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Hybrid Hydrogels with Stimuli-Responsive Properties to Electric and Magnetic Fields

Jose Garcia-Torres

Abstract

Hydrogels are a promising type of soft material featuring great similarity to biological tissues due to their inherent characteristics, such as high-water content, flexibility, softness, or low elastic modulus. Imparting multifunctionality to hydrogels to be triggered by external stimuli is considered to have a high potential for innovative application in the biomedical field by regulatory agencies, such as FDA and EMA. Thus, functional hybrid systems based on the combination of nanomaterials and hydrogels are a new class of materials offering new opportunities for living organisms-machine interfacing for application in a wide variety of fields ranging from biomedical engineering to soft robotics, soft electronics, environmental or energy science. The objective of this chapter is to review the latest advances in multifunctional hybrid hydrogels with responsiveness to electric and magnetic fields and with applications in the biomedical field.

Keywords: hydrogels, nanomaterials, hybrid composites, stimuli-responsive, electric and magnetic field

1. Introduction

Human body is a complex system where multiple processes and reactions take place simultaneously to give an efficient system. A lot of functions in the body are regulated by chemical substances (e.g., proteins) but also by physical (e.g., electric fields, temperature, light, etc.) and mechanical stimuli, such as neuronal communication, embryo development, tissue repair after an injury, or heartbeat [1–3]. Scientists and engineers have been inspired by the natural world in general, but in the human body in particular, to develop materials with new functionalities and unique skills [4, 5]. Recently, hydrogels have been revealed as a promising new class of materials due to their intrinsic properties, such as high-water contents, high porosity, flexibility, or biocompatibility, showing great similarities to biological systems as a result of the 3D porous polymeric structure [6, 7]. Hydrogel flexibility and elasticity are important to diminish the mechanical mismatch with living systems; meanwhile, the high-water contents provide a humid environment rich in ions, such as biological media. Hydrogels also show some other interesting properties, such as self-healing

and self-adhesive capacity, biocompatibility, and biodegradability [8, 9]. For all those reasons, hydrogels have been suitable for different biomedical applications, such as wound healing [10], passive drug delivery [11], or contact lenses [12]. However, one of the main drawbacks of hydrogels is the lack of bioactivity.

To overcome hydrogel's inertness, hydrogels can be successfully modified with nanomaterials (e.g., metallic nanoparticles and carbon nanomaterials) to develop smart nanocomposite hydrogels with improved functionality [13–15]. Thus, nanomaterials can improve the mechanical properties of the nanocomposite hydrogels (e.g., stiffness, toughness, and ductility) but also confer physical properties (e.g., electrical conductivity, magnetism, thermal properties, etc.) to be able to respond to different stimuli, such as electric and magnetic fields, temperature, pH, light or biomolecules, among others. Hydrogel's response is based on phase changes, change in stiffness, or change in volume in response to those stimuli [16]. These nanocomposite hydrogels, named as smart, intelligent, or stimuli-responsive, are being applied in a wide range of applications including bioelectronic devices (e.g., biosensors) [17, 18], energy and environmental science [19, 20], soft robotics [21, 22], or regenerative medicine [23, 24], with promising advances in all those fields. Moreover, these stimuli-responsive hydrogels show the capacity to respond in a reversible and controllable way to different stimuli but also to adapt and conform onto curvilinear and dynamic surfaces improving their performance [25].

Due to the different length scales and physicochemical properties of the two main components of the stimuli-responsive composites—hydrogels, nanomaterials—, hybrid hydrogels with variable and tunable designs are being possible. Hydrogels have similar mechanical properties to biological tissues and they also mimic several features of the extracellular matrix. They also have compliant and permeable structures that can be modified to suit the requirements to create not just a physical but also a chemically favorable environment [6, 7]. To obtain the characteristic three-dimensional hydrogel networks, with the abovementioned innate properties making them very interesting in comparison to other polymer groups, it is required to transform the liquid viscous precursor solution to the final gelled material by inducing crosslinking. The liquid-gel transition can be achieved either via physical (e.g., ionic crosslinking) or chemical (e.g., photo-crosslinking), leading to the formation of non-covalent and covalent hydrogels, respectively. Moreover, hydrogels can be classified as natural and synthetic depending on the source used to fabricate them [26]. Natural polymers have high interest due to their inherent biocompatibility, low toxicity, and biodegradability. There are two main types, polysaccharides and fibrous proteins that are both components of the extracellular matrix, such as alginate (Alg), chitosan (CS), or collagen (Col), among others. Synthetic polymers, such as poly(ethylene glycol) (PEG), poly-(N-isopropylacrylamide) (PNIPAAm), poly(vinyl alcohol) (PVA), or poly(hydroxyethyl methacrylate) (PHEMA), have controllable and good mechanical properties but they lack bioactivity to promote cell-material interaction, the reason why they are required to be modified. On the other hand, the nanometric size of nanomaterials (<100 nm at least in one dimension) confers them higher specific surface areas compared to their bulk counterparts and very unique physical properties as they are size-dependent, such as the electronic, magnetic, and optical properties, due to the quantum size effect [27]. Nanomaterials are very versatile since they can be synthesized using different materials (e.g., metals and metal oxides, carbons, polymers, etc.), sizes (e.g., 0–100 nm), and shapes (e.g., nanoparticles, nanowires, nanotubes, 2D layers, etc.) and can be modified by combining different materials (e.g., core-shell structures)

or functionalized with biomolecules (e.g., peptides, enzymes) [28]. However, some requirements are needed for their application in the biomedical field, such as biocompatibility, non-cytotoxicity, and stability in biological media [29].

Stimuli-responsive hydrogels are able to respond to different stimuli that can be classified as endogenous—pH, enzymes, antigen—or exogenous—light, electric field, magnetic field—depending on if they are present at the implantation site or not, respectively. However, the most common form of classification is as chemical or physical stimuli if the changes in the hydrogels are induced by chemical entities (e.g., molecules and biomolecules) or physical variables (e.g., temperature, light, electricity, etc.). Chemical stimuli include molecules and biomolecules present in the environment where the hydrogel will be located. For example, reactive oxygen species (ROS) are generated in wounds, bacterial infections, or tumors creating a more oxidation environment. Or pH values are lower in cancerous cells than in normal cells due to abnormal metabolism. Thus, chemically responsive hydrogels must be designed to respond to changes in those (bio)molecules that sometimes are very low, making the development more difficult. Meanwhile, physical stimuli include magnetic and electric fields, temperature, light, or ultrasounds. Among them, electrically- and magnetic-responsive hydrogels have been widely researched as they have the advantage to be remotely and non-invasively operated even in narrow and small areas. Moreover, the use of adjustable electric (e.g., voltage) or magnetic (e.g., field intensity) signals as stimulation sources make them even more interesting to develop hydrogels with reversibility and controllability compared with, for example, pH or temperature-responsive hydrogels. Thus, stimuli-responsive scaffolds capable of responding to either electric or magnetic fields have emerged as a promising technology for biomedical applications, including drug delivery systems, tissue regeneration, or soft actuation. For this reason, in this chapter, the author will focus on electrically- and magnetic-responsive hydrogels.

2. Electrically-responsive hydrogels

Electroresponsive hydrogels have been the most studied among the physically stimuli-responsive hydrogels due to their broad applicability in many fields, such as bioelectronics (e.g., sensors), bioengineering (e.g., drug delivery systems and actuators), tissue engineering (e.g., bone regeneration), or soft robotics applications. They are able to undergo changes in their shape and size when swell/deswell under the application of an electric field. Very briefly, the deformation generated by the electric field can be explained by a combination of Coulombic, electrophoretic, and electroosmotic interactions. As a result of the migration of mobile ions from the electrolyte under the applied field, the generated osmotic pressure increases or decreases causing hydrogel swelling or deswelling, respectively [30, 31]. Electrical conductivity has been conferred to the hydrogel mainly following two approaches—(i) The incorporation of conductive nanofillers, and (ii) the preparation of intrinsic conductive hydrogel networks. Multiple electroconductive fillers have been tested, such as metallic nanomaterials (e.g., nanoparticles (NP), nanorods (NR), and nanowires (NW)), made of noble metals, such as Au, Ag or Pt, carbon nanomaterials (e.g., carbon nanotubes (CNT) and graphene) or conducting polymers (CP) (e.g., polypyrrole (PPy), polyaniline (PANI), poly(3,4-ethylenedioxythiophene) (PEDOT)) [32, 33]. Any of those materials can confer, apart from electrical conductivity, many other properties to develop multifunctional hydrogels. More recently, preparing inherently

conductive hydrogels using pure CP or blends with other synthetic/natural polymers has been outstanding [34, 35].

Regarding the first strategy, electrically conductive nanomaterials have been successfully employed to develop electrically-responsive hydrogels. Different hydrogel matrices either natural, Alg, CS, and Col, or synthetic, PVA, PEG, and PNIPAAm, have been used to incorporate the conductive fillers [32, 33]. These conductive nanomaterials that are nanometer-sized particles show different properties (e.g., electrical, optical, etc.) depending on the size, shape, and type of material that make them very useful to tailor hydrogel properties. Among the conductive fillers, metal nanomaterials in general, but Au and Ag in particular, have been by far the most employed. Gold shows excellent electrical, optical, and catalytic properties together with biocompatibility, ease of functionalization, and resistance to oxidation; meanwhile, silver has a unique electrical, optical, chemical, and antibacterial properties to develop multifunctional hydrogels. On the other hand, carbon nanomaterials, especially CNT and graphene, are also excellent conductive materials to incorporate into non-conductive hydrogels. Properties, such as high electrical conductivity, high strength, high specific surface area, or low density, have conferred them very interesting applicability within the biomedical field.

Regarding the second strategy, CP have been essential in the development of intrinsic conductive hydrogels. CP are conjugated polymer materials showing electronic conductivity due to the free motion of the delocalized π -electrons throughout the double bonds and aromatic rings present in the polymeric chain originating electrical pathways for charge carriers' motion. The π -orbitals of these conjugated systems are overlapped along the chain that allows the delocalization of the electrons throughout the macromolecule's backbone [36]. The most employed CP for conductive hydrogels has been PANI, PPy, and PEDOT due to properties, such as high conductivity, high stability, biocompatibility, or water dispersibility [37]. However, their main drawback is their fragility and low mechanical strength. For this reason, CP have been mixed with other non-conductive natural and/or synthetic polymers to form interpenetrated (IPN) or semi-interpenetrated hydrogels (s-IPN) to improve the mechanical properties [38]. The addition of electrically conductive nanomaterials into the blended hydrogels has also been done to overcome the decrease in electrical conductivity attributed to the presence of the non-conductive polymer.

Researchers have employed different methodologies to develop electrically conductive hydrogels—(i) blending, (ii) in situ formation, and (iii) covalent bonding (**Figure 1**). Blending has been one of the most used approaches to develop such hybrid hydrogels due to its simplicity and the wide range of nanomaterials that can be incorporated into the hydrogel. This method consists of mixing the hydrogel precursors with the colloidal NP suspension followed by crosslinking to entrap the NP within the hydrogel network. For example, Baei and collaborators fabricated a AuNP-chitosan (AuNP-CS) hydrogel for cardiac tissue engineering. Gold NP with a diameter of 7 nm were embedded in the hydrogel precursor solution by chemically reducing the tetrachloroauric acid (HAuCl_4) with sodium citrate followed by chitosan crosslinking with β -glycerophosphate. The presence of the NP slightly increases the compressive modulus from 6.1 kPa for the bare chitosan to 6.9 kPa for the AuNP-CS hydrogel. Moreover, they observed that the presence of the NP conferred electrical conductivity to CS in a value close to the native myocardium (0.13 S/m). The sole presence of the NP allowed detecting an increase in the cardiac differentiation-related markers (e.g., Nkx-2.5 and α -MHC) of the mesenchymal stem cells (MSC) seeded on the scaffold [43]. Navaei et al. successfully incorporated Au NRs into gelatine-methacrylate solution that after

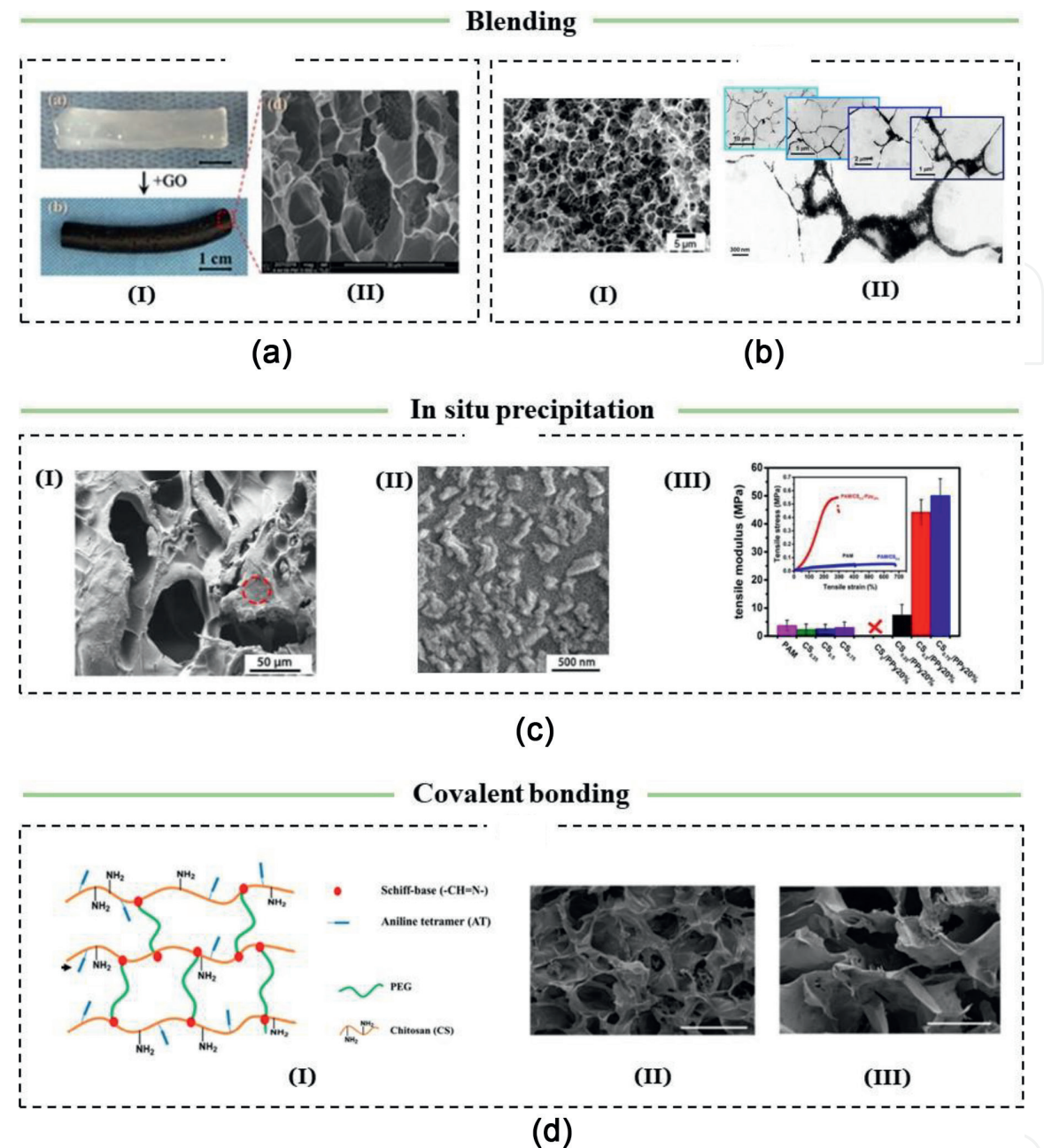


Figure 1.
(a) (I) Photograph of PVA/PEG hydrogel (top) and PVA/PEG/GO (bottom). (II) SEM image of the PVA/PEG/GO hydrogel cross-section. Reproduced with permission from Ref. [39]. (b) (I) SEM image of the PEDOT/Alg hydrogel cross-section. (II) Transmission electron microscopy (TEM) micrographs with different magnifications (from low at the left to high at the right and bottom) of a stained PEDOT/Alg hydrogel. Adapted with permission from Ref. [40]. Copyright (2020) American Chemical Society. (c) (I) SEM image of the PPy/PAM/CS hydrogel and (II) magnified SEM image showing the PPy NR embedded in the hydrogel. (III) Variation of the tensile modulus of PPy/PAM/CS hydrogels with various contents of CS. Adapted with permission from Ref. [41]. Copyright (2018) American Chemical Society. (d) (I) Scheme of the hydrogel showing the covalent crosslinking between the CS and PEG. SEM images of hydrogels (II) before and (III) after swelling. Scale bar: 300 μm . Adapted with permission from Ref. [42]. Copyright (2016) American Chemical Society.

UV-crosslinking led to hydrogels with improved properties for cardiac regeneration. The incorporation of Au NRs (16 ± 2 nm width and 53 ± 4 nm length) led to an increase in the mechanical and electrical properties compared to the pure hydrogel. This hydrogel induced excellent cell retention and proliferation resulting in the formation of cardiac tissue layers with beating behavior [44]. Carbon nanomaterials—CNT, graphene oxide (GO)—have also been widely explored in electrically conductive hybrid

hydrogels. Xiao and collaborators prepared a PVA/PEG/GO hybrid hydrogel with high electrical conductivity and mechanical strength (**Figure 1A**). First, PVA and PEG were dissolved in water at 90°C and cooled to room temperature. After that, GO was dispersed in water, subsequently added to the PVA-PEG solution and mixed until obtaining a homogeneous distribution of GO. Finally, the crosslinking was obtained by the cyclic freezing-thawing method [39]. The blending method has also been employed to develop hybrid hydrogels between CP and insulating polymers either natural or synthetic to confer mechanical properties to the blended hydrogel. It is important to highlight that the electrical performance is normally directly proportional to the content of CP. For example, A. Puiggalí-Jou et al. fabricated an electrochemically active blended hydrogel between PEDOT and alginate biopolymer by an easy one-step process. After thoroughly mixing an aqueous PEDOT:PSS (poly(styrene sulfonate)) dispersion with a fixed amount of an Alg solution, the mixture was placed in a mold and immersed in a CaCl₂ solution to crosslink Alg. As observed by the authors, both polymers showed high porosity and they were organized as segregated PEDOT- and Alg-rich regions (**Figure 1B**). The incorporation of curcumin as a model hydrophobic drug allowed demonstrating that the application of a negative potential allowed controlling its release [40]. Gan et al. prepared an IPN based on CS and polyacrylamide (PAM) by UV photopolymerization [41]. First, CS was dissolved in deionized water followed by the addition of given amounts of the monomer (acrylamide (AM)), the crosslinking agent (e.g., N,N'-methylene bisacrylamide) (MBAM), and the initiator (e.g., ammonium persulfate (APS)). The mixture was crosslinked under UV irradiation for 5 min. The resultant hydrogel also showed high porosity to allow its further modification with PPy NWs. Generally, two main drawbacks have been found with the blending methodology—(i) aggregation of the conductive nanomaterials or phase separation between insulating and CP leading to heterogeneous properties across the hydrogel limiting its electrical conductivity and weakening its mechanical strength and (ii) weak nanomaterial-polymer or CP-insulating polymer interaction hindering the full exploitation of nanomaterials or CP. Therefore, the surfactants, polymer-stabilized dispersions, or functionalized nanomaterials are required to properly disperse, and therefore, process them into homogeneous hybrid hydrogels hindering, in most cases, their electrical properties [45].

An alternative methodology to synthesize the conductive hybrid hydrogels avoiding aggregation is the in situ formation of the conductive material within the hydrogel to improve their interaction and therefore integration. Although this approach is dependent on the type of conductive material, generally is based on homogeneously mixing both the conductive (nano)material and the hydrogel precursors followed by the formation of the (nano)materials and crosslinking of the hydrogel. More specifically, metallic nanomaterials can be incorporated by in situ process by mixing the metal ions with the hydrogel precursors. One important point is achieving a homogeneous dispersion of ions before the metallic NPs are grown in the hydrogel. For example, Dolya and colleagues have reported the in situ formation of Au NP within PAM hydrogels following a one-step process. This step consisted of dissolving AM, MBAAM, and APS involved in the hydrogel formation together with HAuCl₄, poly(ethyleneimine) (PEI), and the ionic liquid (IL) ethyl-3-methylimidazolium ethylsulfate as a gold precursor, reducing and stabilizing agent, respectively. The formation of the hydrogel and Au NP took place simultaneously by heating the solution at 80°C for 30 min. Results show that hydrogels have high porosity and Au NP are better dispersed and stabilized within the hydrogel when PEI and IL form a shell around the NP preventing their aggregation. While the lack of aggregation was

observed by UV-Vis spectroscopy, better immobilization was detected through kinetic studies of the release of unbound charged compounds [46]. Au NP have been successfully synthesized within many natural (e.g., pectin and κ -carrageenan) and synthetic (e.g., poly(N-vinylpyrrolidone) (PVP), PEG, etc.) hydrogels following the in situ method [47]. Incorporation of CP inside a hydrogel can also be achieved by in situ polymerization. First, CP monomers are incorporated either with hydrogel precursors or after crosslinking by immersing it into the monomer solution and followed by introducing the oxidative reagents (e.g., APS, ferric ions, etc.) to initiate the polymerization. Thus, Gan et al. incorporated PPy NW inside a PAM/CS hydrogel by first immersing the template hydrogel into a pyrrole (Py) solution and second adding the ferric chloride as oxidation agent. The PPy NW, clearly observed by scanning electron microscopy (SEM), enhanced the mechanical properties of the PAM/CS hydrogel (**Figure 1C**) [41]. Or Hur and coworkers reported the fabrication of an interpenetrated network of agarose and PPy by pyrrole polymerization within the agarose gel. First, the authors mixed an agarose aqueous solution with CuCl_2 as an oxidizing agent at 40°C. After that, they added a pyrrole monomer to initiate polymerization within the solution. The temperature was decreased down to room temperature to induce agarose gelation, while PPy formation still took place. The addition of the monomer helped to get a homogeneous distribution between agarose and PPy. They developed an electrically conductive hydrogel with self-healing and stretchability [48]. Wu et al. showed the preparation of a conductive hydrogel composed of gelatin methacrylate (GelMA) and PANI. First, GelMA was prepared by UV photopolymerization using irgacure 2959 as initiator. After that, the hydrogel was immersed first in an HCl and APS solution for 4 h followed by immersion in a hexane solution containing the aniline monomer for another 4 h for the polymerization to take place. No significant differences in terms of mechanical properties, swelling, and cell adhesion were observed between the bare GelMA and the GelMA/PANI hydrogel except for an increase in the electrical conductivity of the latter [49]. In situ polymerization can also be achieved by electropolymerization in which an electrical potential or current plays the role of an oxidative reagent inducing polymerization within the template hydrogel [50].

Finally, another strategy to improve even more the interaction between the hybrid hydrogel components (e.g., nanomaterials and polymers), which is normally weak if the previous strategies are used, is through covalent bonding. Here, a covalent bond is formed between the different materials to, for example, stabilize the NP inside the hydrogel but also to boost the chemical and biological properties of the hybrid hydrogel. Skardal et al. synthesize hyaluronic acid (HA), gelatin, and Au NP hydrogels using non-functionalized and thiol-functionalized NP. What they observed is a significant increase in the hydrogel stiffness when the functionalized NP were used, which they attributed to the covalent bond formed with the hydrogel matrix [51]. This methodology has also been explored with carbon nanomaterials. For example, poly(acrylic acid) (PAA) has been grafted onto CNT surface for the promotion of neuron differentiation. First, the authors treated CNT with 4 M nitric acid by reflux to increase surface hydrophilicity. After that, those CNT were dispersed by sonication for 30 min in an acrylic acid-acetone solution followed by the addition of 2'-azobisisobutyronitrile (AIBN) to obtain the PAA. They successfully induced selective differentiation of MSC into neurons [52]. Dong et al. created a covalent bond between a chitosan-graft-aniline tetramer (CS/AT) and a dibenzaldehyde-terminated poly(ethylene glycol) (PEG/DA) to obtain a covalent IPN that they used as drug delivery for cardiac regeneration (**Figure 1D**) [42].

2.1 Biomedical applications

One of the main applications of hybrid hydrogels with electrical conductivity is in the tissue engineering field where hydrogels aim to restore the electrical/electrochemical intercommunication between cells and tissues. These hybrid hydrogel scaffolds have been developing for many tissues especially electroactive ones, such as cardiac, nerve, skeletal muscle, bone, or cartilage. Baei et al. developed a Au NP/CS hydrogel for cardiac tissue engineering. The authors seeded MSC onto the hydrogels, and although they did not observe any significant difference in cell density, morphology, and distribution between bare chitosan and Au NP/CS hydrogels they did observe higher levels of cardiac markers, such as alpha myosin heavy chain (α -MHC) and homeobox protein Nkx-2.5, indicating that the presence of Au NPs electrically stimulating the differentiation of MSC into cardiac cells (**Figure 2A**) [43]. Gan et al. also developed an electrically conductive hydrogel based on PAM, CS, and different amounts of PPy NR as previously explained for skin regeneration. After seeding the scaffolds with muscle myoblasts, the authors analyzed their morphology, adhesion, and proliferation under different electrostimulation voltages (0–900 mV). They found out that not only the incorporation of PPy NR had a clear effect on proliferation and elongation (e.g., 20 v/v% PPy NR led to the highest cell aspect ratio) but also the application of an electric voltage promoted cell activity and elongation (e.g., 300 mV showed the highest elongation) (**Figure 2A**) [41].

Drug delivery has also been widely studied due to the possibility to control the release of the drug out of the conductive hydrogels by the application of different electrical signals (e.g, voltage). A. Puiggali-Jou et al. fabricated Alg/PEDOT hydrogels incorporating curcumin (CUR) as a hydrophobic model drug during the hydrogel fabrication process. Interestingly, the authors showed a different release profile depending on the applied voltage (0, +1 V, –1 V). Thus, they observed a higher release when –1 V was applied during 2 h to the hydrogel (e.g., ~25%) compared to the 0 V (e.g., ~3%) or +1 V (e.g., ~8%), indicating a controlled release of curcumin (**Figure 2B**) [40]. Cho et al. also developed a collagen-CNT hydrogel containing a nerve growth factor (NGF). First, a solution containing the collagen and the NGF was prepared followed by mixing with a COOH-functionalized CNT suspension. Then, the mixture was poured into a mold and heated to induce crosslinking. The hydrogels were electrically stimulated immersing them in PBS solution at 37°C and by applying a voltage of 0.5 V for 2 h per day. The application of the voltage led to an increase in the NGF release during the same period of time. Thus, the 5% collagen hydrogel led to a 10-fold increase compared to the non-stimulated one. Moreover, collagen content in the hydrogel had an effect on the drug release observing a higher release in the order 5% > 1% > 0.5% > 20% collagen. The authors attributed the lower release of the 20% collagen hydrogel to the presence of electrical insulating regions limiting the electrical stimulation [54].

Although less studied, these electrically-responsive hydrogels have been also applied for wound healing or as actuators. For example, the hydrogel PAM/CS/PPy was observed to induce skin reparation in *in vivo* experiments with rats. The authors observed that the wound closed with new epithelial tissue and hair in lesser days than with PAM/CS hydrogels. The good results were attributed to the electroactivity of PPy promoting the electrical communication between cells that at the end controls tissue growth (**Figure 2C**) [41]. On the other hand, Yang et al. developed electrically active hydrogels by incorporating GO into a poly(2-acrylamido-2-methylpropanesulfonic acid-co-acrylamide) (AMPS-co-AM) hydrogel to be used as actuator under an

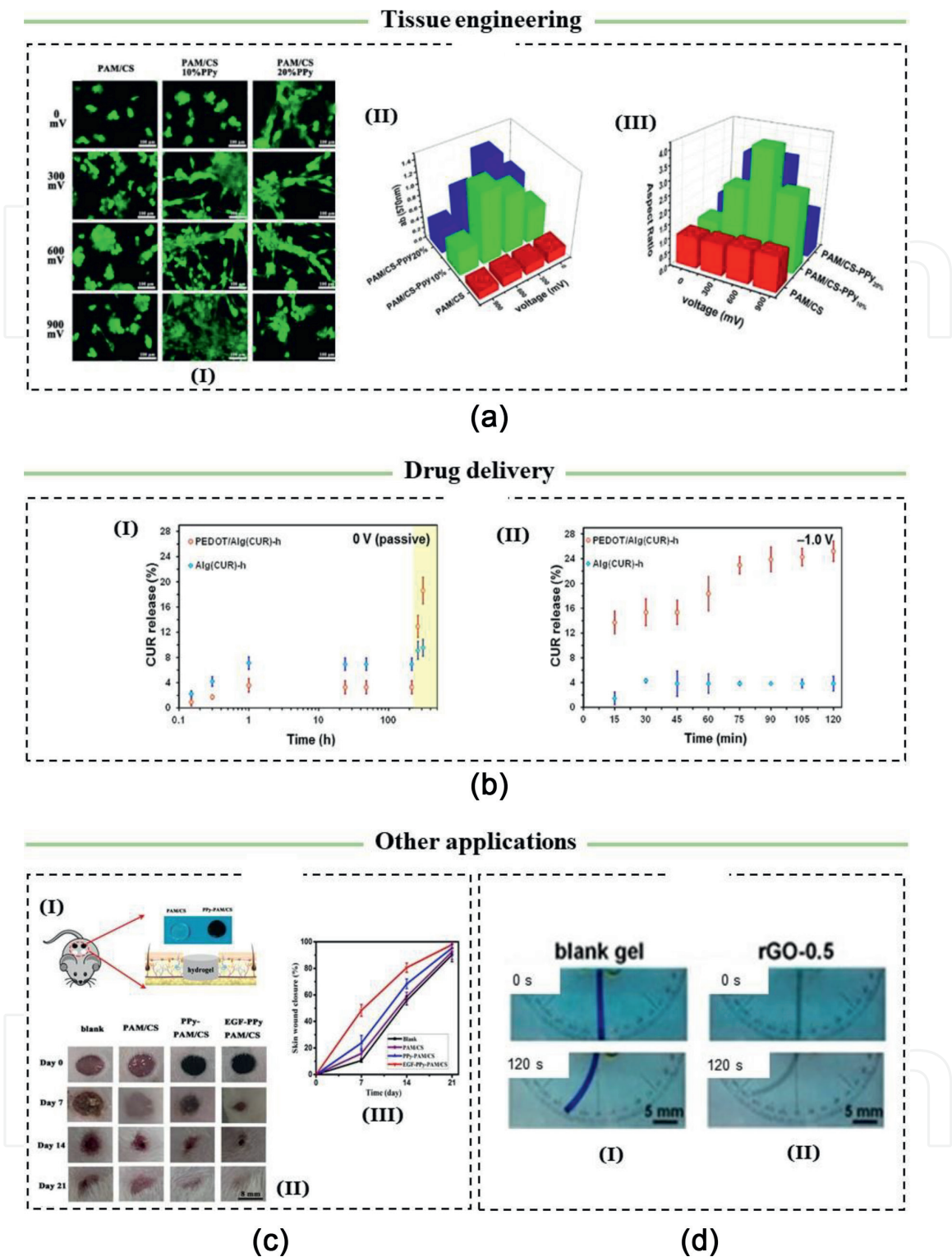


Figure 2.
(a) (I) Fluorescence micrographs of C2C12 cells seeded on PPy/PAM/CS hydrogels and electrostimulated at different electric potentials. (II) Proliferation of cells evaluated by MTT analysis and (III) cell aspect ratio as a function of hydrogel composition and applied voltage. Adapted with permission from Ref. [41]. Copyright (2018) American Chemical Society. (b) Release profile of curcumin from Alg/PEDOT/CUR and Alg/CUR hydrogels by (I) passive diffusion (0 V) and (II) by applying a voltage of -1 V. Adapted with permission from Ref. [40]. Copyright (2020) American Chemical Society. (c) (I) Scheme showing the implantation of hydrogels onto skin defects on rats. (II) Photos of the defects treated with PAM/CS, PAM/CS/PPy, and PAM/CS/PPy loaded with EGF at different time periods. (III) Graph showing the wound closure percentage. Adapted with permission from Ref. [41]. Copyright (2018) American Chemical Society. (d) (I) Optical photographs of the electro-responsive bending behaviors of (I) poly(AMPS-co-AAm) (blank) and (II) rGO/poly(AMPS-co-AAm) hydrogels. Adapted with permission from Ref. [53]. Copyright (2017) American Chemical Society.

electric field. The preparation of the composite hydrogel, which was performed in a two-step process, allowed a good dispersion of the GO leading to a hybrid hydrogel with improved electrical and mechanical properties. An electric field originated the deformation (e.g., bending) of the hydrogel that was reversible and repeatable when a cyclic electric field was applied showing great potential as a remotely controlled electro-responsive actuator (**Figure 2D**). The authors explained the actuation based on the different osmotic pressure between hydrogel's inside and outside as a consequence of ionic flux created during the application of the electric field [53].

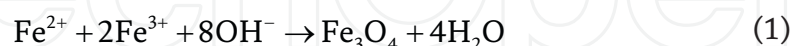
3. Magnetic-responsive hydrogels

Hydrogels with magnetic responsiveness have also recently received great attention to developing the next generation of stimuli-responsive hydrogels that possess unique functional structures with controllability, actuation, and spatiotemporal response properties controlled by an external magnetic field. Such magneto-responsive hydrogels have also been used in a multitude of applications in the biomedical field, such as enhancement of cell growth and differentiation for tissue regeneration, drug delivery controlled by magnetic fields, magnetic hyperthermia for the treatment of cancer or magnetic actuators [55]. Magnetic nanomaterials are composed of magnetic elements (e.g., Fe, Co, and Ni) and their oxides (e.g., Fe_3O_4 , Fe_2O_3 , and CoFe_2O_4) [56], and although widely investigated in terms of their physical, structural, and magnetic properties, little is still known about their full potential impact on the biomedical field. Among those nanomaterials, magnetite (Fe_3O_4) has become the most used for medical applications not only because of its biocompatibility and non-cytotoxicity but also for its tunable magnetic properties [55]. Thus, the size of the NP has an effect on the induced magnetic moment and the magnetic properties (e.g., ferromagnetic, superparamagnetic, etc.), which in turn can be used to control their orientation and accumulation, or aggregation, within the hydrogel. For example, NP aggregation affects the biological fate of the magnetic NP that prevents their internalization into the cells and therefore their further excretion, increasing their cytotoxicity. Therefore, it is essential to control the chemical (e.g., composition) and physical (e.g., size, shape, etc.) characteristics of magnetite NP since they impact the former properties. For more details, see reference [55].

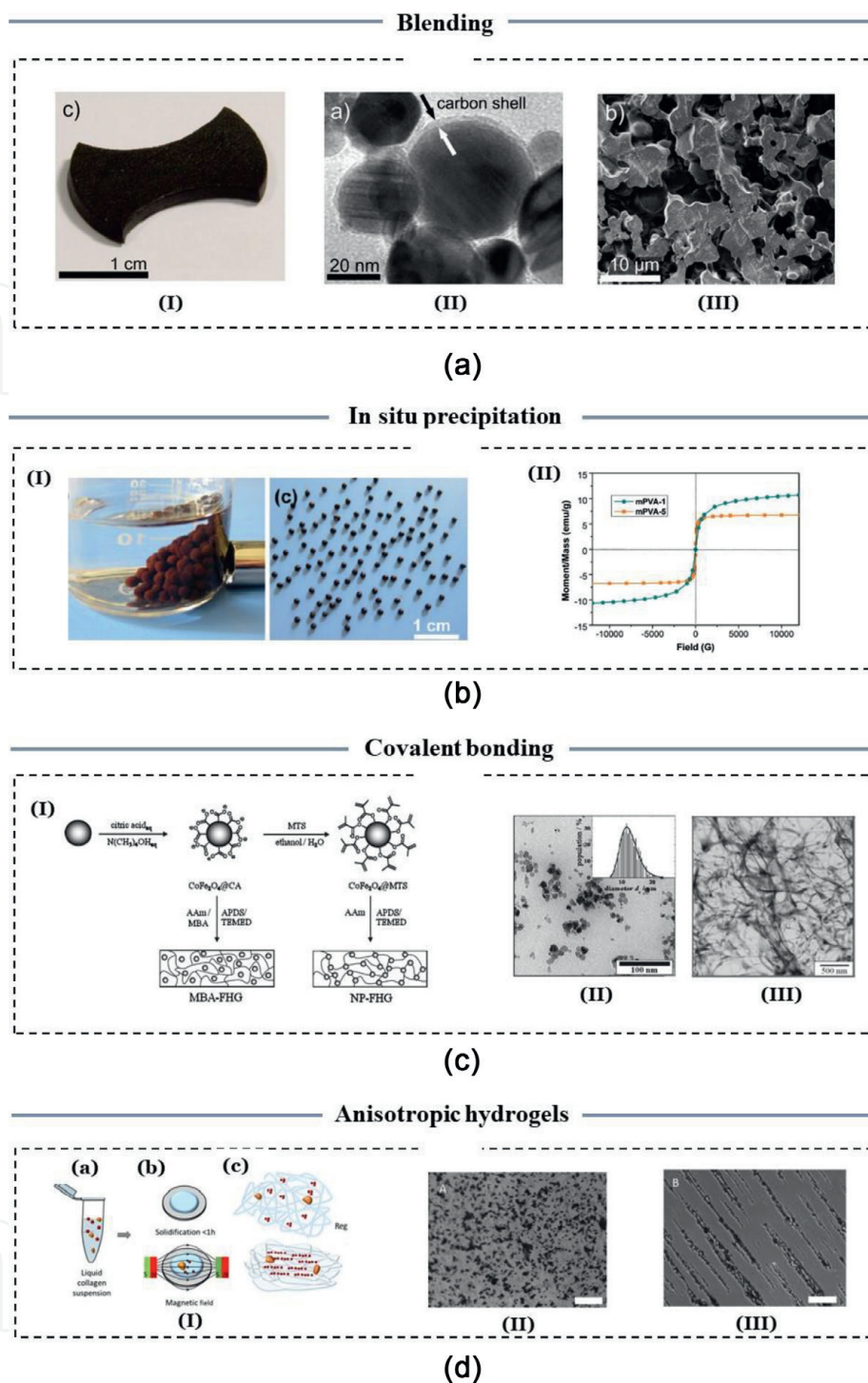
As with the electrically conductive hydrogels, magnetic nanocomposite hydrogels can also be fabricated by following the same strategies—(i) blending, (ii) in situ precipitation, and (iii) covalent bonding. Again, blending methodology has been widely employed for its simplicity since the polymer and the magnetic nanomaterials are physically mixed followed by the polymer chains crosslinking to get the hydrogel network. Sapir et al. successfully developed a magneto-responsive hydrogel by properly dispersing magnetite NP by sonication in an Alg solution and followed by crosslinking with Ca^{2+} ions. The magnetic NP, ranging from 5 to 20 nm, did not seem to have any significant effect on the physicochemical properties of the hydrogel, such as porosity, stability, and wetting, as the NP were perfectly embedded within the polymer network but the mechanical and magnetic properties were improved. However, some NP aggregation was observed [57]. Fuhrer and coworkers developed a more complex magnetic hydrogel formed by the incorporation of 4-vinylbiphenyl functionalized carbon-cobalt core-shell NP into an aqueous solution containing 2-hydroxy-ethyl-methacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), and styrene-maleic anhydride (SMA). A rheology additive (tetramethyl

ethylenediamine) and a crosslinker (APS) were added and the reaction took place in a casting mold for 1 h at room temperature (**Figure 3A**). Although the magnetic properties of the nanomagnets were not reported, the authors did observe an influence of an external magnetic field on cell differentiation [58].

In situ precipitation was employed as a method to avoid NP aggregation since first a mixture of the metal salts (e.g., FeCl_2 and FeCl_3), precursors of Fe_3O_4 , were better mixed within the polymeric solution before cross-linking. After that, formation of magnetite was achieved by precipitating the Fe^{2+} and Fe^{3+} ions with NaOH following the reaction:



Albertsson et al. fabricated a hemicellulose magnetic hydrogel by a one-step method. First, O-acetyl-galactoglucomannan and epichlorohydrin (crosslinking agent) were dissolved in NaOH followed by the addition of an aqueous solution of the metal salts ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, FeCl_2 ($\text{Fe}^{3+}:\text{Fe}^{2+}$ molar ratio = 2:1)). Different concentrations were added to incorporate variable amounts of magnetite (5, 10, and 15%). The crosslinking reaction and the magnetite formation simultaneously took place at 60°C for 20 min. The resultant hydrogel contained Fe_3O_4 NP with an average size of 5.8 nm conferring a superparamagnetic behavior to the hydrogel. Moreover, it was observed that the higher the Fe_3O_4 content, the higher the magnetization of the hydrogel. The presence of the magnetic NP also improved the mechanical properties but a decreased swelling ratio, thermal stability, and pore size was observed as magnetite content increased [62]. Another example by Miyazaki et al. was the in situ incorporation of Fe_3O_4 NP within chitosan hydrogels with different crosslinking degrees achieved changing molar ratios of the crosslinker (glutaraldehyde) from 0.5 to 30 with respect to the amino groups in chitosan. The authors immersed the hydrogels with different crosslinking densities in a 0.1 M FeCl_2 solution for 6 h at room temperature to allow hydrogel swelling and Fe^{2+} diffusion into it. After that, hydrogels were dipped into 0.5 M NaOH solution at 60° to precipitate the magnetic NP. An influence of the hydrogel network structure on magnetite growth was observed. On one hand, the amount of Fe_3O_4 generated in the hydrogel decreased as the crosslinking density increased, which they attributed to the lower swelling meaning that the Fe^{2+} intake was impeded. On the other hand, larger crystallite sizes were obtained as the crosslinking degree was increased. The authors did not show the magnetic properties of the hydrogels but they did analyze the influence of an alternating magnetic field in heat generation for hyperthermia applications. The heat generation was enhanced in hydrogels with higher crosslinking due to the larger crystallite and particle sizes and despite the lower amount of magnetite [63]. Zhou et al. also fabricated hydrogels based on PVA or PVA/PNIPAAm and containing Fe_3O_4 NP as the magnetic material. The one-step process consisted of mixing a PVA or PVA/PNIPAAm solution with the $\text{Fe}^{2+}/\text{Fe}^{3+}$ ions followed by dropwise addition into an alkaline NH_3 solution to obtain the magnetite NP and crosslink the PVA chains in the form of beads (**Figure 3B**). PVA played different roles, the stabilizer to avoid magnetite aggregation and the matrix to support the NP. On the other hand, the Fe_3O_4 NP interacted with the hydroxyl groups of PVA via hydrogen bonds favoring also gelation. Although the authors did not provide the size of the magnetite NP, they did report their superparamagnetic behavior indicating a nanometric size. They finally incorporated congo red inside the magnetic scaffold to be used as a drug delivery system. They found out a different profile release with and without an applied magnetic field [59].

**Figure 3.**

(a) (I) Photo of the magnetic hydrogel with a dog-bone shape. (II) TEM image of the carbon-coated metal nanomagnets. (III) TEM image of the nanomaterials incorporated into the hydrogel. Reproduced with permission from Ref. [58]. (b) (I) Images of magnetic PVA hydrogels in the form of beads. (II) Magnetization-magnetic field curves for the hydrogels with different magnetic contents at 300 K. Adapted with permission from Ref. [59]. Copyright (2012) American Chemical Society. (c) (I) Scheme showing the synthesis of CoFe_2O_4 NP coated with citric acid (CA) ($\text{CoFe}_2\text{O}_4\text{@CA}$) and 3-methacryloxypropyltrimethoxysilane (MTS) and the corresponding hydrogels MBA-FHG and NP-FHG. TEM images of the (II) CoFe_2O_4 NP coated with and (III) the swollen and freeze-dried magnetic hydrogel. Adapted with permission from Ref. [60]. Copyright (2011) American Chemical Society. (d) Scheme showing the experimental procedure to align the magnetic particles and collagen fibres: (a) Liquid collagen suspension with neurons (orange) and magnetic NP (red). (b) Placement of the suspension onto coverslips and allowed to solidify with (bottom) or without (top) magnetic field. (c) Final scheme of the random and aligned hydrogels. SEM image of (II) the random distribution of magnetic NPs within collagen hydrogel and (III) the magnetic strings in the hydrogel solidified under a magnetic field. Adapted with permission from Ref. [61]. Copyright (2016) American Chemical Society.

A third strategy to incorporate magnetic NP has been covalent bonding, which implies the formation of a covalent bond between the functionalized magnetic nanomaterials and the polymer chains. Although this method usually involves more complicated steps and is more time-consuming, the advantage is the prevention of NP leaching out from the hydrogel network. For example, PAA and methacrylic surface-functionalized CoFe_2O_4 NP were employed to assure a covalent bonding between them. First, the CoFe_2O_4 NP were synthesized by precipitation from a CoCl_2 and FeCl_3 (1:2 molar ratio) solution after alkalization and stabilized with citric acid and tetramethylammonium hydroxide in water. And second, functionalization was obtained after mixing the NP first with NH_4OH solution (25%) and second with 3-methacryloxypropyltrimethoxysilane (MTS) allowing the reaction (e.g., condensation of siloxane groups onto particle surface) to take place at room temperature for 15 h. The resultant particles were single-crystalline and had an average size of 12.2 ± 0.23 nm, resulting in a pseudo-superparamagnetic behavior. Finally, the authors synthesized different PAA hydrogels with the citric acid- and methacrylic-functionalized CoFe_2O_4 NP to investigate the effect of the particle-to-polymer interaction (hydrogen bonding in citric acid- and covalent bonding in methacrylic-functionalized particles) on the hydrogel magnetic and mechanical properties [64]. Another example was the formation of covalently bonding hydrogels between siloxane-functionalized CoFe_2O_4 NP and the PVA matrix (**Figure 3C**). The procedure was very simple as they first mixed the monomer (AAM) and the functionalized CoFe_2O_4 NP followed by the crosslinker (N,N,N',N'-tetramethylethylenediamine) and the initiator (ammonium peroxodisulfate). The reaction proceeded at room temperature for 2 h. The magnetic NP had a size around 12 nm showing a superparamagnetic behavior. Moreover, they also showed that the hydrogel swelling was lower when the NP were covalently bonded to the hydrogel compared to the NP physical entrapped [60].

In all previous strategies, a more or less homogeneous but random distribution of the magnetic NP can be achieved. Recently, the development of complex hydrogels architectures has grown by controlling the spatial distribution and orientation of the magnetic nanomaterials within the hydrogel scaffold by using an external magnetic field. Normally, the magnetic nanomaterials are mixed with the hydrogel precursors and subsequently aligned by placing the mixture in an external magnetic field. The nanomaterials become magnetized and reorient along the magnetic field direction. This anisotropic and well-ordered structure is then fixed by crosslinking the precursor solution into the hydrogel. Although this approach can be applied to magnetic nanomaterials with different shapes (e.g., NP, NR, and NW), magnetic NP have been extensively used for the preparation of such anisotropic hydrogels [61, 65]. For example, Fe_3O_4 NP have been successfully aligned within the hydrogel precursor solution containing AM (monomer), MBAM (crosslinker), APS (initiator), and tetraethylethylenediamine (accelerator) using a static magnetic field. After that, the hydrogel formation was triggered by increasing temperature up to 50°C . Such alignment led to an enhanced magnetothermal effect under an external alternating magnetic field compared to the disordered hydrogel [66]. Or Antman-Passig and Shefi embedded Fe_3O_4 NP in a collagen fiber suspension, aligned the NP into strings under an external magnetic field, which also forced the alignment of the fibers, and finally, collagen was allowed to solidify keeping the magnetic field (**Figure 3E**). The seeded neurons had normal electrical activity and viability and their growth was induced and controlled along the fibers and NP string direction acting as a physical cue for the cells [61].

3.1 Biomedical applications

These magnetically-responsive hydrogels have enabled a wide range of potential applications in the biomedical field, such as tissue engineering, drug delivery, artificial muscles, soft actuators, and magnetic hyperthermia, among others. Tissue engineering has been one of the fields where magnetic hydrogels have been widely applied covering a wide range of tissues, such as bone, cartilage, cardiovascular, or neuronal tissues. The ultimate aim of scaffolds is to foster the natural reparative process by guiding the new tissue formation and recovering their functionality, where multiple biochemical, biophysical, and biological cues need to be controlled. Magnetic hydrogels are key in this discipline since hydrogel architectures can be magnetically controlled in a way to confer directionality and or concentration gradient mimicking complex anisotropic tissues. Moreover, these hydrogels can be remotely actuated with external magnetic fields inducing mechanical deformation within the scaffold (e.g., magnetomechanical stimulation or mechanotransduction effect), which has an impact on cell behavior (e.g., growth, migration, proliferation, and differentiation). For example, Huang et al. have reported an effective regeneration of cartilage using magnetic hydrogels composed of PVA, hydroxyapatite particles, and maghemite (Fe_2O_3) NP. The incorporation of the NP improved not only the mechanical properties of the hydrogel but also induced the proliferation and differentiation of the seeded MSC into the chondrogenic lineage [67]. Other approaches have applied either static or time-varying magnetic fields to the cells-containing hydrogels. Thus, Brady et al. developed a three-layer agarose- Fe_3O_4 hydrogel with a stiffness gradient that was achieved using a different agarose concentration in each layer (1, 2, and 3 wt.%). Bovine chondrocytes were embedded in each layer under the application of a 500 mT static magnetic field (**Figure 4A**). After 14 days of magnetic stimulation, they observed an increase in both strain and sulphated glycosaminoglycan content from the 1 wt.% agarose layer to the 3 wt.% agarose layer [68]. Fuhrer and collaborators also observed that the application of a non-continuous (2 s on, 10–225 s off) 800 mT magnetic field to the Fe_3O_4 -styrene-maleic anhydride hydrogel seeded with MSC induced their chondrogenic differentiation without the need of any other chondrogenesis transcription factors [58].

More recently, magnetic hydrogels with anisotropic architectures have been fabricated trying to mimic native tissues. For example, an anisotropic collagen-agarose bilayer containing Fe_3O_4 NP was obtained when a 2 mT magnetic field was applied during hydrogel formation. Collagen fibers aligned as a consequence of the NP alignment parallel to the field direction but only in the layer where the agarose content was lower (0.5 w/v%). The layer with the higher agarose concentration (1 w/v%) hindered collagen and magnetite NP alignment. The authors observed that seeded chondrocytes in the anisotropic scaffolds expressed more collagen type II when compared with the isotropic hydrogels [72]. These anisotropic structures were also recently explored by Araújo-Custódio et al. who reported the fabrication of gelatin hydrogels containing rod-shaped cellulose nanocrystals decorated with magnetite NP that were aligned by applying a static magnetic field (108 mT). The hydrogel, that tried to mimic tendon tissue, showed a directional structure with anisotropic mechanical properties being the storage modulus higher in the direction parallel to the rod long axis. This anisotropy also had an impact on the embedded cells as it induced an elongated morphology and a directional growth again on the rod long axis (**Figure 4B**) [69].

Another application where magnetic nanocomposite hydrogels have been investigated is drug delivery due to the possibility to release the drug on demand

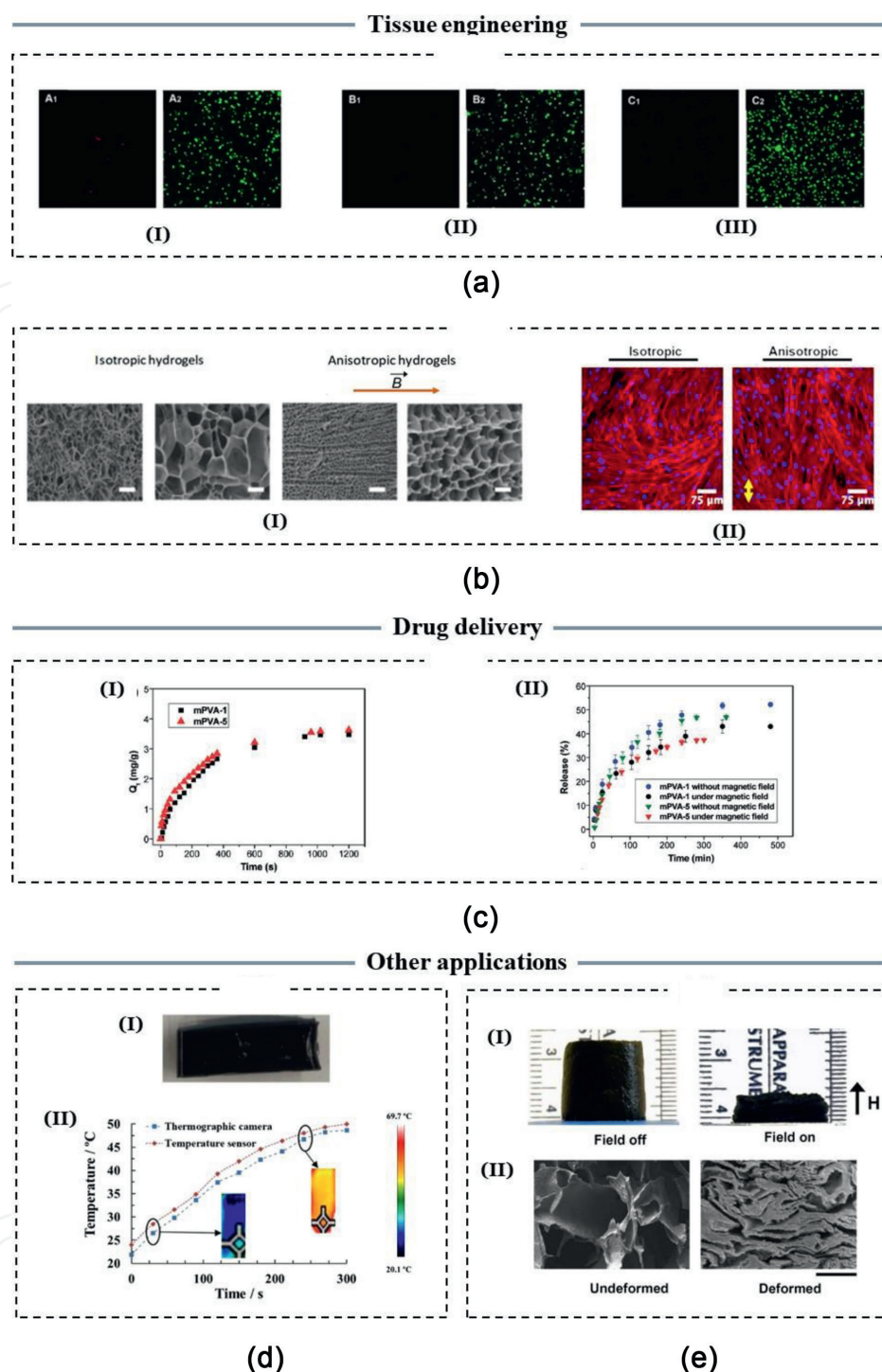


Figure 4.

(a) Live/dead stain images (dead cells (red), live cells (green)) showing the cell viability of chondrocytes embedded into the different layers of the agarose- Fe_3O_4 NP hydrogel at different times (I) day 1, (II) day 7 and (III) day 14. Reproduced with permission from Ref. [68]. (b) (I) SEM images of isotropic and anisotropic hydrogels. Scale bar = 10 μm . (II) Confocal microscope images showing the effect of isotropic and anisotropic hydrogels on cell alignment (red, cytoskeleton; blue, nucleus). Adapted with permission from Ref. [69]. Copyright (2019) American Chemical Society. (c) (I) Graph showing the amount of congo red loaded onto the hydrogels with different magnetic contents with time. (II) Graph showing the release profiles of the hydrogels with different magnetic contents over time with and without applied magnetic field. Adapted with permission from Ref. [59]. Copyright (2012) American Chemical Society. (d) (I) Photo of the Alg/PEDOT/ Fe_3O_4 NP hydrogel. (II) Graph showing the variation of temperature of the Alg/PEDOT/ Fe_3O_4 NP hydrogel with time subjected to an alternating magnetic field (200 Hz, 8 kA m^{-1}). Adapted with permission from Ref. [70]. Copyright (2021) American Chemical Society. (E) (I) Image of the hydrogel without (left) and with an applied magnetic field (right). (II) SEM images of the hydrogel in the undeformed and deformed states. Scale bar: 500 μm . Reproduced with permission from Ref. [71].

and at certain concentrations when magnetic fields are applied. Moreover, the delivery of the therapeutic drug in situ to the specific target can be done remotely. In this line, Mahdavinia and collaborators fabricated a magnetic IPN hydrogel network containing k-carrageenan and PVA as well as FeSO_4 and FeCl_3 to precipitate Fe_3O_4 NP by adding NH_3 . After that, diclofenac sodium as a model drug was added to the previous mixture and further crosslinked by the freezing-thawing method followed by immersion in K^+ solution. The hydrogel, that showed a superparamagnetic behavior with magnetization saturation values between 3.4 and 8.2 emu/g depending on the magnetite content, was subjected to an alternate magnetic field with variable strength in the range 100–500 G. They observed a controlled diffusion of the drug such that the higher the magnetic field was, the higher the amount of diclofenac sodium released. They attributed this behavior to the higher mechanical stress conferred as the magnetic field increased [73]. Another example by Zhou et al. showed that the amount of congo red loaded onto the hydrogels was the same independently of the amount of magnetite inside the PVA hydrogel. However, they did observe a change in the amount of congo red released in the absence and presence of a static magnetic field. After 500 min, the released content was around 55% with no magnetic field and around 42% with the applied magnetic field for the hydrogel with the lowest amount of magnetite (**Figure 4C**) [59].

Some other applications of magnetic hydrogels are magnetic hyperthermia as experimental cancer therapy or soft actuators to develop artificial muscles. Magnetic hyperthermia, which basically consists of the delivery of heat when a high frequency oscillating magnetic field is applied, has been investigated into magnetic nanocomposite hydrogels. For example, Puiggali-Jou et al. observed that when an alternating magnetic field (frequency = 200 kHz) was applied to a Alg/PEDOT/ Fe_3O_4 NP hydrogel, the temperature increased from room temperature to around 50°C after a few minutes, which was attributed to the presence of the magnetic NP (**Figure 4D**) [70]. More recently, hydrogels with ordered structures like the one fabricated by aligning magnetite NP with a PAM hydrogel have also shown magnetothermal effect but direction-dependent. When the magnetic NP chains were aligned parallel to the applied field, the heating rate and the plateau temperature were higher than the values achieved with the non-ordered hydrogels [66]. Magnetically responsive hydrogels can also be used as soft actuators due to the change in volume, shape, or position they experience in response to a magnetic field. Thus, Zhao et al. developed an Alg hydrogel crosslinked with adipic acid dihydrazide (AAD) and containing magnetite NP with a diameter around 10 nm. The application of a magnetic field (38 A/cm²) induced deformation of the hydrogel with a volume change of 70% (**Figure 4E**) [71]. Zhou et al. developed the amphiphilic pentablock copolymer PAA-PC5MA-PEO-PC5MA-PAA (PC5MA: poly(5-cholesteryloxypentyl methacrylate), PEO: poly(ethylene oxide)) and the Fe_3O_4 NP that were directly bonded to the carboxylic groups of PAA. These magnetic hydrogels were bent under the application of a magnetic field [74]. Recently, significant efforts have been put into developing dual electric- and magnetic-responsive hydrogels with even enhanced properties compared to the single stimuli-responsive systems. For example, Liu et al. fabricated a flexible hydrogel containing CNT, PPy NP, and iron oxide with electrical conductivity and magnetic properties with potential applicability as biosensor and bioactuator [75]. Or Garcia-Torres and collaborators synthesized an Alg/PEDOT/ Fe_3O_4 hydrogel for magnetic hyperthermia application and simultaneous measurement of temperature [70].

4. Conclusions

In this chapter, the author has reviewed recent developments in electric- and magnetic-responsive hydrogels from the perspective of materials and properties and applications. Many hydrogels have been employed so far for the fabrication of the hybrid systems comprising natural (e.g., Alg and Col) and synthetic polymers (e.g., PVA and PEG) but mainly a mixture of different polymers to improve the performance of the interpenetrated hydrogel obtained. The different strategies to confer hydrogels with electric and magnetic responsiveness—blending, in situ precipitation, covalent bonding—have been presented. The different methodologies allowed modifying the structure of the hydrogels (e.g., different distribution of the NP within the hydrogel framework) and therefore their properties. The main applications for the electric- and magnetic-stimuli hydrogels have been presented, including tissue engineering, drug delivery, and actuation. It has been shown that the unique presence of the nanomaterials either with electrical conductivity or magnetic properties already improved cell adhesion, proliferation, and differentiation, but it was enhanced even more when the hydrogel was either electrically or magnetically stimulated. These hydrogels can also be used as drug delivery systems with the ability to control the amount of drug release just by modifying the applied signal (e.g., voltage and magnetic field strength). Thus, this field is rapidly emerging with new electric- and magnetic-responsive hybrid hydrogels providing significant advances in the biomedical field. And it has been possible thanks to the versatility in the main components—hydrogels, nanomaterials—providing unique features and properties to the hybrid hydrogels.

Author details

Jose Garcia-Torres^{1,2,3}

1 Biomaterials, Biomechanics and Tissue Engineering Group, Department of Materials Science and Engineering and Research Center for Biomedical Engineering, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain

2 Barcelona Research Center in Multiscale Science and Engineering, Universitat Politècnica de Catalunya, Barcelona, Spain

3 Institut de Recerca Sant Joan de Déu, Barcelona, Spain

*Address all correspondence to: jose.manuel.garcia-torres@upc.edu

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