Analysis on the Application of the Hydrogels in Bioelectronic Sensing

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Abstract: The electronic activities of the nervous system have become an important part of our daily life, such as muscle control, complex memory and reasoning. Bioelectronics was born in the interweaving of biology and electronics. At present, most wearable devices are based on the characteristics of electrodes, which have improved the performance and control. They are actively used in hospitals, laboratories and so on. The advent of hydrogels further advanced the development of electronic biology. This paper introduces a variety of hydrogels, to analyze the characteristics of hydrogels and other applications. The results show that conductive hydrogels have characteristics of high elasticity, high toughness, high mechanical strength, frost resistance, self-healing ability, and stimulating response properties. DNA hydrogel has the super function of transmitting bioelectronic information and can be used as the ideal carrier of drugs. In addition, through the analysis of conductive hydrogels and DNA hydrogels, it can be concluded that they have great potential in the field of bioelectronic sensing and biomedical treatment. Through the analysis of the main components of conductive hydrogels and DNA hydrogels, it is possible that people can select different polymers according to different needs in the future and mix them into the hydrogel matrix to form new hydrogels, so as to meet the needs.

1 INTRODUCTION

The electronic activity of the nervous system has become an important part of our daily life, such as muscle control, complex memory and reasoning. Bioelectronics was born in the interlacing of biology and electronics. At present, most wearable devices are based on the characteristics of the electrode has improved performance and control, they are actively used in hospitals, laboratories and so on. However, the human body biological tissue and the nature of the electronic products fundamentally have a big difference, sometimes biological tissue rejection happens and electronic products can produce irreversible damage to the body's tissues (Yuk et al. 2019). Therefore, the selection and manufacture of materials for human bioelectronic products is still an important direction in the exploration of electronic biology.

However, the emergence of hydrogels has greatly reduced the mechanical resistance between bioelectronic products and human biological tissues. Hydrogel is a kind of hydrophilic three-dimensional network structure gel, which rapidly expands in water and can keep a large volume of water in this swelling state without dissolving (Lu et al. 2016). They can be as high as 99% water or as low as very little water. In addition, under different conditions, the aggregation state of hydrogel can not only maintain a certain shape and volume, but also make solute permeate or diffuse in the hydrogel (Li et al. 2013). This paper is mainly to introduce the application of hydrogels in bioelectronics and explores the characteristics of two different hydrogels - conductive hydrogels and DNA hydrogels. Through the analysis of the composition of the two hydrogels, the functional differences between them and the different applications in the field of bioelectronics are understood. This paper aims to provide a reference for the material selection and manufacture of human bioelectronic products in the future, and has certain significance for the development of electronic biology.

2 CONDUCTIVE HYDROGELS

2.1 Composition, Properties and Application of Conductive Hydrogels

Conductive hydrogel can only be synthesized by conductive polymer, and conductive additives (such

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as conductive polymer, carbon nanotubes (CNT), etc.) can be added to the existing non-conductive hydrogel polymer, to increase the number of active electrons of conductive hydrogel and increase its conductive performance (Fu et al. 2020). Moreover, conductive hydrogel has the characteristics of high elasticity, high toughness, high mechanical strength, frost resistance, self-healing ability, and stimulating response properties and so on (Liu et al. 2020). Table 1 is mainly about the composition of the conductive hydrogels and their related application bioelectronic field. What is more, there are some examples of conductive hydrogels that have been studied to demonstrate some of their functional properties and introduce their applications.

Table 1: The Conductive Hydrogels: Components and Applications.

Hydrogel matrix	initiator	Cross-linking method	additive	application
Graphene oxide (GO)	Ammonium persulfate (APS)	Acrylamide/bisacrylamide	Polyacrylamide (PAM)	Multifunctional muscle-mimicking
Acrylic acid (AA)	A-ketoglutaric acid	ultraviolet (UV) polymerization and freeze-thaw treatment	Poly (vinylalcohol) (PVA) sulfuric acid	stretchable ionic cableflexible electronics
N-hydroxymethyl acrylamidestearyl methacrylate (C_{18})		UV light (intensity of 8 Wand wavelength of 365nm)	sodium dodecyl sulfate (SDS)sodium chloride (NaCl)	wearable flexible electronic devices
poly(3,4-ethylenedioxythiophene)/poly(4-styrenesulfonate) (PEDOT/PSS)	ammonium persulfate (APS)	Freeze-thaw treatment	sulfuric acid phytic acid	flexible solid-state supercapacitors
poly(vinyl alcohol) (PVA)	ammonium persulfate (APS)	4-carbonxybenzaldehyde	Poly (3, 4 ethylenedioxythiophene)/poly(4-styrenesulfonate) (PEDOT/PSS)	silicon anodes in lithium-ion batteries
acrylic acid (AA) nanocrystal cellulose (NCC)	ammonium persulfate (APS)	N, N'-methylenebisacrylamide (MBA)	Pyrrole ferric trichloride ($FeCl_3$)	catalyst supports, nerve regeneration, and carbon capture
2-hydroxyethyl methacrylate(HEMA), 3-sulfopropyl methacrylate(3SPMA)	2-hydroxy-1-4-(hydroxye-thory) phenyl-2-methyl-1-propanone	Methyltrimethoxysilane (MTMS)	polypyrrole(PPy) ferric trichloride ($FeCl_3$)	electrical stimulation treatment of chronic wounds
acrylic acid (AA)	ammonium persulfate (APS)	N, N’ -methylenebisacrylamide (MBA)	Poly (3, 4-ethylenedioxythiophene)/sulfonated lignin (PEDOT/SL)	motion detection and real-time healthcare
Acrylamide (AM)	ammonium persulfate (APS)	N, N’ -methylenebisacrylamide (MBA)	carboxyl-group-functionalized multi-walled carbon nanotube (MWCNT-COOH), N, N, N’, N’-tetramethylethylenediamine (TEMED), poly (vinyl alcohol) (PVA), PEDOT/PSS	biosignal detection and flexible wearable electronics
dopamine hydrochloride (DA) poly (vinyl alcohol) (PVA)		sodium tetraborate (borax)	graphene oxide (GO)	soft strain sensors for human activity detection
acrylic acid (AA) acrylamide (AM)	ammonium persulfate (APS)	N, N’-methylenebisacrylamide (MBA)	Iron (III)chloride hexahydrate ($FeCl_3 - 6H_2O$)	wearable devices and robotics

2.1.1 A Conductive Hydrogel based on the Ice Structuring Proteins/CaCl2 Anti-Freeze System

Conductive hydrogels are an important part of wearable devices, but antifreeze is still a challenge to achieve the normal operation of conductive hydrogels, which can keep good working condition in low temperature environment. Thus, a conductive hydrogel based on the ice structuring proteins/CaCl2 anti-freeze system has been invented. The hydrogel could inhibit ice formation at sub-zero temperature or room temperature. Moreover, the hydrogel shows good flexibility at room temperature and sub-zero temperature (890% at -20 ℃), the ability of the conductivity and recovery is about 0.50 S/m at -20 ℃ (Lu et al. 2021). So, according to the frost resistance of the new conductive hydrogel, it could be used in the temperature strain sensor, or it can also be used for low temperature anti-freezing storage of some biological specimens.

2.1.2 Polyelectrolyte Complex Hydrogel (Fe/CS/PAA)

Making polyelectrolytes with opposite charge and non-covalent interaction in water together could got a new ionic conductive hydrogel named Polyelectrolyte complex hydrogel (PECH). However, the researchers found that in the process of making the new conductive hydrogel, the densification of hydrogen bond network can effectively improve the elongation and endurance of the hydrogel. It is mentioned by Song Hui and her partners in 2021 that as a result of the experimentation, salt prioritize produced a dense hydrogen bonding network between the activated Fe-CS and Fe-PAA, Therefore, the polyelectrolyte complex hydrogel (based on the compact hydrogen bond network) has higher tensile properties (~ 1370%), greater tensile strength (~ 0.34mpa) as well as stronger cold resistance in -25 degrees Celsius and stronger thermal acceleration self-healing than the ordinary polyelectrolyte complex hydrogel (Song et al. 2021). Because of the high ductility, high conductivity and good cold resistance of polyelectrolyte complex hydrogel (based on the compact hydrogen bond network), The PAA ion sensor can be used for resistance mode of wearable polyelectrolyte complex hydrogel (Fe/CS/PAA) for rapid measurement and real-time detection and discrimination of complex human movements. It can be concluded that the polyelectrolyte complex hydrogel (Fe/CS/PAA) has the advantages of high brightness, good endurance and repeatable detection.

2.1.3 A Robust and Tough Alginate Hydrogel (GMA-SA-PAM)

Experiments have proved that hydrogels synthesized by natural polymers have good tensile and ductility in extreme environments. When the hydrogels synthesized by natural polymers are used in electronic equipment with high tensile strength, they are conducive to compressive and tensile resistance in extreme environments. As Liu Tao and his partners mentioned in 'High strength and conductive hydrogel with fully interpenetrated structure from alginate and acrylamide', They adopted a completely cross-linking method, first modified sodium alginate (SA) with glycidyl methacrylate (GMA), then copolymerized with acrylamide (AM) and methylenebisacrylamide (BIS) as crosslinking agents, and finally obtained a tough and strong sodium alginate hydrogel (Liu et al. 2021). Through experiments, it is found that GMA-SA-PAM hydrogel maintains the three-dimensional structure of hydrogel due to its polymer structure, which makes the hydrogel have super tensile strength and high compressive strength (the strain can reach 407% of the extension strain and the compression can reach 57% of the compression strain). In addition, if GMA-SA-PAM hydrogel is placed in 5 wt% NaCl solution, GSP-Na hydrogel with excellent electrical conductivity can be made, and GSP-Na hydrogel is very sensitive to electrochemical signal response, which can be applied to wearable devices and fast response electronic detection field.

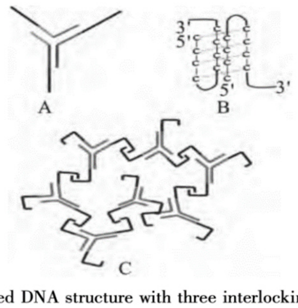
3 DNA HYDROGELS

3.1 Composition, Properties and Application of DNA Hydrogel

DNA hydrogels are three-dimensional polymers containing DNA (Mao, 2018). Deoxyribonucleic acid (DNA) is an important part of human cells, which has the characteristics of information transmission, molecular recognition, and editable. Compared with traditional hydrogels, DNA hydrogels have the characteristics of both DNA molecule and hydrogel. It is widely used in biosensing field because of its good specific recognition function and editable ability (Zhang et al. 2020). Moreover, DNA hydrogels can introduce hydrogels and analytes into another interface because the recognition of analytes will stimulate the reaction of DNA hydrogels, resulting in physical or chemical changes in the matrix of DNA hydrogels, thus converting them into electrical signals that can be detected by the instrument, or controlling the release of certain drugs for the treatment of some diseases (Li et al. 2020). DNA hydrogel has the characteristics of sequential editing, biodegradability, easy to synthesize and modify, and biocompatibility. It has been widely applied in the field of biomedicine control, biosensor and biological 3D printing technology. What is more, several different types of DNA hydrogels and their properties and application areas will be mentioned below.

3.1.1 PH Sensitive and Temperature Sensitive DNA Hydrogels.

In the human body, changes in pH and temperature will release different bioelectronic signals. Moreover, different temperatures will have different effects on the biological signals of human body, so we can apply pH or temperature sensitive DNA hydrogel to biosensor devices to detect biological signals (Zhao et al. 2015). As “the Stimulation-responsive DNA hydrogels and their application in biosensing and controlled drug release” mentioned that the Cheng et al. designed A PH-sensitive DNA hydrogel as shown in figure 2, which forms Y-type unit (A) through base complementing pairing of three DNA single strands, and the paired part is composed of C-rich single strand DNA. When PH values are different, the structure of DNA hydrogel will change. When PH=5, it will look like part B, when PH > 8.0, it will look like part C.



A—Y-shaped DNA structure with three interlocking domains; B—The formation of i-motif by the intermolecular association of the two interlocking domains; C—The formation of DNA hydrogel via i-motif

Figure 1: The different structures of the PH DNA hydrogels when the different PH value.

Thermosensitive DNA hydrogel can be cross-linked by the hydrogen bond of DNA, so the DNA hydrogel will be affected by the melting temperature (Tm) of double stranded DNA. When the temperature reaches the melting temperature, the gel-sol phase transition of DNA hydrogel will occur (Zhao et al. 2015). For example, Xing changed the part B in Figure 1 into double stranded DNA and found that the gel sol phase of DNA hydrogel is about 35~40 degrees Celsius (Xing et al. 2011). Thus, DNA hydrogel has the functions of conducting bioelectrical signals, molecular recognition and stimulus response. PH value and temperature stimulation-responsive DNA hydrosol are mostly used in biosensing or drug-controlled release systems to accept monitoring of human health or to treat some diseases.

3.1.2 DNA-Chitosan Hybrid Hydrogel.

DNA-chitosan Hybrid Hydrogel is an ideal storage layer for continuous delivery of human drugs. Chen Fanghao and his partners designed a new TYPE of DNA hydrogel in their experiments, which can be used for slow injection of drugs and can be used for slow healing of human wounds. Pre-gels were obtained by inducing cross-linking with base pairs, and then crosslinking chitosan and pre-gels to obtain DNA-chitosan via electrostatic interaction (Chen et al. 2021). Here is the figure 2 of DNA-chitosan synthesis and how it works.

From the figure 3, it can be found that DNA-chitosan Hybrid Hydrogel has superior Dex-transport and high biocompatibility, which can promote complete exchange of drugs and cells, and maintain cell activity. It can be seen from Figure 3 that DNA-chitosan Hybrid Hydrogel can promote the growth of RAW264.7 cells.

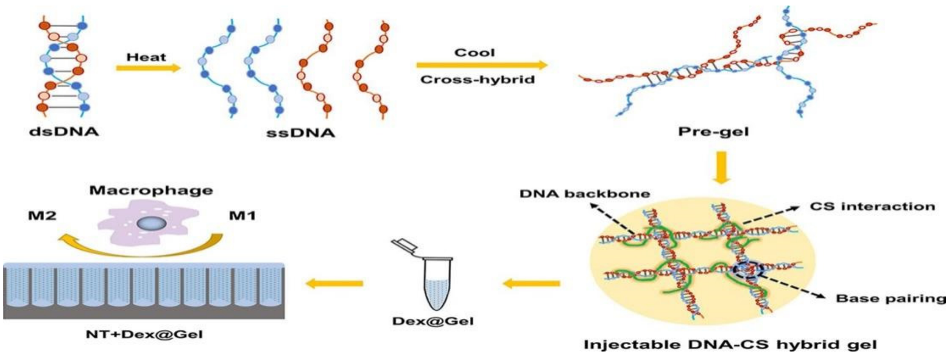


Figure 2: Synthesis of C and induction of M2 polarization in macrophages.

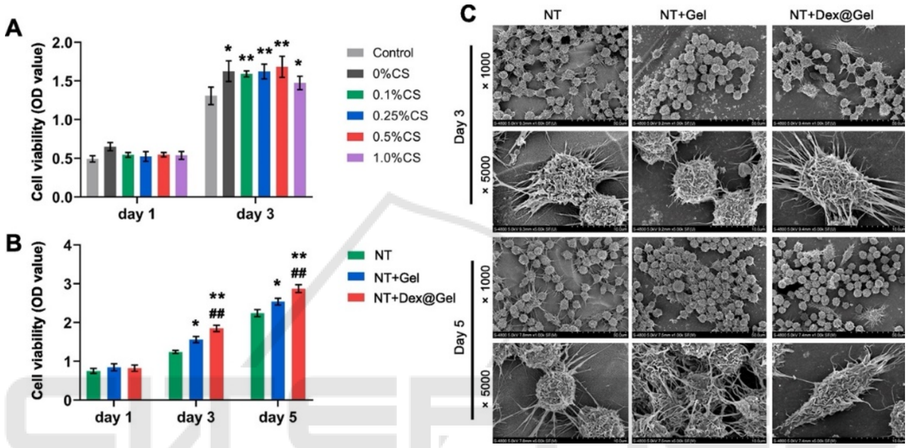


Figure 3: Growth and viability observation of the RAW264.7 cell.

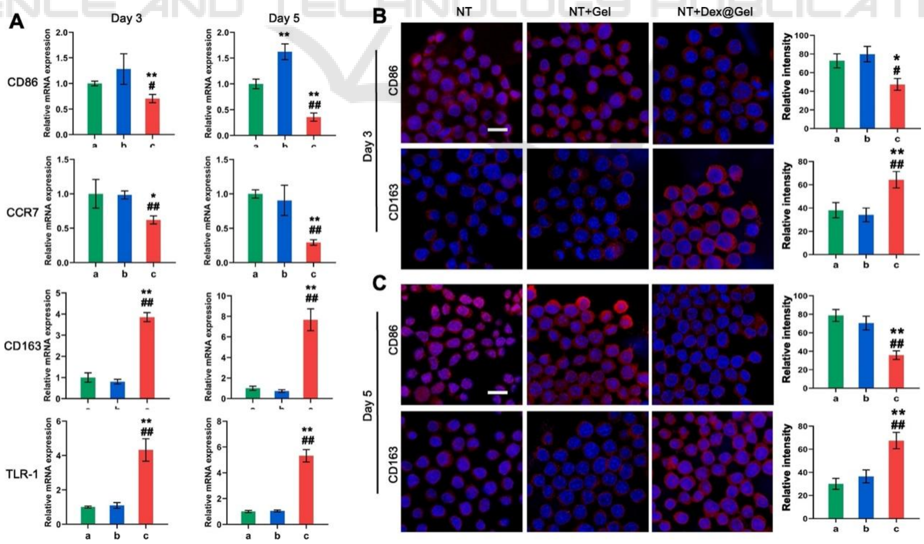


Figure 4: Performance of CD86, CCR7, CD163 and TLR-1 on Dex@Gel coated implant surfaces after Day 3 and Day 5.

From the figure 4, compared with the values of day 3 and day 5, it can be found that the DNA-chitosan Hybrid Hydrogel can inhibit the growth of CD86, CCR7, and promotes the growth of CD163 and TLR-1 (approximately 3-4 times) on Dex-Gel coated implants after day 3 and Day 5.

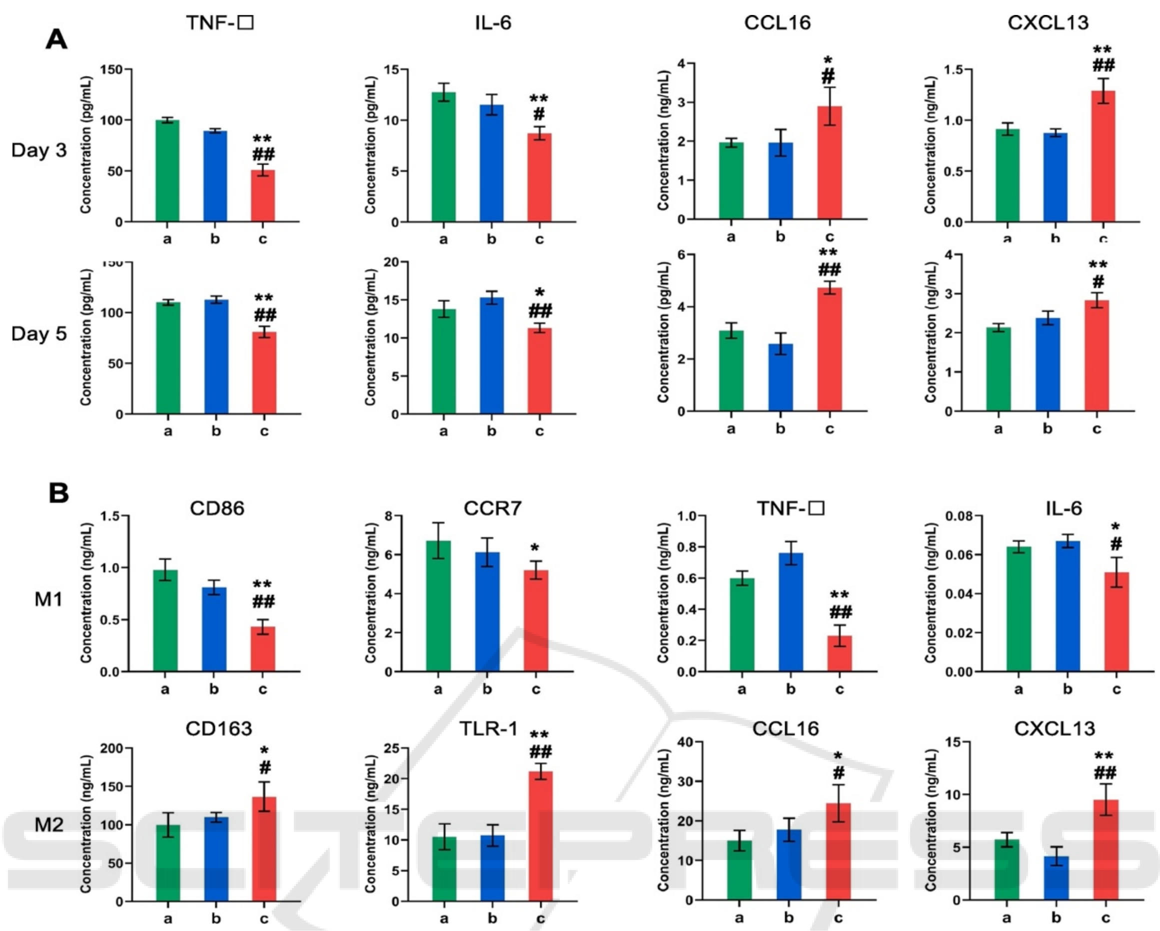


Figure 5: Comparison of macrophage polarization-related cytokines Day 3 and Day 5.

According to the figure 5, Compared with data in the figure 5, it shows that the concentrations of CCL16 and CXCL13 increased, it was proved that DNA-chitosan Hybrid Hydrogel could promote the polarization effect of M2. Therefore, DNA-chitosan Hybrid Hydrogel has a strong biocompatibility, can transmit bioelectronic information, and can be used as a drug carrier to treat some injuries, etc. It can be applied in biomedical field and bioelectronic sensing field.

4 CONCLUSIONS

Through the analysis of various hydrogels, Static dissipative hydrogels based on ice structural protein /CaCl2 antifreeze system have high cold resistance, Polyelectrolyte composite hydrogel (Fe/CS/PAA) has the advantages of high brightness. Besides, alginate hydrogel (GMA-SA-PAM) equips with characteristics of high compressive strength and high tensile strength. In addition, PH sensitive and temperature sensitive DNA hydrogel has a strong electrical conductivity. Conductive hydrogels and DNA hydrogels are basically used in medical fields, bioelectronic sensing fields or human health monitoring fields. The development of hydrogel technology promotes the integration of bioelectronics and human health monitoring, and provides a reference for the selection of electronic biomaterials. Even in the future, it is possible that people can select different polymers according to their different needs in the future and mix them into hydrogel matrix to form new hydrogels.

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