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Self-Healing Polymers Containing Nanomaterials for Biomedical Engineering Applications: A Review

Mohammad Yasin Mollajavadi [1], Fatemeh Forghan Tarigheh [1], Reza Eslami-Farsani [2*]

[1] Department of Chemical and Petroleum Engineering, Sharif University of Technology, Tehran, Iran

[2] Faculty of Materials Science and Engineering, K. N. Toosi University of Technology, Tehran, Iran

* Corresponding author: eslami@kntu.ac.ir

Abstract

Materials that can recover the function of lost or damaged parts, called self-healing materials, have attracted attention due to their wide usage in different fields such as water refinery, coatings, robotics, and especially, biomedical applications. Depending on whether the self-healing component is added to the polymer or is inherent to the polymeric matrix, the self-healing properties of the polymeric materials can be classified into extrinsic and intrinsic self-healing. Hydrogels are one of the most used polymers in self-healing applications for various purposes, including tissue engineering, drug delivery, etc. Nanoparticles can endow some essential features to hydrogels, such as improving mechanical properties, more efficient healing ability, conductivity, and antibacterial and magnetic features. In the current study, various biomedical applications of self-healing polymers using nanoparticles are discussed in detail, showing the impact of addition of nanoparticles. Perfect antibacterial properties with the addition of copper sulfide or silver nanoparticles were achieved. In addition, enhancing compression modulus up to three times and endowing conductivity to the hydrogel as the effect of carbon nanotube addition and better mechanical properties caused by graphene oxide and iron oxide nanoparticles were reported. These are just a few examples of the results achieved by adding nanoparticles to the self-healing polymers described in this study.

Keywords: Biomedical applications, Hydrogels, Nanoparticles, Polymers, Self-healing

1- Introduction

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Throughout history, the endeavor for healthier and longer life has urged humanity to develop materials that can recover the function of lost or damaged bodyparts [1,2]. These materials can recover their properties after damages, such as fatigue, impact, or wear and are called self-healing materials [3,4]. The ability of self-healing materials to detect and autonomously repair damage has drawn the attention of many researchers in recent years. Every year, various efforts are made with the goal of making new self-healing systems and integrating them into large-scale manufacturing [5]. Self- healing materials can be classified into extrinsic and intrinsic types. In extrinsic self-healing, a healing agent has to be added to the matrix of the material in the form of microcapsule structures [6-8]. When microcracks propagate through the matrix, the healing agent is released from ruptured microcapsules [9-11]. In intrinsic self-healing [12-14], materials can self-heal on their own based on reversible dynamic covalent [15,16] or non- covalent bonds, host-guest interaction [17-19], and metallo/ ligand complexation [20] without the need to add any healing agents. As an example of intrinsic self-healing, Saiz et al. studied on self-healable resins. The disulfide groups were able to exchange upon heating, leading to a renewal of the crosslinks across the damaged surfaces [21] .

Self-healing structures can be made from different materials, such as metals [22,23], epoxy [24,25], and hydrogels [26,27] for different applications. Self-healing structures can also be reinforced by shape memory alloy strips [28,29], fibers [30] or nanoparticles [31-33].

Hydrogels are useful and attractive materials for biomedical scientists because of their high water content. They are suitable for cell culture and tissue engineering because of their favorable oxygen and nutrient transport [34-36]. Hydrogels have a similar structure to biological soft tissues and can be used to resemble an extracellular matrix [37]. Self-healing hydrogels are a special kind of hydrogel that can autonomously repair cracks or focal damage and their integrity as well as their mechanical properties can recover after being destroyed [38]. So, they have been widely used in biomedical applications, e.g., wound dressing[39-41], tissue regeneration [42-44], and controlled/ targeted delivery of bioactive compounds [45-47]. Their most essential properties include their ability to encapsulate drug molecules, gene sequences, or cells, low surface friction, suitable morphology for cell growth, and stimuli-responsive characteristics [48]. The disadvantage of hydrogel-based self-healing materials is insufficient mechanical stiffness for some specific applications. For example, the mechanical properties of the human skull are in the MPa to GPa range, precisely in the radial direction of the skull up to 10000 psi and in the transverse and tangential direction up to 15000 psi. The use of self-healing hydrogels cannot monitor these mechanical properties of the skull due to the presence of water in the hydrogels structure [49]. So, Mechanical properties of these hydrogels may need to be improved for applications that require stiffer scaffolds [50,51].

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Since nanoparticles (NPs) expand material mechanical properties much further than just possible by molecular design of the network component [52], the inclusion of nanoparticles to produce composite hydrogels has acquired significant interest over the years [53-54]. So, one of the most effective methods for enhancing the characteristics of polymers, mainly mechanical properties, has been demonstrated to be the incorporation of nanoparticles [55-58]. Nanoparticles can also endow important properties to polymers, such as more efficient healing ability, conductivity [59], antibacterial, and magnetic features [60,61]. That is why nanoparticle-based self-healing polymers have attracted attention recently for use in different fields, such as coatings, robotics, water refinery, and biomedical applications [62-64].

Excellent reviews go into great detail about the development of self-healing hydrogels and their mechanisms. Mechanisms to fabricate self-healing hydrogels can be generally divided into two categories. These two include the non-covalent bonding (physical crosslinking), and the dynamic covalent bonding (chemical crosslinking). Non-covalent bonding includes hydrogen bonding, hydrophobic bonding, host-guest interactions, and ionic bonding. Non-covalent bonding is thought to be mechanically weaker than covalent bonding because of its weak intermolecular force and reversible interactions. Dynamic covalent bonding includes disulfide bonds, acylhydrazone bonds, imine bonds, boronate ester bonds, Diels-Alder reactions [65], and oxime bonds. Hydrogels based on dynamic covalent chemistry are involved with the ability of self-healing because the dynamic covalent bond crosslinking the networks could break and reform autonomously [66-68]. However, there is no review paper about self-healing polymers using nanomaterials. So, there is a need to review relevant literature, especially in biomedical applications, to help further advance developments in this field. In this study, as a novel idea, self-healing polymers, especially those that are based on hydrogels containing nanomaterials used in biomedical applications are reviewed. After reviewing different biomedical fields, a summary of the article and a future perspective of the work are given in the last part of the study.

2- Nanomaterial Based Self-Healing Composites Applications

2.1- Drug Delivery

Today, surgeries are often associated with postoperative infections or significant defects in normal tissue. Therefore, inhibiting the proliferation of bacteria and tumor cells and promoting wound healing is very important in the healing process. In recent years, light therapy, especially photothermal therapy (PTT), has caught attention due to its low side effects and wide application [69,70]. Photothermal agents (PTA), such as gold nanoparticles, carbon-based nanomaterials, indocyanine green dye, polydopamine, and other organic and inorganic compounds are used in this method [71,72]. CuS is a semiconductor nanoparticle with absorption in the intrinsic near-infrared (NIR) region. These particles are used in the

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photodynamic therapy (PDT) treatment method in addition to the treatment method described above and lead to the production of reactive oxygen species (ROS). Self-healing hydrogels are widely used in drug delivery systems and medical engineering. Hydrogels appear as very efficient drug delivery systems with very good tunable physical features that confer excellent controlled drug release properties and the ability to protect drugs from degradation [73-75]. Hydrogels are very suitable for drug delivery due to their porous and hydrophilic structure. In addition, they are good choices for wound dressings since their high-water content helps accelerate wound healing [76].

Zhou et al. used a complex injectable hydrogel with CuS nanoparticles due to antibacterial properties for wound healing. Oxidized dextran (ODex) and polyethylene glycol (PEG) were used for the hydrogel substrate, and CuS nanoparticles were incorporated into these hydrogel compounds. ODex has an aldehyde or hemiacetal functional group, and PEG has an amine functional group. The reversible covalent bond between these two functional groups creates a Schiff base and cross-links [76].

The presence of CuS nanoparticles causes the release of copper ions into the physiological environment (in vivo and in vitro). As a result, it increases the proliferation of fibroblast and vascular endothelial cells. Subsequently, the migration of cells increases, during which the amount of angiogenesis is also increased, leading to faster wound healing. Moreover, the presence of CuS nanoparticles under NIR radiation can cause more heat and ROS production, which can destroy bacterial proteins and DNA, leading to antibacterial properties. Antibacterial properties were tested against Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus) which are the most common pathogens causing bacteremia [76].

This system showed excellent self-healing properties, biocompatibility, good injectable properties, and anti-tumor and antibacterial properties. Structure and properties of the mentioned hydrogel is shown in Figure 1. In addition, adding CuS nanoparticles to these hydrogels made the compounds in PTT and PDT methods effective in removing melanoma cells and bacteria [76].

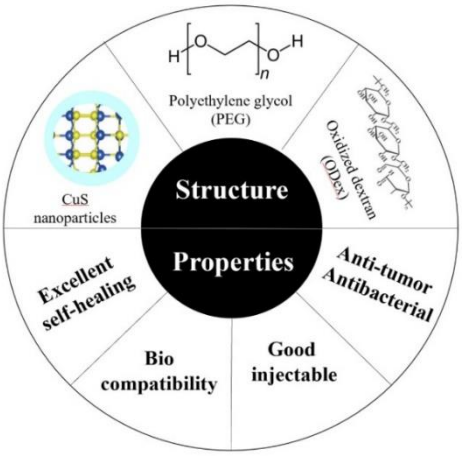

Figure 1. Schematic of structure and properties of the injectable hydrogel.

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Roth et al. used a self-healing hydrogel with nanoparticles, which can store the human immunodeficiency virus (HIV) vaccine (antibody) in itself and can continuously provide this vaccine to the cells. They used hydrogels with polymer nanoparticles (PNPs) which are supramolecular hydrogels in which polymer components and nanoparticles are put together by multivalent non-covalent dynamic interactions [77]. The components of the PNP used in this study are:

1) Dodecyl-modified hydroxypropyl methylcellulose (HPMC−C12)

2) Poly ethylene glycol- b-poly lactic acid (PEG−PLA) nanoparticles

3) Vaccine cargo, including ovalbumin (OVA: the main protein found in egg white) and polyinosinic: polycytidylic acid (Poly (I: C))

Following the injection of the hydrogel into mice, it was observed that the antibody profile is different from the one for a single dose of vaccine and has several antibody peaks. Additionally, the decrease in mice antibody concentration is gradual. Then, two samples with different ratios of polymer and nanoparticles (5:1 and 10:2) were used, and their rheological properties, including viscosity, yield stress, and strength modulus were characterized. It was observed that in the second sample, the cargo is released more slowly compared to the first sample. Finally, it was concluded that using this combination of self-healing polymer and nanoparticles is very practical because it has better rheological properties and can continuously provide antibodies to body cells. Saouaf et al. also used similar conditions. However, they added a different nanoparticle (TLR7/ 8a nanoparticles) to the PNP hydrogel to study the flu vaccine instead. They reported similar results [78].

Drug release is controlled by the matrix's cross-linking density and interactions between the drug and the matrix, according to the encapsulation of drugs within hydrogels' polymer matrix, as discussed before. Shi et al. mixed hyaluronic acid (HA) with a bisphosphonate (BP) functionalization and magnesium silicate nanoparticles ($MgSiO_3$ NPs) loaded with drugs uniformly to create a self-healing colloidal hydrogel. It was predicted that $MgSiO_3$ NPs would function as cross-linkers for HA chains and drug carriers. They conclusively proved that hydrogel formation depends on the BP groups on the HA polymer and the Mg^{2+} ions on the NPs. Doxorubicin (DOX), an aromatic medication frequently used in chemotherapy, was encapsulated inside $MgSiO_3$ NPs with a drug loading of 17 μg/mg. Cytotoxicity of $MgSiO_3$ NPs was minimal. The composite hydrogel demonstrated shear-thinning and self-healing properties, which are incredibly regarded in biomedical applications [79].

Li et al. employed a simple procedure to make self-healing hydrogels by Schiff base linkage, which consisted of branched polyethylenimine (BPEI), BPEI-linked graphene oxide (BPEI-GO), and chondroitin sulfate multialdehyde (CSMA). The hydrogel's backbone component, chondroitin sulfate

(CS), was selected due to its high hydrophilicity, biocompatibility, and biodegradability. BPEI-GO was doped in the network, participated in the Schiff-base reaction, stabilized the structure, and produced a photothermal effect driven by near-infrared lasers (NIR). After combining the three components at room temperature for 30 seconds, the CSMA/BPEI/BPEI-GO self-healing hydrogel was created. A hydrogel without BPEI-GO was created (CSMA/ BPEI hydrogel) as control. A three-dimensional porous structure was present in both hydrogels. CSMA/ BPEI/ BPEI-GO hydrogel had fewer pores on average (13.85 μm) than CSMA/ BPEI hydrogel (22.57 μm). This variation was attributed to the BPEI-GO nanoparticles covalently bound to the CSMA backbone. Pore size decreases as the degree of cross-linking increases. The storage modulus was greatly enhanced by adding BPEI-GO (0.2–0.6 wt.%), with a maximum G′ of 7,000 Pa. Also, increased optical absorption in the near-infrared (NIR) region was observed after grafting BPEI on GO. In addition, when CSMA/ BPEI/ BPEI-GO hydrogel's cytotoxicity was examined, no observable toxicity was seen in any of the ranges after 24 hours. Photothermal treatment should be combined with other therapeutic methods and might not be enough to cure the tumor on its own. DOX, waschosen as the model medicine to investigate its therapeutic potential. In comparison to CSMA/ BPEI hydrogel loaded with stoichiometric free DOX, CSMA/ BPEI/ BPEI-GO hydrogel displayed a moresustainable drug release profile. Combination of DOX and photothermal therapy in the CSMA/ BPEI/ BPEI-GO hydrogels reduced tumorrecurrence to 33.3% in breast cancer postoperative recurrence prevention mice model, compared to 66.7% for DOX-loaded hydrogels without NIR irradiation and 66.7% for local administration of free DOX. The schematic application of CSMA/ BPEI/ BPEI-GO hydrogel is shown in Figure 2 [80].

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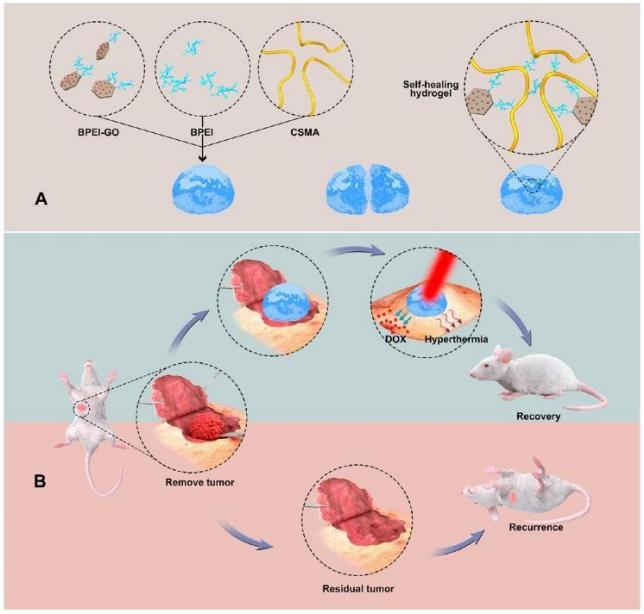

Figure 2. Schematic application of CSMA/ BPEI/ BPEI-GO hydrogel in preventing locoregional breast cancer recurrence [80].

A hydrogel containing iron oxide and magnetic field sensitivity is called a ferrogel. Superparamagnetic iron oxide nanoparticles (SPIONs) were employed to create a ferrogel by Ko et al. owing to their attraction to magnets and their role in different biomedical applications, such as targeted drug delivery, magnetic resonance imaging, and tissue engineering. Oxidized hyaluronate (OHA) and glycol chitosan (GC) were used as the primary materials for the hydrogel. Their imine bond formation actively contributed to the cross-linking of OHA/ GC hydrogel. In addition, reversible imine bond formation caused the gel to self-heal. A cylindrical mold was used to make the ferrogel, which was then broken into pieces. After 10 minutes, the ferrogel nearly took on its former cylindrical shape. The GC/OHA/SPION ferrogel showed almost complete self-healing at a SPION concentration of 5%. Also, the results confirm that the storage shear modulus of the ferrogel decreased as the SPION concentration in the gel was increased [81]. Some of the discussed articles in this section are summarized in Table 1.

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Table 1. Summary of some self-healing hydrogels for drug delivery applications

Composition of hydrogel matrices	Composition of nanomaterials	Self-healing ability	Reference
Dodecyl-modified hydroxypropyl methylcellulose/ polycytidylic acid	Poly (ethylene glycol) − b-poly (lactic acid) (PEG−PLA) nanoparticles	-	76
Dodecyl-modified hydroxypropyl methylcellulose/ polycytidylic acid	TLR7/ 8a nanoparticles	Recovered after 100 sec	78
Polyethylenimine/ chondroitin sulfate multialdehyde	Graphene oxide nanoparticles	Recovered after 30 sec	80
Oxidized hyaluronate /glycol chitosan	Superparamagnetic iron oxide nanoparticles	Recovered after 10 min	81

2.2- Gene Delivery

Gene delivery technologies are crucial for gene-based treatments of human genetic illnesses [82]. Gene therapy is a unique approach that can employ an adaptable gene to cure illness [83]. The viral gene delivery techniques based on DNA and RNA have been discussed.

Self-healing and shear-thinning hydrogels based on PNP interactions were fabricated by Van der Ven et al for miRNA delivery. For this purpose, hydroxy propyl methyl cellulose derivative (HPMC-C12) and core-shell nanoparticles) gold nanoparticles (AuNP) functionalized with poly ethylene-glycol (PEG) were used. The miRNAs molecules were attached to the functionalized gold nanoparticles to improve biostability and reduce degradation. For a minimally invasive, local, and sustained administration, these functionalized AuNPs (AuNP-miR) were loaded into a self-healing, biocompatible, and shear-thinning injectable hydrogel based on the PNP gel platform. The results showed that AuNP-miRs were released from the PNP hydrogel in a linear profile over multiple days, and about 20% of AuNP-miRs were released from the hydrogel over five days. Furthermore, it was discovered that AuNP-miR-214 continued to function after delivery in a 3D bioprinted human CAVD model and a 2D in vitro miR-214 target luciferase reporter test. In addition, AuNP-miRs were cleared by 11 days in mice following subcutaneous injection of the hydrogel [84]. Schematic structure of hydrogel is shown in Figure 3.

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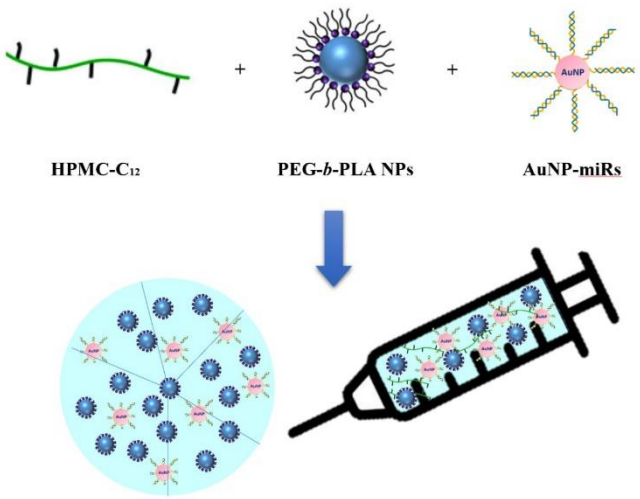

Figure 3. Schematic structure of the PNP hydrogel and the functionalized AuNP-miRs.

Uzumcu et al. reported development of DNA/ clay hydrogels using in situ N, N-dimethylacrylamide (DMAA) polymerization in the presence of laponite (LA) nanoparticles in aqueous solutions of ds-DNA (2-8 w/v%). Most poly (DMAA) chains cluster on the surface of clay particles following the polymerization of DMAA in an aqueous LA dispersion, forming numerous hydrogen bonds with the particles to produce hydrogels with exceptional mechanical characteristics. DNA strands can slide between the particles because clay cannot surround the particles due to the negative charges on DNA strands and the surface of clay particles.This prohibits hydrogen bonding between DNA and clay. Fluorescence analysis demonstrated that the heat denaturation/renaturation cycles experienced by ds-DNA molecules in the gel network increase the hydrogels' mechanical capabilities. When damaged gel samples are heated above the ds-DNA's melting point, hydrogels can self-heal. Great tensile strength (between 20 and 150 kPa) and high stretchability (up to 1500%) are two characteristic features of DNA/ clay hydrogels [85].

Inflammatory reactions of the nucleus pulposus can lead to an uneven anabolism and catabolism of extracellular matrix, and the buildup of cytosolic double stranded DNA (dsDNA) and activation of the stimulator of interferon genes-nuclear factor-kappa B (STING-NF-κB) pathway observed in nucleus pulposus inflammation are thought to be a significant contributor to the degeneration of the intervertebral disc (IVD). Chen et al. developed a short interfering STING (siSTING) delivery hydrogel using aldehyde hyaluronic acid (HA-CHO) and poly(amidoamine)/short interfering RNA (PAMAM/siRNA) complex to interfere with the abnormal STING signal for IVD degeneration treatment. The system was able to overcome drawbacks like a short half-life, low cellular uptake, and rapid degradation of siRNA-based strategy through the formation of dynamic Schiff base bonds. PAMAM acted as a dynamic crosslinker to create hydrogel and not only produced complexes with

siRNA to facilitate siRNA transfection but also effectively and gradually inhibited STING expression in nucleus pulposus cells using the injectable and self-healing hydrogel. Finally, in a puncture-induced IVD degeneration rat model, the system significantly reduced IVD inflammation and slowed IVD degeneration by prolonging STING knockdown, demonstrating that the STING pathway was a therapeutic target for IVD degeneration and that such a novel hydrogel had great potential to be used to treat many other diseases by delivering genes [86].

2.3- Tissue Engineering

2.3.1- Muscle Tissue Engineering

Tissue engineering is a very promising therapeutic method for tissue regeneration and replacement [87,88]. One of the essential features of polymers used in tissue engineering is conductivity, which promotes the differentiation and proliferation of electrically responsive cells, such as cardiac cells, nerve cells, and stem cells. The hydrogel used for this purpose must be strong and self-healable due to the mechanical load of the heart or other targeted tissues, which may cause hydrogel breakage during its service period. Also, it must be self-adhesive to eliminate the need for additional adhesive tapes [89]. Jing et al. used chitosan (CS) as the primary material of the hydrogel because of its good conductive, self-healing, and injectable properties. Dopamine mimics adhesive proteins of mussels, which are rich in amine and catechol functional groups. Polydopamine (PDA) used here with a tremendous binding abilityto nanofillers like graphene. GO was also used as an ideal nanofiller due to its excellent mechanical properties, conductivity, and optical properties. The results showed that the elastic modulus of the sample increased with the increase of GO content in the hydrogel. Additionally, the hydrogels containing GO showed excellent adhesive abilities compared to the control samples without GO. This led to good interactions between biomaterials and tissue. However, at GO contents of 0.75 and 1 mg/mL, the adhesive strength decreased. In addition, cell viability results demonstrated that the hydrogel sample with a high GO content (1 mg/mL) had less cell viability than other groups because aggregation of GO layers induced more oxidative stress and affected the toxicological responses of adherent cells. Results confirmed that the chitosan-based hydrogel proposed in this study could be suitable for electroactive tissue engineering applications [90].

Jiang et al. used ultrasmall aluminum hydroxide nanoparticles (AH NPs) as a multifunctional cross-linker (Al-NC gel) to prepare a nanocomposite hydrogel based on a combination of acrylamide (Aam) and 2-acrylamido-2-methyl propane sulfonic acid (AMPS). Al-NC gel showed improved toughness and a high self-healing rate thanks to the non-covalent interactions between AH NPs and polymer chains. The compressive stress of Al-NC gels increased from 1.2 to 18.9 MPa, and the tensile fracture stress increased from 139 to 512 kPa with an increase in AH NP concentration. Moreover, the lengthy and

flexible polymer chains inside the AH NPs were responsible for the Al-NC gels' excellent stretchability and elongation at break. Al-NC gel with 3 wt.% AH NPs showed elongation at break of as high as 2090%. Due to increased hydrogen bonding between polymers and AH NPs, the self-healing process was also noticeably accelerated with the addition of AH NPs. However, the increase in AH NP concentration led to a reduction in healing effectiveness because the moving polymer chains were constrained, and the shorter polymer chains could not diffuse deeper. This novel self-healing hydrogel may present a potential choice in tissue engineering [91]. In another study, this team also fabricated a similar self-healing nanocomposite hydrogel containing zirconium hydroxide (Zr-NC gel). Without external stimuli, Zr-NC gels exhibit remarkable self-healing efficacy at ambient temperature. Swelling test showed that the hydrogel in the urea solution exhibited significantly more swelling than in pure water due to the weakening of hydrogen bond interactions between the polymer chains and $Zr(OH)_4$ NPs. So, this could be evidence of existence of physical cross-linking networks. The gels show an increased tensile and compressive strength with increasing zirconium hydroxide contents. The highest self-healing abilities were seen in the healed Zr-NC gel with 4 wt.% zirconium hydroxide, showing a self-healing efficacy of 75% and 86% for the strength and elongation, respectively, and suitable for use in healable artificial cartilage applications [92].

Magnetic nanoparticles (MNP) made of iron incorporation in a biocompatible and biodegradable hydrogel were studied by Manas-Torres et al. and is schematically shown in Figure 4. Fluorenylmethoxycarbonyl- arginine-glycine- aspartic acid (Fmoc-RGD) and Fmoc diphenylalanine (Fmoc-FF) were used as the primary materials for the hydrogel. Through a shear-thinning/ self-healing process, adding MNP to the hydrogel matrix significantly improved the hydrogels' toughness and stability while enhancing their injectability. The study showed that these hybrid hydrogels stimulated cell growth and did not degrade after 30 days of culture, when used as scaffolds for the 3D formation of osteoblasts. Subcutaneous injections in mice were used to assess these biomaterials' injectability in vivo. One month after treatment, these hydrogels were still present in the injection site without degrading. Furthermore, it was shown that the hydrogel does not have any toxicity for cells. This magnetic hydrogel with high mechanical stiffness would be a proper choice as a tissue scaffold [93].

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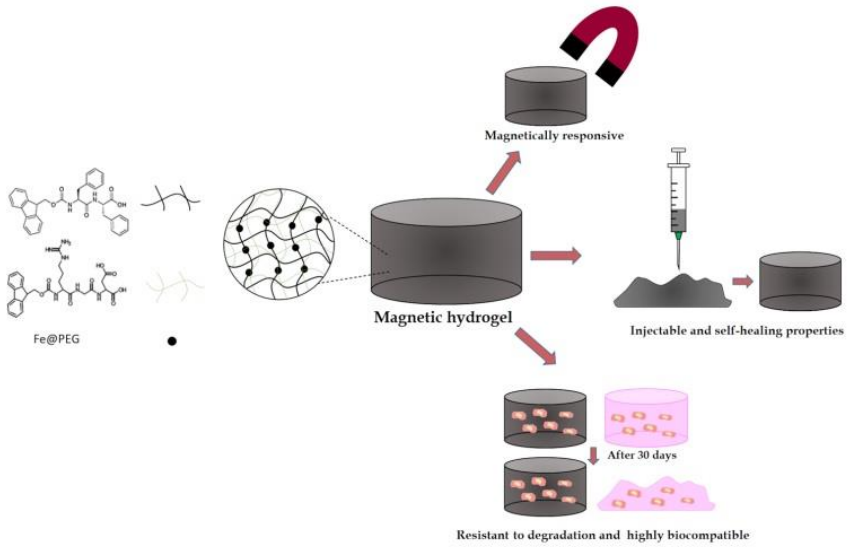

Figure 4. Schematic of the properties of supramolecular magnetic hydrogels [93].

2.3.2- Bone Tissue Engineering

Bone is a regenerative organ with the capacity for self-renewal. It is a dynamic tissue constantly being remodeled to maintain its form and function. However, in cases of injury, individuals can exhibit poor bone healing, necessitating medical intervention to rebuild the tissue using either natural or synthetic bone grafts [94]. Self-healing hydrogels can be used widely in bone regeneration applications, especially with the incorporation of nanoparticles for improving the mechanical properties of the hydrogel [95,96].

In a study, Nejadnik et al. exploited the reversible bonds between calcium phosphate nanoparticles (CaP) and bisphosphonate (BP)-functionalized hyaluronic acid to create an injectable, cohesive nanocomposite self-healing hydrogel. Different concentrations of CaP nanoparticles, hyaluronan-bisphosphonate (HABP) content, and bisphosphonate substitution degree were studied to investigate the effects on the gel formation, stiffness, and the self-healing property of the nanocomposite hydrogel. At a low polymer concentration of 0.5 w/v%, hyaluronan-bisphosphonate liquid-like behavior (defined by storage modulus G' < loss modulus G") was noted. By increasing the bisphosphonate substitution degree from 2.5 to 8.1%, the hyaluronan-bisphosphonate content from 0.5 to 2.0 w/v%, and the CaP content from 1.5 to 6.0 w/v%, the storage modulus increased by five times, one hundred times, and two times, respectively. This emphasizes the importance of the number of interactions between CaP and bisphosphonate for forming HABP. CaP hybrid nanocomposites. It has been demonstrated that CaP nanoparticles are necessary for the gel formation and stiffness of non-covalently cross-linked HABP.CaP due to the creation of powerful yet breakable bindings between CaP and bisphosphonate ligands. The optimum formulation contained 6% w/v CaP nanoparticles and 2% w/v hyaluronan-

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bisphosphonate (DSBP=8.1%). As shown in Figure 5, self-healing tests proved that HABP. CaP hybrids showed recovery of cohesiveness within less than 5 s. Since such a hydrogel with reversible bonds promotes bone formation, it is particularly interesting for bone regeneration applications [97].

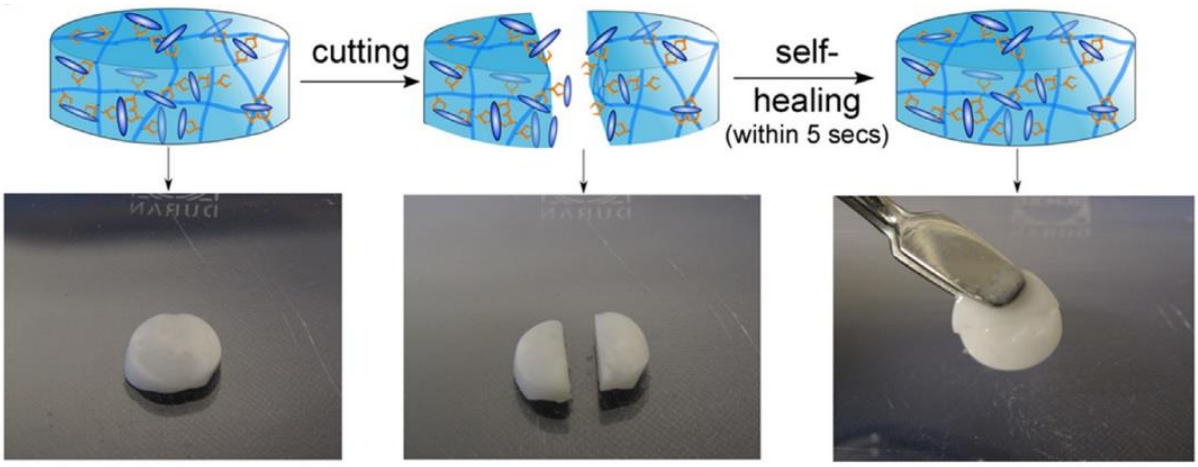

Figure 5. Schematic illustration and photographs of self-healing after failure induced by cutting [97].

Bioactive compounds like bioactive glass (BAG) incorporation into self-healing hydrogels use in tissue engineering applications. Gantar et al. used Au-based 4-arms thiol terminated poly (ethylene glycol)(Au-$(PEGSH)_4$) dynamic hydrogel as the primary material with self-healing ability. The dynamic hydrogel, known as Au-$(PEGSH)_4$, has a constant composition of 10 wt.% $(PEGSH)_4$ and 20 mol.% $HAuCl_4$. Different concentrations with 5, 10, and 20 wt.% of BAG nanoparticles were added to the nanocomposite hydrogel. BAG nanoparticles did not influence the hydrogels' gelation or self-healing ability. However, the dynamic hydrogel became stiffer after the BAG nanoparticles were added. It was established that there were no chemical or electrostatic interactions between the BAG nanoparticles and the polymeric network of Au-$(PEGSH)_4$-BAG hydrogel nanocomposites. This stiffness was due to an increase in polymer entanglements. In the case of free BAG nanoparticles, the rapid release of Si^{4+} and Ca^{2+} ions from the degradation of BAG nanoparticles in aqueous media to a sharp rise in pH, which led to cell death. The hydrogel's slow water diffusion avoided this sudden rise in pH. Cell proliferation was not much slower compared to the positive control consisting only of cells because the media's pH remained steady, promoting favorable cell viability. The presence of BAG nanoparticles helped improve the osteoconductivity of the injectable biocompatible PEG-based hydrogel even though the PEG homopolymer is biocompatible, but not bioactive. So, Injectable bioconductive Au-$(PEGSH)_4$-BAG hydrogel nanocomposites could be used in bone self-repairing applications [98]. Some of the discussed articles in this section are summarized in Table 2.

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Table 2. Summary of some self-healing hydrogels for tissue engineering applications

Composition of hydrogel matrices	Composition of nanomaterials	Self-healing ability	Reference
Chitosan/dopamine	Graphene oxide nanoparticles	91% recovery	90
Acrylamide (Aam) and 2-acrylamido-2-methyl propane sulfonic acid	Aluminum hydroxide nanoparticles	86% recovery	91
Acrylamide (Aam) and 2-acrylamido-2-methyl propane sulfonic acid	Zirconium hydroxide nanoparticles	Recovered after 5 min	92
Fluorenylmethoxycarbonyl-arginine-glycine- aspartic acid/ Fmoc diphenylalanine	Magnetic nanoparticle (iron)	Recovered after 120 min	93
Bisphosphonate (BP)-functionalized hyaluronic acid	Calcium phosphate nanoparticles	98% recovery	97
Au-based 4-arms thiol terminated poly ethylene glycol	Bioactive glass nanoparticles	-	98

2.4- Wound Dressing

Wound dressings assist the local wound environment and speed up the healing process. [99,100] However, bacteria can grow in a wet wound environment quickly, causing a secondary infection. Therefore, moist environments need hydrogel wound dressings with high antibacterial activities. Excellent antibacterial properties can be obtained from silver nanoparticles (AgNPs) [101].

Different types of cross-linking methods can be used for hydrogel preparation. Chemical cross-linking methods may lead to residues of cytotoxic agents remaining in the hydrogel. For this issue, physical cross-linking methods can be used, but they usually create hydrogels with poor mechanical characteristics. An innovative method for creating physical hydrogels using natural anionic and cationic polyelectrolytes is polyelectrolyte complexation (PEC). Yang et al.created a multifunctional chitosan/ carboxymethyl chitosan/ silver nanoparticles (CTS/ CMCTS/ AgNPs) polyelectrolyte composite physical hydrogel by in situ photoreduction of silver ions with α-hydroxy of CMCTS. The results suggested that the composite hydrogel made at a mCTS: mCMCTS ratio of 2:4 has the best overall characteristics, with a mechanical strength of 37 kPa, an elongation of 170%, and maximum water absorption of 12.8 g/g. The CTS/ CMCTS/ AgNPs hydrogel also showed good self-healing properties because of its physically cross-linked structure. After being tied for 30 seconds, the hydrogel can support its weight, and the crack disappears after 5 minutes. Additionally, it is a highly effective antibacterial substance against the main antibiotic-resistant bacteria in wound infections, including Gram-positive(S. aureus) and Gram-negative (P. aeruginosa) bacteria [102].

Pandian et al. also used silver nanoparticles to induce conductivity and antibacterial properties in a self-

healing N, O-carboxymethyl chitosan (CMC)-based hydrogel. Ethylenediaminetetraacetic acid-ferric ion (EDTA: Fe^{3+}) was used as a cross-linker. Free Fe^{3+} ions create a coordination connection with COO in the N, O- CMC/ AgNPs, facilitating hydrogel formation instantly. As a result, AgNP-containing samples showed the same swelling ratio but higher conductivity and antibacterial properties than samples with free AgNPs. Also, higher tissue adhesion makes N, O-CMC/ AgNPs hydrogel suitable as an injectable adhesive glue for the tissue closure of incisional wounds [103].

Furthermore, Talodthaisong et al. used silver nanoparticles as an antibacterial agent in a guar gum hydrogel cross-linked with borax. The prepared hydrogel showed good self-healing ability and could recover its original properties only within 6 minutes. The optimum borax to guar gum ratio reached the hydrogel's proper viscosity, pore size, and other mechanical properties. Adding silver nanoparticles with a diameter of around 17 nm to the hydrogel leads to outstanding antimicrobial activity against Gram-positive S. Aureus and Gram-negative bacteria, E. coli, and P. aeruginosa. Incorporating more nanoparticles also increased the hydrogel's swelling properties because an abundance of OH functional groups may result in increased H-bonding with water and enhanced water absorption. This injectable and self-healing hydrogel suggests future potential in wound healing applications [104].

Khamrai et al. fabricated a bacterial cellulose (BC)-based transdermal patch through a layer-by-layer method via a Schiff base reaction. Carboxymethylated bacterial cellulose (CMBC) properties as a BC derivative include biocompatibility, oxygen permeability, water absorption ability, and excellent porosity, making it suitable for cellular proliferation and migration. The amino group of CMBC-modified with ethylenediamine (EDA) reacts with the aldehyde group of the oxidized pectin and undergoes a Schiff base reaction as can be seen in Figure 6. Because of the imine linkage, the prepared hydrogel showed an ultimate tensile strenght of 4.72 MPa and an elongation at break of 23%. Adding AgNPs improved the ultimate tensile strength (UTS) and elongation break (EB) to 5.56 MPa and 32%, respectively. However, the presence of AgNPs hindered the diffusion of water to the hydrogel causing up to a 30% reduction in swelling ratio. The prepared hydrogel containing AgNPs showed almost complete self-healing. It also demonstrated significant antimicrobial properties against Gram positive and Gram negative bacteria and would be a suitable candidate for wound-healing applications [105].

In another study, Li et al. added polydopamine (PDA) nanoparticles to the N, N- diethylacrylamide, and acrylic acid mixture to induce light, thermo-, and pH sensitivity in the triple-responsive PDA@P (DEAA-AA) hydrogel. The catechol groups of PDA chains also cross-linked the hydrogel and reduced its water absorption. PDA can also give self-adhesion ability to the hydrogel, as discussed before. The high adhesive degree makes these hydrogels suitable for surgical operations without the need for other bandages. Dynamic strain measurements with cycles of damaging 0.4 wt.% PDA@P(DEAA-AA) hydrogel confirmed around 91% of self-healing efficiency after 1 minute, demonstrating excellent self-

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healing features [106]. Some of the discussed articles in this section are summarized in Table 3.

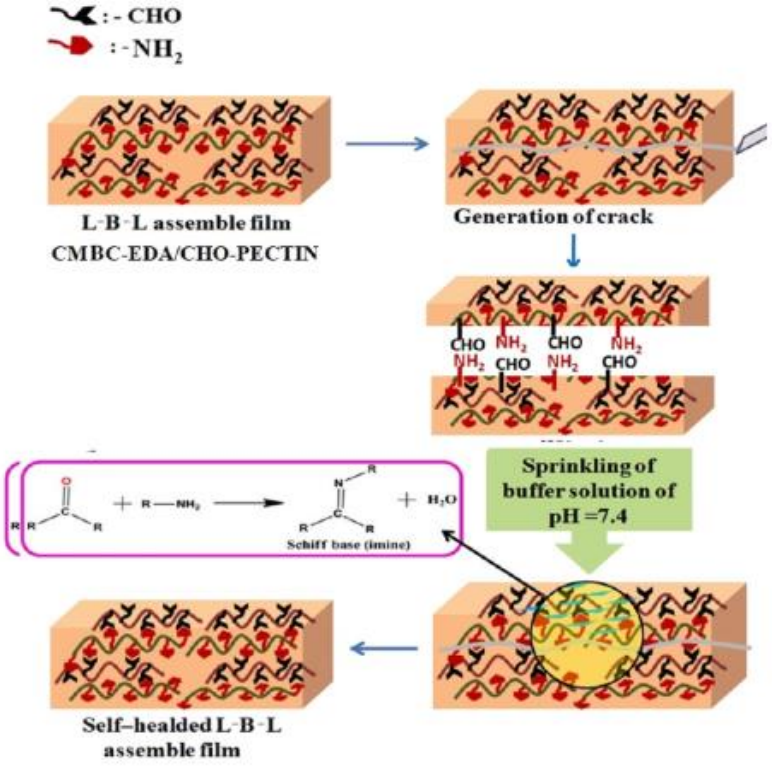

Figure 6. Oxidized pectin and EDA-modified carboxymethyl cellulose promote self-healing via the Schiff base reaction [105].

Table 3. Summary of some self-healing hydrogels for wound dressing applications

Composition of hydrogel matrices	Composition of nanomaterials	Self-healing ability	Reference
Chitosan/ carboxymethyl chitosan	Silver nanoparticles	Recovered after 5 min	102
N, O-carboxymethyl chitosan/ Ethylenediaminetetraacetic acid-ferric ion (crosslinker)	Silver nanoparticles	Recovered after 1 min	103
Guar gum hydrogel cross-linked with borax	Silver nanoparticles	-	104
Carboxymethylated bacterial cellulose/ ethylenediamine/ oxidized pectin	Silver nanoparticles	Recovered after 10 min	105
N, N- diethylacrylamide/ acrylic acid	Polydopamine nanoparticles	91% recovery after 1 min	106

2.5- Use of Self-Healing Hydrogels for 3D Bioprinting

In recent years, there has been an increase in the use of nanoparticles to make bioinks. The presence of nanoparticles in bioinks has three positive effects. Firstly, through physical and chemical interactions, it strengthens the mechanical properties of the existing hydrogel, integrates their structures and provides flexibility in a wider range to the bioinks. Secondly, they can introduce new bio-functionalities to the hydrogels; and finally they can give smart properties to the bioinks in such a way that they can respond to external stimuli, such as magnetic and electric fields [107,108].

Bioinks have properties like injectability, biocompatibility, and biodegradability. Also, bioinks should interact well with cells and not destroy them [109-111]. Self-healing hydrogels used in 3D printing are often composed of natural polymers such as gelatin, sodium alginate, and chitosan. However, these polymers have poor mechanical properties which can be remarkably improved by adding nanoparticles [112,113].

Figure 7 shows some applications and Figure 8 illustrates four applications of nanoparticles in bioinks. Figure 8A explained carbon nanodiamonds modified with methacryloyl gelatin polymer were used to support stem cells derived from human fat. In Figure 8B hydrogels made from DNA, oxidized alginate, and nano silicate show shear thinning properties. Aldehyde groups in alginate chemically bond and react with amines in DNA. The positive charge of nano silicates interacts with the negative charge of DNA, leading consequently to a physical bond. Therefore, this combination can be injected since applying strain to this hydrogel exhibits a liquid-like behavior, and when the strain is removed, it shows a hydrogel-like behavior. It is an injectable nanocomposite hydrogel in Figure 8C that responds to the external magnetic field. The nanoemulsion of silicone oil in water is composed of poly ethylene glycol diacrylate (PEG-DA), zinc ferrite magnetic nanoparticles, and indocyanine green. This material behaves like a fluid at room temperature, and in the body of diacrylate, it can enter the interface between water and oil and create a solid hydrogel network. In Figure 8(D), 2D light-sensitive nanoplates are shown. These sheets are composed of hydrogels formed by four-armed polyethylene glycol and react dynamically with sulfur in the thiol group to cross-link the polymers. These hydrogels can be combined with medicinal substances, releasing the medicine by applying infrared light near them [114].

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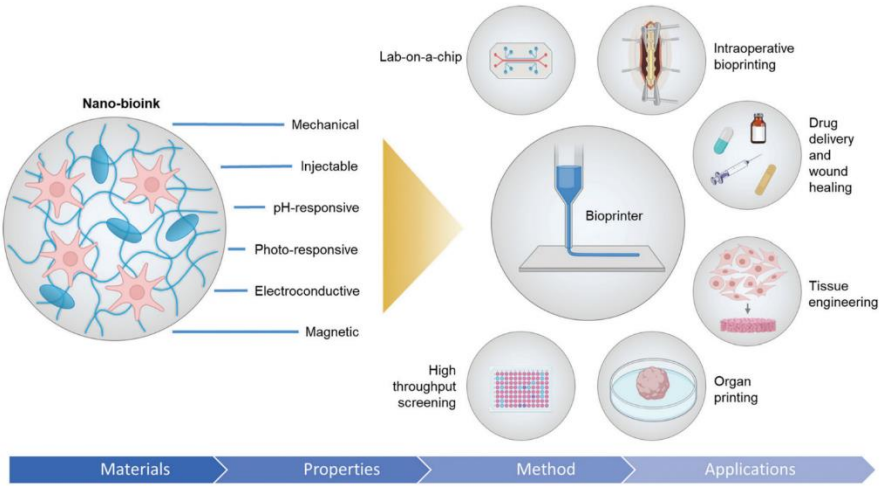

Figure 7. Multifunctionalities of nanocomposite hydrogel-based bioinks. Illustrating the conceivable applications of nanocomposite hydrogel-based bioinks schematically [107].

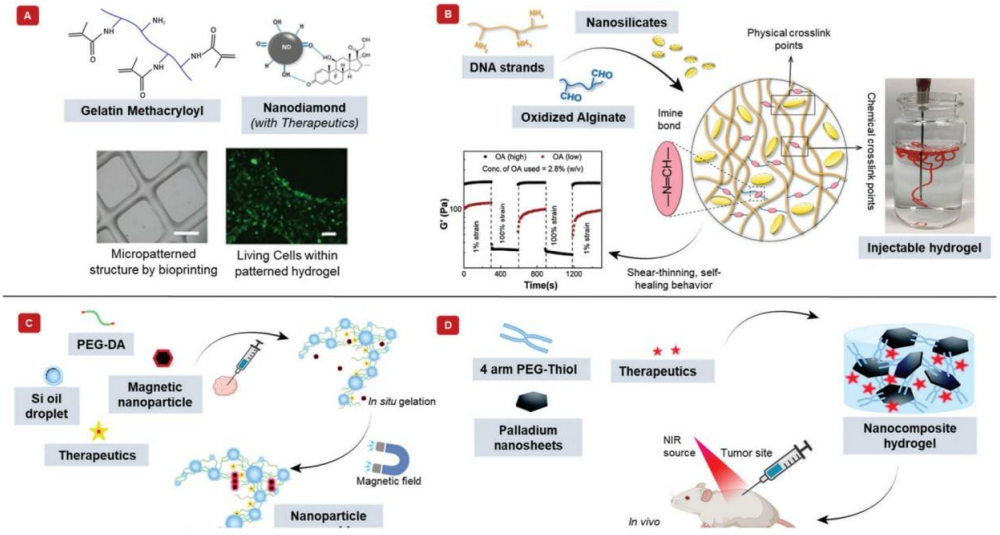

Figure 8. Four applications of nanoparticles in bioinks, A) Carbon nanodiamonds modified with methacryloyl gelatin polymer, B) Hydrogels made with DNA, oxidized alginate, and nano silicate show shear thinning properties, C) The nanoemulsion of silicone oil in water is composed of poly ethylene glycol diacrylate (PEG-DA), zinc ferrite magnetic nanoparticles, and indocyanine green, D) Sheets composed of hydrogels formed by four-armed PEG and its reaction with sulfur in the thiol group to cross-link the polymers [114].

Gao et al. also used a thermal inject 3D printer to produce scaffolds containing mesenchymal stem cells derived from bone marrow using Bioactive ceramic nanoparticles, bioglass, and hydroxyapatite. Finally, it was observed that the presence of bioglass nanoparticles had a higher control over the amount of cell viability and the biological and rheological characteristics of the scaffolds. Besides, this figure indicates that the nanoparticles can perfectly interact with living cells. Moreover, the presence of

hydroxyapatite nanoparticles improved the compressive strength of printed scaffolds [114].

Ferrogels are widely used in hydrogels due to their reaction to magnetic stimuli, and iron oxide is used as a nanoparticle in them. Normally when printing a cross-linked hydrogel, it is difficult to extrude the gel and break through the nozzle. So, post-cross-linking is essential for many hydrogel systems in 3D printing. Cross-linking leads to tunable high strength, better extensibility, improved thermostability, and healable property. Typical ferrogels also require cross-linking. Some studies have suggested that the self-healing properties could overcome this limitation. In one of the investigations [115], a scaffold was made, combining self-healing hydrogels and self-healing ferrogels due to their magnetic properties. This compound does not need post-cross-linking, and its main ingredients are oxidized hyaluronate (OHA), glycol chitosan (GC), and adipic acid dihydrazide (ADH). These ingredients can form a reversible imine bond between aldehyde and amine functional groups. The viscoelastic properties of the OHA/GC/ADH hydrogel were managed by changing the polymer concentration in order to reach the best hydrogel composition as a bioink for 3D printing [116]. So, increasing ADH can change the viscosity of the compound and optimize it to use for printing. The desired scaffold includes two simultaneously printed discs in such a way that the inner disc is made of hydrogel, and the outer one is made of ferrogel. The contact surface of the two discs shows self-healing properties, just like each [115]. As mentioned in the drug delivery section, the combination of OHA and GC shows self-healing properties [81]. With the increase of ADH in both the presence and absence of nanoparticles, this compound can still show its self-healing properties, and after the introduction of strain, it returns to its original state with time [115]. A viability test was also performed to check the viability of ATDC5 cells on the constructed scaffold. After passing one to seven days, the observations show no significant cell death was observed, and cell viability did not decrease after the addition of ferrogel and ADH. As a result, 3D printing can benefit from this combination in many ways [115].

Diba et al considered nanoparticles consist of organic compounds. The biomaterial proposed for 3D printing has shape memory and photo-reactive properties. For example, gelatin is a nanoparticle that can bind colloidally under the name of colloidal-building-block. Also, gelatin nanoparticles are colloidal gel, not hydrogel and they can create non-covalent bonds and can be printed at room temperature [117]. If the methacryloyl group is added to gelatin, it can be cross-linked with ultraviolet (UV) light. So, in addition to the non-covalent bond between nanoparticles, covalent cross-links can also be created using UV light. After creating the cross-link, it is possible to control properties such as swelling, degradation, and biomolecule release behavior in the 3D structure. Furthermore, these colloidal gels can have self-healing properties due to non-covalent bonds between particles. When cross-links are created, this composition becomes stable [117].

To perform the degradability test, before adding methacryloyl to gelatin, gelatin is degraded to 65%

after three days and loses its form. However, after adding methacryloyl, this compound does not degrade for 14 days. Therefore, if an enzyme is used to degrade gelatin that does not have methacryloyl, it will be thoroughly destroyed after three days instead of 65%, and nothing will be left after 14 days. However, when methacryloyl is present, only 25% is destroyed after 14 days, and it can better show its self-healing properties [117].

Zandi et al. offered laponite (LA), silicate nanomaterials, and glycosaminoglycan nanoparticles (GAGNPs)-based hydrogels whose printability and shear-thinning properties make them suitable for bioprinting applications. Different nanocomposite hydrogels (GLgel) formulations were created using various LA concentrations (20, 25, 30, and 35 mg/mL^{-1}) and a fixed GAGNPs/ LA weight ratio (1:120). These samples were named as 20GLgel, 25GLgel, 30GLgel, and 35GLgel, respectively. The cross-links produced by the electrostatic interactions between GAGNPs and LA could lead to the production of gels. In comparison with 20GLgel with a compressive modulus of 0.7 ± 0.1 kPa, the value of this modulus for 25GLgel and 30Glgel increased to 2.4 ± 0.3 and 4.6 ± 0.2 kPa, respectively. However, for 35GLgel, the modulus dropped to 3.1 ± 0.1 kPa. This reduction might result from insufficient GAGNPs and LA interactions at this concentration. The metabolic activity of the NIH 3T3 cells seeded on 30GLgels continued to rise for up to 7 days of culture, demonstrating the GLgels' in vitro cytocompatibility. There were no malignancies, infections, or abscesses at the injection sites during the entire research on any animal. Several unfavorable effects, including inflammation and fibrosis, were observed in the tissues surrounding the gel, but there was no necrosis or muscle degeneration [118].

In the following, some articles in which self-healing samples have been made using a 3D printer are explained briefly and their ingredients are given. Hydrogel is composed of alginate (8 w/v%) and hyaluronic acid (5 w/v%) along with manganese silicate nanospheres (0-2 w/v%) which is suitable for live cells of murine-derived macrophage cell line RAW 264.7 and murine umbilical vein endothelial cells. This hydrogel can be used as a bioink in tissue engineering, especially for vascular applications [119]. Hydrogel is composed of methacrylate-collagen (0.6 w/v%) and alginate (2.5 w/v%) along with CNT (1 w/v%) which is for human coronary artery endothelial cells. This hydrogel can be used as a bioink in tissue engineering for cardiac applications [120]. Hydrogel is composed of alginate 2-3 w/v% with Alpha-tri calcium phosphate 2-6 w/w% for live cells mouse osteoblasts. This hydrogel for bioink in tissue engineering has multiple applications like vascular, muscle multiple, cartilage, and skeletal [121]. Hydrogel is composed of alginate (2 w/v%) and methylcellulose (2-4 w/v%) along with nano hydroxyapatite (2.5×10^{-5} w/v%) which is for living cells of porcine marrow mesenchymal stem cells [111]. A hydrogel is composed of Agarose (0.3–1.0 w/v%)/ collagen (0.1–0.3 w/v%) along with Streptavidin-coated iron nanoparticles (10 v/v%) for living human knee articular chondrocytes. This hydrogel is also used for bioink in tissue engineering for cartilage [122]. Hydrogel is composed of

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Alginate/methyl cellulose (3/9 w/v%) and Nano-silicate clay (3 w/v%) for human mesenchymal stem cells. This hydrogel is also used for bioink in tissue engineering for the skeleton [123]. Hydrogel is composed of collagen (5 w/w%) along with gold nanowires for live mouse myoblasts (C2C12) cells. This hydrogel is also used for biological ink in tissue engineering for muscle [124]. Hydrogel is composed of hyaluronic acid (5 w/v%)/alginate (1 w/v%) along with Ti_3C_2 MXene nanosheets (1 w/v%) for living human embryonic kidney 293 cells. This hydrogel is used for bioink in tissue engineering in neurological or multiple applications [125]. Hydrogel is composed of chitosan (2 w/v%) and alginate (3 w/v%) along with Nano-bone hydroxyapatite (0.2 w/v%) which is for living mouse MC3T3-E1 pre-osteoblast cells. This hydrogel is used for bioink in tissue engineering in bone applications [126]. Some of the discussed articles are summarized in Table 4.

Table 4. Summary of some 3d printed self-healing hydrogels in biomedical applications

Composition of hydrogel matrices	Composition of nanomaterials	Live cells	Application	Reference
Hydrogel is composed of alginate (8 w/v%) - hyaluronic acid (5 w/v%)	Manganese silicate nanospheres (0-2 w/v%)	Murine-derived macrophage cell line RAW 264.7 and murine umbilical vein endothelial cells	Vascular	119
Methacrylate-collagen (0.6 w/v%), alginate (2.5 w/v%)	CNT (1 w/v%)	Human coronary artery endothelial cells	Human coronary artery endothelial cells	120
Alginate (2-3 w/v%)	Alpha-tri calcium phosphate (2-6 w/w%)	Mouse osteoblasts	Multiple	111
Alginate (2 w/v%) - methylcellulose (2-4 w/v%)	Nano hydroxyapatite (2.5×10^{-5} w/v%)	Porcine marrow mesenchymal stem cells	Multiple	121
Agarose (0.3–1.0 w/v%)/ collagen (0.1–0.3 w/v%)	Streptavidin-coated iron nanoparticles (10 v/v%)	Human knee articular chondrocytes	Cartilage	122
Alginate/methyl cellulose (3/9 w/v%)	Nano-silicate clay (3 w/v%)	Human mesenchymal stem cells	Skeletal	123
Collagen (5 w/v%)	Gold nanowires (0.05 w/v%)	Mouse myoblasts (C2C12)	Muscle	124
Hyaluronic acid (5 w/v%)/ alginate (1 w/v%)	Ti_3C_2 MXene nanosheets (1 w/v%)	Human embryonic kidney 293 cells	Neurological, multiple	125
Chitosan (2 w/v%), alginate (3 w/v%)	Nano-bone hydroxyapatite (0.2 w/v%)	Mouse MC3T3-E1 pre-osteoblast cells	Bone	126

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2.6- Other Applications

A biosensor is a receptor-transducer device with integrated functionality that may transform a biological reaction into an electrical signal [127]. A flexible nanoparticle-based sensor array with promising self-healing capability and high sensitivity in monitoring the pressure variation was fabricated by Jin et al [128]. In their research, disulfide cross-linked polyurethane with self-healing properties is considered as the polymer substrate interacting with functionalized gold nanoparticles (GNP) as the sensing film to fabricate the biosensor. Besides, Fast self-healing rate (within 3 hours) and excellent healing efficiency in all areas of the sensor array were obtained with the integration of the self-healable polymer substrate with five types of GNP films containing those functionalized with 3-ethoxythiophenol, tert-dodecanethiol, decanethiol, hexanethiol, and benzyl mercaptan. Except for the benzyl mercaptan-functionalized GNP film, most other GNP films restored 90% of their initial condition in their scratching grooves within an hour. Furthermore, the hexanethiol- and decanethiol-functionalized GNP films seemed entirely recovered after about one hour.

Konwar et al. used iron-coated graphene oxide (GIO) nanoparticles in the chitosan-based hydrogel to reach antimicrobial and higher mechanical properties. Chitosan was cross-linked by electrostatic interaction between the –OH group of glycerol and the NH_3^+ group of chitosan. The hydrogel had self-healing properties due to the chitosan's electrostatic and hydrogen bonding interactions. The mechanical strength was improved after the addition of nano GIO to the chitosan hydrogel matrix system, and the amount of the nanomaterials could be adjusted to achieve the desired mechanical strength. By achieving the mechanical properties of chitosan film, it exhibits a tensile strength (TS) of 17 MPa, a maximum elongation at break of 10%, and a modulus of 0.8 MPa. Following the addition of 0.05% nano GIO, the TS of the hydrogel nanocomposite films increased abruptly to 29 MPa, and their modulus value increased to 2.3 MPa. This enhancement may be attributed to the strong secondary interactions, including hydrogen bonding and polar-polar interactions between various functional groups present in the matrix and the reinforcing nanomaterial phase. In addition, CH-GIO films showed significant antibacterial properties against pathogenic bacteria. Comparing the antibacterial inhibition of the individually generated chitosan iron oxide and chitosan-graphene oxide hydrogel nanocomposite films to that of the chitosan-GIO hydrogel nanocomposite films, the last one exhibited a more significant antibacterial inhibition. This biofilm may have several potential uses in food industries and biomedical applications [129]. Althaqafi et al. created an experimental self-healing composite model composed of SiO_2 nanoparticles with different percentages of triethylene glycol dimethacrylate (TEGDMA) monomer and N,N-dihydroxyethyl-p-toluidine (DHEPT) amine microcapsules. One day after polymerization, the degree of conversion of the composite evaluated around 76%. Hardness

measurements ranged from 22 to 26 VHN; however, the flexural strength was adversely affected from 80 to 55 MPa with increasing microcapsules of up to 10 wt.% in the composites [130]. As described in this section, the use of self-healing polymers is not limited to conventional applications such as tissue engineering or drug delivery, and every day it opens its place in larger parts of the world of biomedical engineering and even other industries such as the food industry.

3- Summary and Perspectives

The ability of hydrogels to self-heal makes them particularly intriguing since they can reestablish original functionalities and restore structural damage in the same way that organism tissues do [131,132]. Also, self-healing hydrogels with shear-thinning capabilities may be employed as bioinks for 3D printing or vehicles for transporting drugs or cells [133]. Many studies have discussed about the advanced functions of hydrogel dressings like adhesion, anti-inflammatory, antimicrobial property, substance delivery, and the recently emerged wound monitoring feature [134]. As a result, interest in self-healing hydrogels as biomedical materials has been developing quickly in recent years. Adhesion-enhanced self-healing multifunctional hydrogels with stimuli-responsive metformin release ability is an example which has shown a developing effect on the healing of chronic athletic diabetic wounds [135]. Even though hydrogels are good at simulating the natural cellular environment, they require reinforcement to improve their mechanical and structural integrity. As described earlier, hydrogels may be reinforced with various nanoparticle kinds and sizes to improve their mechanical properties [136,137]. To create nanocomposites with better characteristics and customized functionality, various nanoparticles, including polymeric, carbon-based, ceramic, and metallic nanomaterials, can be added inside the hydrogel networks [138]. Nano composites could provide enhanced mechanical, antibacterial, antioxidant, anti-inflammatory, stimuli-responsive, and electrically conductive properties of hydrogels [139]. Numerous promising fields, such as biomedical devices, wound healing, medication delivery, magnetic resonance imaging (MRI), and wastewater treatment, can benefit from using magnetic hydrogels as described in different sections of this paper [140-143]. There are two distinct functions associated with MNPs such as iron oxide. First, as a nanofiller that interacts with the polymer backbone and changes its physicochemical characteristics, and second, as a function provider that causes a nanocomposite to be magnetic [144,145]. By adding MNP to the hydrogel matrix, the hydrogels' stiffness and stability were markedly increased, and their injectability was enhanced [146,147]. Bacterial infection is a severe problem that is responsible for an increase in mortality and high healthcare expenses. In this regard, silver and copper-based nanoparticles are often used when making nanocomposite hydrogels due to their antibacterial capabilities to control bacteria that are resistant to antibiotics. Systemic antibiotic administration has been replaced by incorporating antimicrobial

compounds in the bulk material or as surface coatings [148,149]. Also, the self-healable hydrogel should exhibit tissue adhesiveness, flexibility, and well adaption to motion wounds [150]. GIO and CuS are two examples of these kinds of nanoparticles discussed in detail in previous sections of this paper. Wound dressing applications in biomedical, food packaging, environmental, and agriculture industries are the most important fields that use antibacterial nanoparticles [151-153]. Functionalized gold nanoparticle's reaction with hydrogel backbone can add a photothermal response. These different nanocomposite hydrogels are used to create tissue engineering scaffolds, biosensors, bioactuators, drug delivery systems, and more [154-156].

Due to their wide range of applications, self-healing nanocomposites are recently becoming increasingly popular in the next generation of intelligent devices [157]. Although nanoparticles can noticeably improve the properties of hydrogels, they also face limitations that should be resolved in future studies. For example, some have toxic properties and are dangerous for cells, so their biocompatibility should be investigated. Also, determining whether the structure, thickness, size, and even the combination of these nanoparticles will affect improving their performance is one of the other options that can be investigated. Moreover, the approval of federal agencies has not yet been obtained for using nanoparticles in bioinks that are used in 3D printing. This approval by the federal agency is very important because it shows the clinical viability of these bioinks [114].

4- Conclusion

Self-healing materials have gained interest because of their widespread use in various industries, including coatings, water filtration, robotics, and biomedical applications. However, problems such as the hydrogels' strength and durability still need to be handled. Additionally, there is ongoing research into enhancing the self-healing hydrogels' capabilities by adding nanoparticles to the matrix to have adhesion, electro-conductivity, magnetism, and luminescence, making them better candidates for the creation of novel applications, especially in biomedical cases. Copper sulfide, carbon nanotube and iron oxide are examples of nanoparticles which can enhance antibacterial, compression modulus and mechanical properties of the self-healable hydrogel, respectively. The unique properties of the interactions between nanoparticles and polymers result in external stimulus-sensitive, extremely functional, intelligent nanocomposite hydrogels. Solving the limitations of adding nanoparticles should be discussed more in future studies.

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