conductive mediums, natural polymer hydrogel matrices, and the application of electro-conductive hydrogels in the fields of bioengineering and biomedicine. We delve into the properties of different conductive mediums and the principle of combining different hydrogel matrices and discuss the advantages and disadvantages of emerging composite hydrogels. Our focus extends to the forefront of conductive hydrogel research in various fields, while also elucidating the current problems and challenges in terms of performance integration, preparation process and practical applications.

Keywords: Conductive hydrogel, biomedical engineering, conductive mediums, natural polymer, flexible sensors

Introduction

Hydrogels, polymer with three-dimensional (3D) networks formed through physical or chemical cross-linking, can contain a large amount of water while remaining insoluble in water [1]. The network pore size of the polymer is about 10 nm, much larger than the size of water molecules, which allows the water molecules in the hydrogel to maintain the same physical and chemical properties as liquid water [2]. At the same time, the microscopic network structure like sponge ensures that the hydrogel has a certain toughness. Hydrogel is an excellent biomaterial with excellent water absorption, controllable mechanical properties, biocompatibility, and biodegradability.

Nowadays, electricity is indispensable in human activities. If hydrogel is given a conductive property, the application range of hydrogels can be greatly improved. However, hydrogels made from natural polymers are not conductive or only weakly conductive, so combining hydrogel matrices and conductive materials provides a simple and efficient route to fabricate strong conductive hydrogels [3]. Conductive materials can be classified as nanomaterials, ionic materials and conducting polymers. **Figure 1** shows the composite hydrogel synthesized by incorporating conductive polymers, namely, electrically conductive hydrogels (ECHs). By harnessing the individual advantages of conductive materials and natural polymer hydrogel matrices, composite hydrogels not only maintain superior biocompatibility and biodegradability, but also

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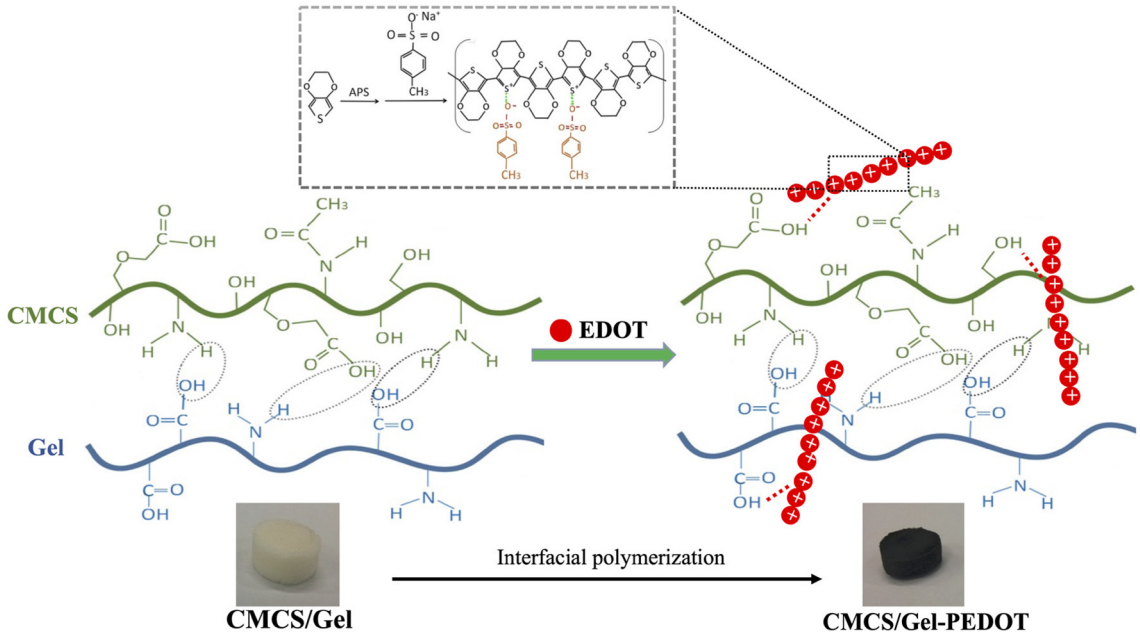

Figure 1. Conductive polymer ECHs. This figure is cited from [16]. ECHs, electrically conductive hydrogels; PEDOT, poly (3,4-ethylenedioxythiophene).

have high electrical conductivity. Many studies have shown that introducing different conductive materials into hydrogels can also improve their strength, toughness, and other mechanical properties. Powered by these biological and tunable features, ECHs have recently attracted growing attention in biomedical engineering.

Classification of conductive materials

Nanomaterials

The nanomaterials used to prepare ECHs mainly contain carbon-based nanomaterials, such as graphene and carbon nanotubes (CNTs), and metallic nanomaterials. Introducing nanomaterials to hydrogels not only enhances the electrical conductivity of ECHs, but also improves their mechanical, optical and thermal properties. Nanomaterials have attracted growing interest as conductive mediums for ECHs and have become one of the preferred components for the preparation of ECHs.

The physical interaction between hydrogel polymer chains and carbon-based nanomaterials contributes to the mechanical properties of hydrogels and makes the ECHs exhibit high electrical conductivity and excellent environmental stability [4]. However, the preparation process of combining nanomaterials and hydrogels is difficult to control because nanomaterials are hydrophobic and tend to aggregate in water, which may lead to uneven distribution of nanomaterials in the manufactured hydrogels, resulting in discontinuous electrical conductivity and inhomogeneous mechanical properties.

Metallic nanomaterials, which are inherently conductive, can conduct electricity under the action of electric current when they are free in the hydrogel network. However, metallic materials are unstable in humid environments and are susceptible to oxidation. For example, MXene, which has been studied by many researchers as an electrode material, has excellent conductivity and rich varieties, but its brief shelf life, susceptibility to oxidation, and use of environmentally harmful reagents in synthesis impose many limitations on its application [5].

Ionic materials

The high-water contents and 3D networks of hydrogels permit ions to migrate between the electrodes in the presence of electric current. Current research generally uses salts as a source of ions. Salts ionize into metal ions and anions in water, and both of which can act as conductors. The ECHs is prepared using an immersion method that utilizes the water absorption and swelling properties of hydrogels to incorporate the ions into the polymeric network. Metal ions can form complex coordination structures with functional groups on the soft chains of hydrogels, including monodentate coordination, bidentate chelate bidentate bridging and interchain cross-linked structures. The hydrogen bonds between the soft and rigid chains of hydrogels, as well as the stronger physical cross-linking points formed between the ions and chains make the ECHs have high

Table 1. Comparison of different conductive mediums

Type	Materials	Advantage	Disadvantage
Nanomaterials	Carbon-based (graphene, CNTS)	Excellent mechanical, optical, and thermal properties, chemical stability	Hydrophobic, complex synthesis process
	Metal-based (MXene)	High conductivity, self-healing ability, ductility	Unstable, harmful synthesis process
Ionic materials	Fe^{3+}, Ag^{+}, Ca^{2+}	High conductivity, low cost, simple synthesis process, functional specificity	Toxic at high concentrations
Conducting polymers	PPy, PANI, PEDOT, PEDOT: PSS	Excellent mechanical, optical, and thermal properties, high conductivity	Non-degradability, low solubility

Note: CNTS, carbon nanotubes; PPY, polypyrrole; PANI, olyaniline; PEDOT, poly (3,4-ethylenedioxythiophene); PEDOT: PSS, polystyrene sulfonate.

tensile strength while ensuring the toughness. Meanwhile, the reversible association and dissociation abilities of the ligand bonds provide ECHs excellent recoverability and durability [6]. Therefore, ions combine with water molecules to form hydrated ions. This hydration effect usually changes the freezing point of the hydrogels and increases their low temperature resistance [7, 8]. Different ions can also bring different specific properties to hydrogels. For instance, introducing Ag^{+} can endow hydrogels with antibacterial properties, and introducing Ca^{2+} can contribute to hemostasis of wound healing and promote cell proliferation and migration [9, 10].

Compared with ordinary ionic gels, the hydrogels based on salt electrolytes have the advantages of high conductivity, controllable cost, and simple preparation, with an irreplaceable practical application value.

Conducting polymers

Conducting polymers, including polypyrrole (PPy), polyaniline (PANI), poly (3,4-ethylenedioxythiophene) (PEDOT), and polystyrene sulfonate (PEDOT: PSS), are new generation of organic materials characterized by electrical conductivity. They have the electrical property of metallic and optical property of inorganic semiconductors, known for their redox stability, hydrophobicity, ability for reversible oxidation, and ease of synthesis and processing [11]. These properties, which give them advantages and potentialities in tissue engineering and regenerative medicine, have attracted great interest from researchers.

Therefore, the introduction of conducting polymers into hydrogels is an effective strategy to obtain ECHs. This approach highlights the idiosyncratic functions of polymers while leveraging the biocompatible and degradable qualities of natural hydrogels, creating a suitable milieu for applications in biomedical engineering.

The physical and chemical properties of conducting polymers can be designed by surface functionalization technology and electronic means, and the intensity and length of the electrical stimulus can be controlled when conducting polymers are used [11]. However, conducting polymers have two major disadvantages, non-degradability and low solubility in organic solvents and water, which greatly limits their processability, versatility, and applicability [12]. As shown in **Table 1**, we summarized and compared the advantages and disadvantages of introducing different conductive media into hydrogels.

Classification of natural polymer hydrogel matrices

Sodium alginate (SA)

SA is a natural polysaccharide separated from seaweed, which is composed of polymannuronic acid and polyguronic acid segments. SA forms a stable network by replacing sodium ions on the carboxyl group of the skeleton with other divalent metal ions. It has been widely used in medicine, biology and other fields due to it is non-irritating and biocompatible nature [13]. However, the mechanical properties of pure alginate networks are poor. Recently, researchers introduced other networks into alginate to form interpenetrating double network hydrogels with stable mechanical properties through hydrogen bonding.

Mo et al. crosslinked Zn^{2+} with SA networks, and then introduced it into the covalently crosslinked polyacrylamide (PAAm) networks to form an interpenetrating double-network structure [14]. The ionic crosslinking points formed by Zn^{2+} and SA can effectively dissipate energy when they are broken under strain, and then recover bond after stress unloading. Additionally, surplus free Zn^{2+} in the hydrogel networks

provides conductivity to hydrogels. These double-network ECHs present porous micro morphology, which is conducive to the transport of ions. The ionic conductivity of the hydrogel is as high as 32.4 MS/cm. A wearable application test showed that the hydrogel exhibited a sensitive and repeatable response to the movement of human limb joints, showing great potential in this field.

Liu et al. developed an alginate-PAAm ECHs with Fe^{3+} secondary crosslinking to adjust local stiffness [15]. Because the trivalent Fe^{3+} combines three different alginate polymer chains by interacting with the carboxyl group on each chain, a 3D compact structure is established, which improves the mechanical stiffness of the hydrogel. The local stiffness is related to the concentration of Fe^{3+}. So, changing the local stiffness of the hydrogel by controlling the concentration of Fe^{3+} and the immersion position is helpful to promote the coupling of flexible rigid electronic components and soft matrices materials. This design strategy provides an effective solution to the problems in the field of soft and stretchable electronics.

Based on double-network hydrogel, SA based ECHs has been developed and applied to flexible sensors, drug delivery and release, cell scaffold and other scenarios.

Gelatin

Gelatin is a hydrolysate biopolymer of collagen. A large number of carboxyl groups in gelatin is very suitable for molecular grafting, while the high level of amino groups easily interacts with aldehyde groups, making them very suitable for producing characteristic hydrogels. At the same time, gelatin is cheap, and has the properties of biocompatibility and biodegradability, making them good matrices for cell adhesion and proliferation. Therefore, gelatin-based ECHs have been widely used in cell scaffolds, 3D biological printing, and have great potential in complex tissue engineering such as bone, muscle, and nerve regeneration.

Guan et al. developed a carboxymethyl chitosan/gelatin composite hydrogel [16]. PEDOT nanoparticles were assembled on the hydrogel surface by in-situ chemical polymerization to obtain a new type of electroactive hydrogel scaffold. The conductivity of this ECH can reach 1.5210^{-3} S/cm, and its mechanical properties are similar to brain tissue [16]. The incorporation of PEDOT nanoparticles significantly improved the adhesion of neural stem cells and supported long-term cell growth and proliferation in a 3D microenvironment. It is an attractive conductive matrix for nerve tissue repair and regeneration.

In addition, gelatin-based conductive hydrogels can also be used as flexible sensors to monitor human movement. Gao et al. designed a humidity- and temperature- sensitive chitosan/gelatin/glycerin/NaCl organic ion conductive hydrogel film with only 0.1 mm in thickness [17]. The sensor prepared with this ECH film has a wide detection range of relative humidity (20-90%) and temperature (-30-50 °C), and also shows good antifreeze and water retention capabilities, which can accurately record and real-time feedback the changes in humidity and temperature on skin surface, holding great application potential in detecting human respiratory activity.

The hydrogels formed only by gelatin have disadvantages of brittleness and poor flexibility, which greatly limits their practical application. They can only play their role through cross-linking modification or nano composition. Therefore, it is particularly important to improve the mechanical strength of gelatin-based ECHs.

Cellulose

Cellulose is the largest polysaccharide material among natural polymers in the world. It not only exists in plants, but also can be synthesized by some specific microorganisms, such as Acetobacter xylinum. As a renewable organic substance in nature, cellulose is used to prepare natural hydrogels. The design of conductive cellulose hydrogel functional materials based on cellulose's good mechanical, dielectric, and piezoelectric properties has become a recent research hotspot [18].

The main raw materials for preparing cellulose based ECHs include cellulose molecules, nano cellulose, and cellulose derivatives. Wu et al. used Tannic acid (TA) to modify bacterial cells (BCs) to achieve an even distribution within the hydrogel, forming a stable double-network structure with the P(AA-AMPS) chain. The hydrogen bond between TA and PAAM chains also improved the mechanical properties of the hydrogels [19]. Then a high concentration of Ca^{2+} was introduced to obtain P(AA-AMPS)-TA@BA-Ca^{2+} ECHs, which exhibited excellent conductivity (1.92 S/m at room temperature), mechanical properties, and freezing resistance (0.36 S/m at -35 °C).

Bian et al. used carboxyl cellulose nanofibers to help conductive PEDOT: PSS to be evenly dis-

tributed in the PAAm network [20]. In addition to its conductivity, the addition of carboxyl cellulose nanofibers makes ECHs have excellent humidity sensitivity and strain sensing performance. It has quick response, reliable stability and reproducibility in a wide range (0-837%), showing great potential as a human breath detection sensor.

All these have proven that cellulose-based ECHs have great potential as a new generation material for flexible wearable electronic equipment. However, the crystalline region of cellulose is difficult to dissolve, which is a limitation in the preparation of cellulose based ECHs. Currently, cellulose is mainly dissolved in water or common organic solvents by polar composite solvents or modification methods, which provides an available strategy for preparing cellulose based ECHs.

Chitosan

Chitosan is the deacetylated derivative of chitin, the second largest natural polymer after cellulose, and the only natural alkaline polysaccharide found at present. Due to its excellent properties such as low cytotoxicity, biocompatibility, as well as antibacterial, degradation and regeneration ability, it has been developed in the fields of drug release, wound healing and tissue engineering [6].

Au-Yong et al. crosslinked chitosan and polyethylene glycol into a double network [21]. They introduced PPy derivatives to synthesize ECHs that capable of carrying the cancer drug pemetrexed through photopolymerization and oxidative chemical polymerization. Experiments showed that under electrical stimulation, the release of pemetrexed was increased by about 10-15%. If this ECH is integrated into coatings and electrodes for electrochemical therapy, the triggered release may be helpful for surgery.

Cong et al. developed a dual network ECH with PANI doping, which is dynamically crosslinked by chitosan and PAAm [22]. The synergy of hydrogen bonding involving hydroxyl, amide, and aniline groups, along with the interaction of high concentrations of ions in both networks, bestows the resulting ECH with excellent mechanical properties, amazing conductivity, and impressive frost resistance. The highest conductivity of PCPD hydrogel can reach 4.83 S/m, but the PANI concentration can impact the degree of crosslinking of the hydrogel, and then affect the movement of free ions in the network, that is, there is a certain competition between the two conductive mechanisms. The tensile strength of this ECH is 2.62 MPa, and the excellent fatigue resistance and long-term durability of PCPD hydrogel are verified through cyclic tensile test, which is very important for chitosan-based ECHs as flexible sensors, soft robots, and wearable devices materials.

But like cellulose, chitosan is insoluble in water and most organic solvents, which severely limits its application scope. Therefore, modification of chitosan is an important aspect of its research, which can be cross-linked in the form of esterification and etherification to fabricate chitosan-based ECHs [23].

Others

In addition to the polymers mentioned above, there are also hyaluronic acid, starch, agarose, collagen, and other nature polymers that can be used as ECH matrices.

Sharifisistani et al. designed a hyaluronic acid-based ECH [24]. They introduced phenol-substituted gelatin for cell adhesion and phenol-substituted CNT as conductive medium through laccase-mediated cross-linking, creating a microcapsule and microcarrier for myocardial cell encapsulation. Their experiment showed that cell viability was affected during the encapsulation process, and myocardial cells proliferated well and expressed proteins and genes. Besides, the cardiogenic characteristics of the developing spherical tissue structure could be regulated by electrical stimulation.

Zhou et al. developed an AA-AM hydrogel by cross-linking starch as a conductive hydrogel matrix with acrylamide [25]. They found that starch improved the adhesion of hydrogel to various materials, and the adhesion strength did not decrease with time. This starch-based ECH has good flexibility, and the maximum strain reach 1290%. At the same time, as a biosensor, it shows excellent conductivity and strain response sensitivity and can accurately detect various human movements in a wide strain range of 0-1200%. It provides a new idea for the development of ECH materials in the field of new-generation electronic skin.

In general, natural polymer based ECHs have advantages of non-toxic, biodegradable, excellent flexibility, and conductivity, so they are very promising in practical applications. However, most natural hydrogels have disadvantages of low mechanical strength and lack of toughness. Therefore, in order to promote the practical application and improve their poor mechanical

Table 2. Comparison of different natural polymer hydrogel matrices

Materials	Advantage	Disadvantage
Sodium alginate	Biocompatibility, biodegradability, low cost	Poor mechanical properties
Gelatin	Tunable degradation, low cost, specific processing	Brittleness, poor mechanical properties
Cellulose	Good mechanical properties, dielectric properties	Difficult to dissolve
Chitosan	Antibacterial ability, regeneration ability, adsorption capacity, thermosensitive properties	Difficult to dissolve
Others	Adhesion, high amenability, multifunctional properties	Poor mechanical properties

properties, complementary matrices are constructed to study the conductivity and mechanical properties of ECHs through dual networks and interlocking cross-linking networks strategies. As shown in **Table 2**, we summarized and compared the properties advantages and disadvantages of different hydrogel matrices.

Applications

Bioelectronic flexible sensors

The popularity of smart terminals has greatly contributed to the development of wearable electronic devices. Traditional electronic devices made of rigid materials cannot achieve close contact with the skin, resulting in a lack of wear resistance and functionality [26]. Therefore, flexible and comfortable electronic devices have attracted extensive research attention and have been applied in health monitoring, medical diagnosis, and human health care. Among these devices, flexible sensors, as the most indispensable part, limit the functional development and future design of wearable devices.

ECHs have mechanical properties similar to human skin, such as notable stretchability, elasticity, recoverability, and fatigue resistance, and also have high electrical conductivity, sensitive responsiveness, and biocompatibility, which are preferred properties for the fabrication of flexible sensors. Currently developed ECHs for flexible sensors can effectively detect human activities such as finger bending, elbow bending, walking, and running. They are also sensitive to small movements, such as talking, swallowing, and small pulses [27].

You et al. prepared a porous organic Gel/PPy/rGO hydrogel with stretchability, high electrical conductivity, ultra-permeability, low-temperature tolerance, and long-term stability [28]. The sensor made from this porous organic hydrogel exhibits excellent sensing sensitivity, fast response capability, and good endurance. It can effectively monitor various human activities, such as finger flexion, elbow bending, walking, running, as well as small pulse beats.

Sun et al. prepared a PAAm-oxCNTs hydrogel by in situ free radical polymerization, using gelatin to modify oxidized CNTs by hydrogen bonding, and homogeneously introducing oxidized CNTs into the PAAm matrices [27]. The mechanical properties and electrical conductivity of this hydrogel are directly related to the content of oxidized CNTs. Therefore, the mechanical properties and electrical conductivity of Gel/PPy/rGO hydrogel can be adjusted within a certain range according to the demand. In addition to that, it has excellent durability, recoverability, and fast mechanical response when detecting human motions without significant delay. The PAAm-oxCNTs hydrogel has a sensitive response to minor strain variations, allowing for accurate articulation tracking, which has great potential for applications in voice recovery and articulatory readaptation.

Skin adhesion is a basic requirement for hydrogels as sensors, and the currently developed hydrogels have achieved this. However, since most of the flexible sensors are designed for in vitro adhesion, where one side adheres to the skin and the other side is susceptible to external interferences like dust, grass, or paper, the sensor's signal detection and analysis may be compromised. Gong et al. developed a PAA/TA@HC/Fe^{3+} hydrogel with great mechanical and tissue adhesive properties and electrical conductivity, which can be used as a flexible sensor [29]. In addition, they treated the hydrogels with asymmetric adhesion. A 1 M/L solution of Fe^{3+} was applied to the top of one side of the hydrogel, and the adhesion force of the treated hydrogel side was 0 kPa. Fe^{3+} served as an effective sealant for the treated hydrogel, effectively chelating available carboxylates and other functional groups, which prevented signal disruption and analysis interference from external factors on the other side of the hydrogel.

The sensors can be applied not only for health

monitoring but also for medical diagnosis and treatment. Gao et al. simultaneously improved the mechanical properties and electrical conductivity of a wearable hydrogel sensor by introducing sodium carboxymethyl starch, which has ultra-sensitivity and fast response [30]. Assembling multiple sensors into a 3D sensor array allows the detection of stress and strain distributions in three dimensions. This capability facilitates the recording of the ECG signal peaks and waveforms, showing significant potential in human medical diagnostics.

The electrical conductivity and mechanical properties of ECHs can be affected by the environment, such as temperature, pH, and light, and these issues need to be addressed for sensors as long-term use medical products. Chen et al. developed hydrogels with excellent freeze protection (-33 °C) by introducing zinc chloride into cellulose-based hydrogels, which are of great value in extreme environmental applications [31]. Lu et al. developed SPAE hydrogels with reduced swelling properties using electrostatic repulsion, which can be applied to underwater wearable flexible sensors [32]. Chen et al. developed a chitosan-P(AM-MPC-$AA_{0.20}$)-Fe^{3+} hydrogel with anti-fouling and anti-bacterial properties [33]. Shen et al. developed a PEDOT:PSS-PVA hydrogel that can be combined with 3D printing [34].

However, the integration of hydrogel-based flexible sensing systems still presents challenges in terms of cost, multifunctionality, and device fabrication, hindering application potential in specific scenarios.

Wound healing patch

Wound healing is a common health burden affecting all humans, and the lengthy healing process of severe wounds can be both physical and economical burdens. Accelerating wound healing and restoring normal activities is beneficial to both patients and the society. To date, various methods have been developed to treat wounds, including micro needling, wound dressings, negative pressure, and ultrasound, but the average time to complete wound closure is still long.

Currently, researchers have made progress in the application of hydrogels in the field of wound healing by combining hydrogels with specific materials, such as silver and its derivatives with antibacterial properties and calcium ions with hemostatic properties, or therapeutic drugs, such as collagen and dopamine [35-38]. Those composite patches can effectively facilitate wound healing [39]. Electrical field stimulation is a novel method to accelerate wound healing. This method can limit the side effects associated with conventional therapies. Studies have demonstrated that electrical field stimulation at the wound site can guide the migration and proliferation of skin cells through electrical signals [40]. In addition, electrical stimulation increases angiogenesis and immunomodulation, both of which play important roles in tissue remodeling [41].

Wang et al. synthesized silver nanowires and methacrylate alginate to make a flexible electronic patch [42]. The silver nanowires have electrical conductivity and antibacterial properties, while the methacrylate alginate has clinical applicability in wound healing. The hydrogels were shown to promote epithelial re-formation, enhance angiogenesis, and mediate immune response. The composition of this ECHs was optimized to be printed on medical-grade patches for personalized wound treatment. Animal experiments confirmed that the wounds that originally required 20 days to heal, were completely healed in only 7 days after patch treatment, and the skin thickness and other characteristics after healing were similar to those of healthy skin.

Pressure wounds are a worldwide concern because they are difficult to heal and easily infected due to repeated pressure over time [43]. ECHs can be used not only for the prevention of pressure injuries but also for long-term treatment [44].

Liu et al. designed a pressure-resistant amphoteric CH-OSNP ionic hydrogel to monitor wound conditions and prevent injury progression [45]. This hydrogel can detect and differentiate multiple parameters for analysis due to its sensitivity to temperature, pressure, and exudate. Additionally, its robust swelling properties keep the wound environment moist, regulate oxygen tension and foster capillary formation while aiding necrotic tissue dissolution. Moreover, the hydrogel preserves active exudate substances, giving a favorable environment for wound healing.

Drug release

Hydrogels have been extensively studied for drug release, and the rate of drug release can be increased by applying external stimulations such as pH, temperature, electric or magnetic fields. Among these stimulations, electrical stimulation is not only easy to generate and control, but also can avoid frequent invasive

surgery. The application of small current stimulation on human skin allows for remote application without the need for large and specialized devices. In addition, programmable drug release can allow repeated drug delivery and even wireless implants [46].

The solubility of ECHs is affected by electric current, a property that has attracted researchers to delve more deeply into its application in drug release. The drug release behavior of ECHs can be controlled by three forces: polymer affinity, ionic pressure, and rubber elasticity, which are collectively referred to as osmotic pressure. The osmotic pressure difference between the hydrogel and the solution is the driving force for drug release from electro-responsive hydrogels [47]. Under electrical stimulation, the balance of these forces is disrupted, causing the dissolution or deswelling of the hydrogel. When an electric field is applied to an electro-responsive hydrogel in an aqueous medium, the ions on the polymer chains shift to positions with opposite charges, resulting in an uneven ion distribution and increased osmotic pressure within the polymer. This leads the hydrogel to an environment where osmotic pressure is not in equilibrium, whereupon the volume of the hydrogel is transformed [48].

Injectable ECHs

Injectable ECHs, a promising candidate for topical drug and cellular delivery, are now attracting increasing interest. It allows for the release of drugs through electrical stimulation and can be adapted to the needs of individual patient. This type of drug delivery offers new avenues for chronic diseases that require frequent injections or precise doses of drugs.

In fact, there are several degrees of freedom to optimize the effective release and delivery of drugs. For example, Qu et al. developed a dual-response hydrogel for electrical stimulation and pH [49]. This hydrogel was made by mixing oxidized dextran (OD) with chitosan grafting polyaniline (CP) onto the amino group of chains. Among them, chitosan and polyaniline are inherently conductive and biocompatible, and exhibit good antimicrobial properties. The Schiff base bond formed between chitosan and dextran can be decomposed in an acidic environment, which make them good candidates for preparing injectable antimicrobial conductive hydrogels with on-demand drug release. Experiments have shown that the release rate of model drugs carried in CP/OD hydrogels is positively correlated with the voltage. Upon reduction of CP under electrical stimulation, the positive charge in the CP/OD hydrogel is reduced, and the absorbent molecules are expelled from the hydrogel, then the hydrogel shrinks. After the drug molecules are released from the CP/OD hydrogel through the electrochemical reduction process, the charged object with the drug moves to the electrode, realizing drug escape. Meanwhile, the positively charged groups in CP/OD hydrogels (including amino and acid-doped polyaniline) can break through the bacterial wall and release intracellular fluid through electrostatic adhesion between polymer chains and bacteria.

Ge et al. developed a temperature and electric field stimulated dual-responsive hydrogel consisting of a conducting polymer PPy and a thermosensitive polymer poly(lactic-co-glycolic acid) (PLGA)- polyethylene glycol -PLGA [50]. The erythromycin was polymerized with PPy nanoparticles and then uniformly distributed in the PLGA- polyethylene glycol -PLGA. The hydrogel is in a liquid state at room temperature and can be accurately injected subcutaneously. After entering the body, the hydrogels form rapidly into a gel state at body temperature and remain immobile at the target location. Under the stimulation of electric field, erythromycin is released from PPy nanoparticles by electrochemical oxidation. Simultaneously, PPy nanoparticles move towards the electrode driven by electric field, and drug release is achieved in this process.

Transdermal ECHs

Transdermal drug delivery is a technique that introduces drugs into the blood system through the skin. This method not only avoids gastric degradation and hepatic first-pass metabolism, but is also very helpful in popular chronic treatments, eliminating the phobias and pain associated with injections [51]. Transdermal drug delivery is expected to be an alternative to subcutaneous injections due to it is non-invasiveness. It allows prolonged release of the drug, can be applied by the patients themselves, and can improve patient compliance.

Sangsuriyonk et al. investigated the effect of cross-linker concentration and electric field strength on drug release [52]. They found that the higher the concentration of cross-linker, the higher the cross-linked density of the hydrogel, and the lower the mass ratio and release rate of carried drug. The higher the electric field strength, the higher the rate of drug release. The amount of drug release may be different at the cathode and the anode because different drugs and drug-carrying particles have different

electrical properties. Under the action of electric current, the negatively charged drug is released by reduction of the conducting polymer, while the positively charged drug is released by oxidation [46].

In other words, in the absence of electrical stimulation, the slow release of the drug is due to the concentration difference through free diffusion. On the other hand, the electrically driven drug release from the ECHs is directly related to the electric field that drives the migration of charged objects and the change in the total charge within the polymer upon reduction or oxidation [53]. Moreover, the rate of drug release is directly related to the strength of current and voltage, the stronger the current and voltage, the faster the rate of drug release. However, at very high voltages, the drug may be susceptible to degradation. Although it is possible to reduce the release time at high voltages, this approach is also undesirable because high voltages may cause adverse side effects in complex mediums in vivo.

Implantable biomaterials

ECHs has the potential to be implantable biomaterials in the field of medical engineering due to its biocompatible and degradable properties. It may be applied to neuronal tissue with intrinsically weak electrical fields to induce the release of specific neurotransmitters or combined with electrical activity of brain regions.

Ding et al. designed a hydrogel matrix consisting of silk fibroin compounded with aldehyde-hyaluronic acid, forming a dynamic network that delays or interrupts the hardening induced by silk fibroin chain β-sheet formation [54]. This results in a hydrogel matrix that mechanically aligns with biological tissues. Functionalized CNTs were incorporated to impart electrical conductivity to the hydrogel, which was experimentally demonstrated through in vivo implantation, showing effective stimulation and recording of neural signals. Han et al. developed an SG hydrogel by blending poly with graphene, creating a physically cross-linked structure that mimics human tissue mechanics [55]. This hydrogel exhibits strong adhesion to living tissue in humid environments and can be cleanly peeled off without leaving residue. In particular, the hydrogels do not change its volume in aqueous solution. In the other words, it does not swell, which helps the hydrogels to maintain stable when implanted in the body and do not cause stress to the surrounding tissues. It has been experimentally demonstrated that the hydrogel is electrically conductive and can be implanted in the sciatic nerve of rats to achieve neuromodulation by low-current electrical stimulation.

In recent years, cell scaffolds have also been increasingly investigated. ECHs have been shown to be used as biological scaffolds for culturing cardiomyocytes, providing a suitable microenvironment for cell attachment, spreading and proliferation, especially for cardiac tissue engineering, because the expression of linker proteins in cardiomyocytes can be enhanced in response to electrical stimulation [24, 56].

Conclusion

When talking about the prospective of conductive hydrogels, we cannot help but notice the great potential they show in several fields. Conductive hydrogels have unique physical, chemical and electrical properties that make them attractive in many applications like never before.

Their biocompatible and conductive properties make them ideal candidates for biosensors, smart drug delivery systems, and biological tissue engineering. Conductive hydrogels are capable of integrating sensor technologies to enable real-time monitoring of physiological parameters in living organisms, such as blood glucose levels, heart rate and muscle activity, to support personalized medicine. With the development of wearable technology, conductive hydrogels can be used to create flexible and comfortable biosensors and health monitoring devices. These devices can fit closely to the skin, enabling seamless monitoring of body status and transmission of data to mobile devices for analysis and diagnosis.

Meanwhile, conductive hydrogels, as a new type of material with multifunctionality and tunability, have also been widely researched and applied in the fields of environmental detection, energy reserve and conversion, showing a wide range of application prospects. However, integrating the properties of ECHs, their fabrication, and practical applications in humans still faces significant challenges.

ECHs have the physicochemical properties of hydrogels and also have excellent electrical conductivity. The structure and properties of ECHs can be imparted and adjusted by controlling the type of synthetic materials, composition ratio, and cross-linking method. Therefore, it is important to select appropriate polymer matrices and conductive mediums for ECHs in different application fields, so as to leverage

their synergistic benefits.

For example, introducing conductive mediums usually increases the crosslink density and strength of the hydrogels, but decreases the toughness and tensile properties. However, the conductivity of ECHs is positively correlated with the content of conductive mediums, and only trade-offs can be made between the two. In addition, although many self-healing, recoverable ECHs have been reported, it takes 30 minutes or more to recover 90% properties of the original hydrogel.

The synthetic production of ECHs is also a major challenge because the properties of hydrogels are easily affected by the composition ratio, production process, and external environment, so even a small change in the composition ratio may largely affect the cross-linking of hydrogels. The combination between the hydrophobic materials such as metal nanoparticles and the polymer matrices also requires special introduction methods to ensure uniform structure, which poses challenges for stable mass production of ECHs.

Research on ECHs in the field of biomedical engineering is developing rapidly, extending from external applications to internal use. However, numerous studies are confined to animal experiments and have progressed to clinical trials. The functionalities and potential side effects are yet to be thoroughly explored. Therefore, there is still a long way to go before ECHs can be used as bioelectronic therapeutic tools.

References

[1] Yang C, Suo Z. Hydrogel ionotronics. Nature Reviews Materials 2018;3(6):125-142.

[2] Yang J, Bai R, Chen B, et al. Hydrogel Adhesion: A Supramolecular Synergy of Chemistry, Topology, and Mechanics. Advanced Functional Materials 2020;30(2):1901693.

[3] Rong Q, Lei W, Liu M. Conductive Hydrogels as Smart Materials for Flexible Electronic Devices. Chemistry 2018;24(64):16930-16943.

[4] Shao H, Wu YC, Lin Z, et al. Nanoporous carbon for electrochemical capacitive energy storage. Chem Soc Rev 2020;49(10):3005-3039.

[5] He Y, Deng Z, Wang YJ, et al. Polysaccharide/Ti(3)C(2)T(x) MXene adhesive hydrogels with self-healing ability for multifunctional and sensitive sensors. Carbohydr Polym 2022;291:119572.

[6] Li X, Liu Z, Liang Y, et al. Chitosan-based double cross-linked ionic hydrogels as a strain and pressure sensor with broad strain-range and high sensitivity. J Mater Chem B 2022;10(18):3434-3443.

[7] Li S, Pan H, Wang Y, et al. Polyelectrolyte complex-based self-healing, fatigue-resistant and anti-freezing hydrogels as highly sensitive ionic skins. Journal of Materials Chemistry A 2020;8(7):3667-3675.

[8] Hu O, Chen G, Gu J, et al. A facile preparation method for anti-freezing, tough, transprent, conductive and thermoplastic poly(vinyl alcohol)/sodium alginate/glycerol organohydrogel electrolyte. Int J Biol Macromol 2020;164:2512-2523.

[9] Jiang P, Huang L, Wang J, et al. Carboxymethyl chitosan-based multifunctional hydrogels incorporated with photothermal therapy against drug-resistant bacterial wound infection. Int J Biol Macromol 2022;209(Pt A):452-463.

[10] Li S, Lu D, Tang J, et al. Electrical Stimulation Activates Fibroblasts through the Elevation of Intracellular Free Ca(+2+): Potential Mechanism of Pelvic Electrical Stimulation Therapy. Biomed Res Int 2019;2019:7387803.

[11] Ferrigno B, Bordett R, Duraisamy N, et al. Bioactive polymeric materials and electrical stimulation strategies for musculoskeletal tissue repair and regeneration. Bioact Mater 2020;5(3):468-485.

[12] Kenry, Liu B. Recent Advances in Biodegradable Conducting Polymers and Their Biomedical Applications. Biomacromolecules 2018;19(6):1783-1803.

[13] Dodero A, Donati I, Scarfì S, et al. Effect of sodium alginate molecular structure on electrospun membrane cell adhesion. Mater Sci Eng C Mater Biol Appl 2021;124:112067.

[14] Mo F, Huang Y, Li Q, et al. A Highly Stable and Durable Capacitive Strain Sensor Based on Dynamically Super-Tough Hydro/Organo-Gels. Advanced Functional Materials 2021;31(28):2010830.

[15] Liu H, Li M, Liu S, et al. Spatially modulated stiffness on hydrogels for soft and stretchable integrated electronics. Materials Horizons 2020;7(1):203-213.

[16] Guan S, Wang Y, Xie F, et al. Carboxymethyl Chitosan and Gelatin Hydrogel Scaffolds Incorporated with Conductive PEDOT Nanoparticles for Improved Neural Stem Cell Proliferation and Neuronal Differentiation. Molecules 2022;27(23).

[17] Gao Y, Jia F, Gao G. Ultra-thin, transparent, anti-freezing organohydrogel film responded to a wide range of humidity and temperature. Chemical Engineering Journal 2022;430:132919.

[18] Zhao D, Zhu Y, Cheng W, et al. Cellulose-Based Flexible Functional Materials for

Emerging Intelligent Electronics. Adv Mater 2021;33(28):e2000619.
[19] Wu Y, Liu J, Chen Z, et al. High Multi-Environmental Mechanical Stability and Adhesive Transparent Ionic Conductive Hydrogels Used as Smart Wearable Devices. Polymers (Basel) 2022;14(23).
[20] Bian Z, Li Y, Sun H, et al. Transparent, intrinsically stretchable cellulose nanofiber-mediated conductive hydrogel for strain and humidity sensing. Carbohydr Polym 2023;301(Pt A):120300.
[21] Au-Yong S, Firlak M, Draper ER, et al. Electrochemically Enhanced Delivery of Pemetrexed from Electroactive Hydrogels. Polymers (Basel) 2022;14(22).
[22] Cong J, Fan Z, Pan S, et al. Polyacrylamide/Chitosan-Based Conductive Double Network Hydrogels with Outstanding Electrical and Mechanical Performance at Low Temperatures. ACS Appl Mater Interfaces 2021;13(29):34942-34953.
[23] Wang W, Meng Q, Li Q, et al. Chitosan Derivatives and Their Application in Biomedicine. Int J Mol Sci 2020;21(2).
[24] Sharifisistani M, Khanmohammadi M, Badali E, et al. Hyaluronic acid/gelatin microcapsule functionalized with carbon nanotube through laccase-catalyzed crosslinking for fabrication of cardiac microtissue. J Biomed Mater Res A 2022;110(12):1866-1880.
[25] Zhou Y, Fei X, Tian J, et al. Biomass-based hydrogels with high ductility, self-adhesion and conductivity inspired by starch paste for strain sensing. Int J Biol Macromol 2022;222(Pt A):1211-1220.
[26] Lee Y, Song WJ, Sun JY. Hydrogel soft robotics. Materials Today Physics 2020;15:100258.
[27] Sun X, Qin Z, Ye L, et al. Carbon nanotubes reinforced hydrogel as flexible strain sensor with high stretchability and mechanically toughness. Chemical Engineering Journal 2020;382:122832.
[28] You L, Shi X, Cheng J, et al. Flexible porous Gelatin/Polypyrrole/Reduction graphene oxide organohydrogel for wearable electronics. J Colloid Interface Sci 2022;625:197-209.
[29] Gong X, Fu C, Alam N, et al. Preparation of Hemicellulose Nanoparticle-Containing Ionic Hydrogels with High Strength, Self-Healing, and UV Resistance and Their Applications as Strain Sensors and Asymmetric Pressure Sensors. Biomacromolecules 2022;23(6):2272-2279.
[30] Gao Y, Zhang Z, Ren X, et al. A hydrogel sensor driven by sodium carboxymethyl starch with synergistic enhancement of toughness and conductivity. J Mater Chem B 2022;10(30):5743-5752.
[31] Chen D, Zhao X, Wei X, et al. Ultrastretchable, Tough, Antifreezing, and Conductive Cellulose Hydrogel for Wearable Strain Sensor. ACS Appl Mater Interfaces 2020;12(47):53247-53256.
[32] Lu L, Huang Z, Li X, et al. A high-conductive, anti-freezing, antibacterial and anti-swelling starch-based physical hydrogel for multifunctional flexible wearable sensors. Int J Biol Macromol 2022;213:791-803.
[33] Chen D, Zhao X, Gao H, et al. High-Strength, Conductive, Antifouling, and Antibacterial Hydrogels for Wearable Strain Sensors. ACS Biomater Sci Eng 2022;8(6):2624-2635.
[34] Shen Z, Zhang Z, Zhang N, et al. High-Stretchability, Ultralow-Hysteresis ConductingPolymer Hydrogel Strain Sensors for Soft Machines. Adv Mater 2022;34(32):e2203650.
[35] Huang W-C, Ying R, Wang W, et al. A Macroporous Hydrogel Dressing with Enhanced Antibacterial and Anti-Inflammatory Capabilities for Accelerated Wound Healing. Advanced Functional Materials 2020;30(21):2000644.
[36] Yu J, Su H, Wei S, et al. Calcium content mediated hemostasis of calcium-modified oxidized microporous starch. J Biomater Sci Polym Ed 2018;29(14):1716-1728.
[37] Xu L, Liu Y, Tang L, et al. Preparation of Recombinant Human Collagen III Protein Hydrogels with Sustained Release of Extracellular Vesicles for Skin Wound Healing. Int J Mol Sci 2022;23(11).
[38] Rao KM, Narayanan KB, Uthappa UT, et al. Tissue Adhesive, Self-Healing, Biocompatible, Hemostasis, and Antibacterial Properties of Fungal-Derived Carboxymethyl Chitosan-Polydopamine Hydrogels. Pharmaceutics 2022;14(5).
[39] Liu J, Qu M, Wang C, et al. A Dual-Cross-Linked Hydrogel Patch for Promoting Diabetic Wound Healing. Small 2022;18(17):e2106172.
[40] Talikowska M, Fu X, Lisak G. Application of conducting polymers to wound care and skin tissue engineering: A review. Biosens Bioelectron 2019;135:50-63.
[41] Luo R, Dai J, Zhang J, et al. Accelerated Skin Wound Healing by Electrical Stimulation. Adv Healthc Mater 2021;10(16):e2100557.
[42] Wang C, Jiang X, Kim HJ, et al. Flexible patch with printable and antibacterial conductive hydrogel electrodes for accelerated wound healing. Biomaterials 2022;285:121479.
[43] Hajhosseini B, Longaker MT, Gurtner GC. Pressure Injury. Ann Surg 2020;271(4):671-679.
[44] Li Y, Fu R, Guan Y, et al. Piezoelectric Hydrogel for Prophylaxis and Early Treatment of Pressure Injuries/Pressure Ulcers. ACS Biomater Sci Eng 2022;8(7):3078-3086.
[45] Liu X, Tian S, Xu S, et al. A pressure-resistant zwitterionic skin sensor for domestic real-time

monitoring and pro-healing of pressure injury. Biosens Bioelectron 2022;214:114528.
[46] Samanta D, Hosseini-Nassab N, Zare RN. Electroresponsive nanoparticles for drug delivery on demand. Nanoscale 2016;8(17):9310-9317.
[47] Merino S, Martín C, Kostarelos K, et al. Nanocomposite Hydrogels: 3D Polymer-Nanoparticle Synergies for On-Demand Drug Delivery. ACS Nano 2015;9(5):4686-4697.
[48] Deng Z, Hu T, Lei Q, et al. Stimuli-Responsive Conductive Nanocomposite Hydrogels with High Stretchability, Self-Healing, Adhesiveness, and 3D Printability for Human Motion Sensing. ACS Appl Mater Interfaces 2019;11(7):6796-6808.
[49] Qu J, Zhao X, Ma PX, et al. Injectable antibacterial conductive hydrogels with dual response to an electric field and pH for localized "smart" drug release. Acta Biomater 2018;72:55-69.
[50] Ge J, Neofytou E, Cahill TJ 3rd, et al. Drug release from electric-field-responsive nanoparticles. ACS Nano 2012;6(1):227-233.
[51] Sabbagh F, Kim BS. Recent advances in polymeric transdermal drug delivery systems. J Controll Release 2022;341:132-146.
[52] Sangsuriyonk K, Paradee N, Sirivat A. Electrically controlled release of anticancer drug 5-fluorouracil from carboxymethyl cellulose hydrogels. Int J Biol Macromol 2020;165(Pt A):865-873.
[53] Pérez-Martínez CJ, Morales Chávez SD, del Castillo-Castro T, et al. Electroconductive nanocomposite hydrogel for pulsatile drug release. Reactive and Functional Polymers 2016;100:12-17.
[54] Ding J, Chen Z, Liu X, et al. A mechanically adaptive hydrogel neural interface based on silk fibroin for high-efficiency neural activity recording. Mater Horiz 2022;9(8):2215-2225.
[55] Han IK, Song KI, Jung SM, et al. Electroconductive, Adhesive, Non-Swelling, and Viscoelastic Hydrogels for Bioelectronics. Adv Mater 2023;35(4):e2203431.
[56] Alvarez-Primo F, Anil Kumar S, Manciu FS, et al. Fabrication of Surfactant-Dispersed HiPco Single-Walled Carbon Nanotube-Based Alginate Hydrogel Composites as Cellular Products. Int J Mol Sci 2019;20(19).